

As: 04.273

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Rad: 00-028953-00010-0000

Fec: 2006-05-16 15:48:51 Dep. 2020 NUECREACIONES

Tra. 2 PATENTES

Eve: 1 REGDEPOSITO

Act 444 RESPUESTAREQUE Folios: 31

Señora

JEFE DE DIVISIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E.

S.

D.

Respuesta a Oficio No. 1759 del 16 de febrero de 2006

REF: Expediente No. 00 028.953 - Solicitud de patente de invención a favor de SYNGENTA LIMITED

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado sustituto de la Sociedad SYNGENTA LIMITED, domiciliada en Guildford, Surrey, Reino Unido, según lo acredita el documento de sustitución de poder a mi favor presentado en esta misma fecha en esa División, me permito dar respuesta a las observaciones de carácter técnico y jurídico, relacionadas con la patentabilidad, para la concesión de la patente de acuerdo con la Decisión 486 según el concepto técnico No. 088 notificado por fijación en lista de fecha 16 de febrero de 2006.

Atendiendo las observaciones del señor Examinador, en relación con el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito anexar al presente escrito los siguientes documentos:

- 1) Reporte de Examen de la Oficina Europea de Patentes en la fase regional de la solicitud extranjera correspondiente a la misma invención.
- 2) Copia de la respuesta presentada por el solicitante al Reporte de Examen de la Oficina Europea de Patentes.

428
428

- 3) Nota de la de la Oficina Europea de Patentes acerca de la intención de conceder la patente. (La Solicitud Europea ha sido concedida como Patente EP 1171437B1).
- 4) Copia del Reporte de Examen Preliminar Internacional sobre la solicitud PCT correspondiente a la misma invención, junto con su correspondiente traducción al castellano.
- 5) J. MARSH: Advanced Organic Chemistry, tercera edición, John Wiley and Sons, new Cork, 1985, páginas 370-376.
- 6) A.R. KATRIZKY et al. J. Org. Chem., (1993) 58, 2086.

De la Señora Jefe,

Atentamente,



JUAN PABLO CADENA SARMIENTO

T.P. No. 57.492 del C.SJ.

C.C. 80.410.337 de Usaquén

Carrera 7 No. 16-56 piso 9

Bogotá, 15 de mayo de 2006

MEV/yg

Anexos



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Patentamt

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429

Waterman, John Richard
Syngenta Limited,
Intellectual Property Department,
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P.O. Box 3538
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Berkshire RG42 6EY
GRANDE BRETAGNE



Application No. 00 919 009.1-2117	Ref. PPD 50402/EPT	Date 11.02.2003
Applicant Syngenta Limited		

Communication under Rule 51(4) EPC

You are informed that the Examining Division intends to grant a European patent on the basis of the above application with the text and drawings as indicated below:

Text for the Contracting States:

AT BE CH LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE

Description, pages:

2-110 as originally filed

1 as received on 18.07.2002 with letter of 16.07.2002

Claims, No.:

1 (part), 2-12 as originally filed

1 (part) as received on 18.07.2002 with letter of 16.07.2002

A copy of the relevant documents is enclosed.

The title of the invention in the three official languages of the European Patent Office, the International patent classification, the designated Contracting States, the registered name of the applicant and the bibliographic data are shown on the attached EPO Form 2056.

You are requested within four months of this notification

1. to file 1 set of translations of the claim(s) in the two other EPO official languages;

EUR

Registered Letter

EPO Form 2004 07.08CSX

3



Date 11.02.2003

Sheet 2

Application-No.: 00 919 009.1

438
430

2a.	to pay the fee for grant including the fee for printing up to and including 35 pages;		
		Reference 007	715.00
2b.	to pay the printing fee for the 36th and each additional page;		
	number of pages: 87		
		Reference 008	870.00
3.	to pay the additional claim fee(s) (Rule 51(7) EPC);		
	number of claims fees payable: 0		
		Reference 016	0.00
		Total amount	1585.00

Concerning the possibility of a request for accelerated grant pursuant to Article 97(6) EPC, reference is made to OJ EPO 2001, 459.

If the grant, printing or claims fees are not paid, or the translations not filed, in due time the European patent application will be deemed to be withdrawn (Rule 51(8) EPC).

For all payments you are requested to use EPO Form 1010 or to refer to the relevant reference number.

If additional copies of the patent specification are required, you should request this in writing and quote Fee reference code 058 when making payment.

Translation of the priority document(s)

If the translation of the priority document(s), as required by Article 88(1) EPC, or the declaration according to Rule 38(5) EPC has not yet been filed, Form 2530 will be despatched separately. The translation is to be filed within the above mentioned time limit (Rule 38(5) EPC).

Note on payment of renewal fees

If a renewal fee falls due between notification of the present communication and the proposed date of publication of the mention of the grant of the European patent, publication will be effected only after the renewal fee and any additional fee have been paid (Rule 51(9) EPC).

Under Article 88(4) EPC, renewal fees are payable to the European Patent Office until the year in which the mention of the grant of the European patent is published.

Filing of translations in the Contracting States

Pursuant to Article 65(1) EPC the following Contracting States require a translation of the specification of the European patent in their/one of their official language(s) (Rule 51(10) EPC), insofar this specification will not be published in their/one of their official language(s)

- within three months of publication of the mention of such decision:

AT	AUSTRIA	FR	FRANCE
BE	BELGIUM	GB	UNITED KINGDOM
CH	SWITZERLAND / LIECHTENSTEIN	GR	GREECE
CY	CYPRUS	IT	ITALY
DE	GERMANY	NL	NETHERLANDS
DK	DENMARK	PT	PORTUGAL
ES	SPAIN	SE	SWEDEN
FI	FINLAND	TR	TURKEY

4

433
431

- within six months of publication of the mention of such decision:

IE IRELAND

The date on which the European Patent Bulletin publishes the mention of the grant of the European patent will be indicated in the decision on the grant of the European patent (EPO Form 2008).

In case of a valid extension the following Extension States require a translation of the claims in their official language within three months after publication of the mention of the grant of the European patent:

AL ALBANIA
LT LITHUANIA
LV LATVIA
MK MACEDONIA

RO ROMANIA (requires translation
of the specification)
SI SLOVENIA

The translation must be filed with the national Patent Offices of the Contracting or Extension States in accordance with the provisions applying thereto in the State concerned. Further details (e.g. appointment of a national representative or indication of an address for service within the country) are given in the EPO information brochure "National law relating to the EPC", and in the supplementary information published in the Official Journal of the EPO, or available on the EPO website.

Failure to supply such translation to the Contracting and Extension States in time and in accordance with the requirements may result in the patent being deemed to be void ab initio in the State concerned.

Note to users of the automatic debiting procedure

Unless the EPO receives prior instructions to the contrary, the fee(s) will be debited on the last day of the period of payment. For further details see the Arrangements for the automatic debiting procedure (see Supplement to OJ EPO 2, 2002).



Date

11.02.2003

Sheet 4

Application-No.: 00 919 009.1

434
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Examining Division:

Chairman: HELPS I M
2nd Examiner: OUSSET J
1st Examiner: FRITZ M



Ruiz Fernandez, J
For the Examining Division
Tel. No.: +49 89 2399-2152

Enclosure(s): Form 2056
120 Copies of the relevant documents

4

435
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Richard Waterman
European Patent Attorney

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syngenta

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GERMANY

EPO - Munich
69
18. Juli 2002

16 July 2002

European Patent Application No.00919009.1-2117
SYNGENTA LIMITED
Our Ref: PPD50402/EPT

Dear Sirs,

I refer to the Communication pursuant to Article 96(2) dated 4 February 2002. A period of four months was set for reply and this was extended to six months in your Communication of 26 June.

The applicants are pleased to note that the subject matter of the claims is acknowledged to be novel and also to involve an inventive step if certain terms in the claims are more precisely defined according to the description at page 5 line 4 - page 7 line 9. The applicants submit an amended claim 1 (pages 114, 114a and 114b) in which the passage referred to by the Examiner has been inserted into the claim. An amended page 1 is also enclosed. The amendments are shown in handwritten form on the relevant pages of the application.

The applicants believe that the application now fully meets the requirements of the EPC but if any matters remain outstanding the Examiner is requested to contact the undersigned.

Yours faithfully



Richard Waterman
European Patent Attorney

ENC

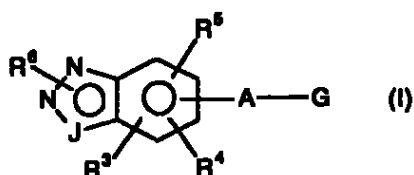
Syngenta Limited - Registered in England No 2710846
Registered Office: Syngenta, European Regional Centre, Priestley Road,
Surrey Research Park, Guildford, Surrey GU2 7YH, United Kingdom.



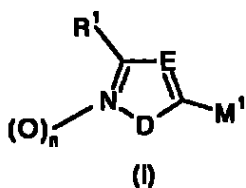
The present invention relates to azine and azole derivatives, to processes for preparing them, to fungicidal, insecticidal, acaricidal, molluscicidal and nematocidal compositions comprising them, to methods of using them to combat fungal diseases (especially fungal diseases of plants) and to methods of using them to combat and control insect, acarine, mollusc and nematode pests.

Azole and azine derivatives are disclosed in WO95/31448, WO97/18198, WO98/02424 and WO98/05670.

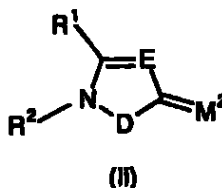
The present invention provides a compound of formula (I):



wherein G is either



or



where M¹ or M² is bonded to A; n is 0 or 1; A is optionally substituted C₁₋₆ alkylene, optionally substituted C₂₋₆ alkenylene, optionally substituted C₂₋₆ alkynylene, optionally substituted C₁₋₆ alkyleneoxy, optionally substituted oxy(C₁₋₆)alkylene, optionally substituted C₁₋₆ alkylenthio, optionally substituted thio(C₁₋₆)alkylene, optionally substituted C₁₋₆ alkylenamino, optionally substituted amino(C₁₋₆)alkylene, optionally substituted [C₁₋₆ alkyleneoxy(C₁₋₆)alkylene], optionally substituted [C₁₋₆ alkylenthio(C₁₋₆)alkylene], optionally substituted [C₁₋₆ alkylenesulfinyl(C₁₋₆)alkylene], optionally substituted [C₁₋₆

6

(C₁₋₆)alkyl], optionally substituted [C₂₋₆ alkynyl(C₁₋₆)alkyl], optionally substituted C₃₋₇ cycloalkyl, optionally substituted C₁₋₁₀ alkylcarbonyl, optionally substituted C₁₋₁₀ alkoxy carbonyl, formyl, optionally substituted C₁₋₁₀ alkylaminocarbonyl, optionally substituted di(C₁₋₁₀)alkylaminocarbonyl, hydroxy, amino, optionally substituted C₁₋₆ alkylamino, optionally substituted di(C₁₋₆)alkylamino, or optionally substituted phenoxycarbonyl; R¹⁶ is hydrogen, cyano, nitro, optionally substituted C₁₋₆ alkyl, optionally substituted C₃₋₇ cycloalkyl, optionally substituted (C₂₋₆)alkenyl(C₁₋₆)alkyl, optionally substituted (C₂₋₆)alkynyl(C₁₋₆)alkyl, optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted C₁₋₆ alkylcarbonyl, optionally substituted C₁₋₆ alkoxy carbonyl, optionally substituted C₁₋₆ alkylamino, optionally substituted di(C₁₋₆)alkylamino, optionally substituted C₁₋₆ alkylcarbonylamino, optionally substituted C₁₋₆ alkoxy carbonylamino, optionally substituted C₁₋₆ alkoxy, optionally substituted C₁₋₆ alkylthio, optionally substituted C₁₋₆ alkylsulfinyl, optionally substituted C₁₋₆ alkylsulfonyl, optionally substituted arylthio, optionally substituted arylsulfinyl, optionally substituted arylsulfonyl or C₁₋₆ acyloxy; R¹⁷ is hydrogen, halogen, nitro, cyano, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted C₃₋₇ cycloalkyl, optionally substituted C₁₋₆ alkoxy carbonyl, optionally substituted C₁₋₆ alkylcarbonyl, optionally substituted C₁₋₆ alkylaminocarbonyl, optionally substituted di(C₁₋₆)alkylaminocarbonyl, optionally substituted phenyl or optionally substituted heteroaryl; R¹⁸ and R¹⁹ are, independently, optionally substituted C₁₋₆ alkyl or R¹⁸ and R¹⁹ together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further hetero atoms selected from O, N or S and which may be optionally substituted by one or two C₁₋₆ alkyl groups; R²⁰ is hydrogen, optionally substituted phenyl, optionally substituted phenyl(C₁₋₄)alkyl or optionally substituted C₁₋₂₀ alkyl; R²¹ is hydrogen, optionally substituted phenyl or optionally substituted C₁₋₆ alkyl; and R²² and R²³ are, independently, optionally substituted C₁₋₆ alkyl or R²² and R²³ together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further hetero atoms selected from O, N or S and which may be optionally substituted by one or two C₁₋₆ alkyl groups;

-114a-

wherein the optional substituents, when present, on the alkylene, alkenylene or alkynylene moieties are, subject to valency constraints, one or more of halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ cyanoalkyl, C₁₋₆ alkoxy(C₁₋₆) alkyl, C₁₋₆ alkoxy, cyano, =O, =NR²⁴ and =CR²⁵R²⁶, wherein R²⁴ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, OR²⁷ or R²⁸R²⁹N; where R²⁵ and R²⁶ are, independently, hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, cyano, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylcarbonyl or R³⁰R³¹N; R²⁷ is C₁₋₆ alkyl, C₁₋₆ haloalkyl or phenyl(C₁₋₂)alkyl; R²⁸ and R²⁹ are, independently, hydrogen, C₁₋₈ alkyl, C₃₋₇ cycloalkyl, C₂₋₆ alkenyl(C₁₋₆)alkyl, C₂₋₆ alkynyl(C₁₋₆)alkyl, C₂₋₆ haloalkyl, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkoxycarbonyl(C₁₋₆)alkyl, carboxy(C₁₋₆)alkyl or phenyl(C₁₋₂)alkyl or R²⁸ and R²⁹ together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further hetero atoms selected from O, N or S and which may be optionally substituted by one or two C₁₋₆ alkyl groups; R³⁰ and R³¹ are, independently, hydrogen, C₁₋₈ alkyl, C₃₋₇ cycloalkyl, C₂₋₆ alkenyl(C₁₋₆)alkyl, C₂₋₆ alkynyl(C₁₋₆)alkyl, C₂₋₆ haloalkyl, C₁₋₆ alkoxy-(C₁₋₆)alkyl, C₁₋₆ alkoxycarbonyl(C₁₋₆)alkyl, carboxy(C₁₋₆)alkyl or phenyl(C₁₋₂)alkyl; or R³⁰ and R³¹ together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further hetero atoms selected from O, N or S and which may be optionally substituted by one or two C₁₋₆ alkyl groups; and wherein each alkyl moiety is a straight or branched chain and, when present, the optional substituents on alkyl are one or more of halogen, nitro, cyano, HO₂C, C₁₋₁₀ alkoxy (itself optionally substituted by C₁₋₁₀ alkoxy), aryl-(C₁₋₄)alkoxy, C₁₋₁₀ alkylthio, C₁₋₁₀ alkylcarbonyl, C₁₋₁₀ alkoxycarbonyl, C₁₋₆ alkylamino-carbonyl, di(C₁₋₆ alkyl)aminocarbonyl, (C₁₋₆)alkylcarbonyloxy, optionally substituted phenyl, heteroaryl, aryloxy, arylcarbonyloxy, heteroaryloxy, heterocyclyl, heterocyclyloxy, C₃₋₇ cycloalkyl (itself optionally substituted with (C₁₋₆)alkyl or halogen), C₃₋₇ cycloalkyloxy, C₅₋₇ cycloalkenyl, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfinyl, tri(C₁₋₄)alkylsilyl, tri(C₁₋₄)alkylsilyl-(C₁₋₆)alkoxy, aryl-di(C₁₋₄)alkylsilyl, (C₁₋₄)alkyl-diarylsilyl, triarylsilyl, =N-OR' and =N-NR'R"; where R' and R" are, independently, C₁₋₆ alkyl or C₁₋₆ haloalkyl; and where the alkenyl and alkynyl moieties are in the form of straight or branched chains, and the alkenyl moieties, where appropriate, can be of either the (E)- or (Z)-configuration; and, when present, the optional substituents on alkenyl or alkynyl are one or more of halogen, aryl and C₃₋₇

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- 1141 -

cycloalkyl; and wherein acyl is optionally substituted C₁₋₆ alkylcarbonyl, optionally substituted C₂₋₆ alkenylcarbonyl, optionally substituted C₂₋₆ alkynylcarbonyl, optionally substituted arylcarbonyl or optionally substituted heteroarylcarbonyl; and wherein halogen is fluorine, chlorine, bromine or iodine; haloalkyl groups are alkyl groups which are optionally substituted with one or more of the same or different halogen atoms; aryl is phenyl, naphthyl, anthracyl, fluorenyl and indenyl; heteroaryl is an aromatic ring containing up to 10 atoms including one or more heteroatoms selected from O, S and N; heterocycle and heterocyclyl are a non-aromatic ring containing up to 10 atoms including one or more heteroatoms selected from O, S and N; cycloalkyl is cyclopropyl, cyclopentyl and cyclohexyl and the optional substituents for cycloalkyl are halogen, cyano and C₁₋₃ alkyl; cycloalkenyl is cyclopentenyl and cyclohexenyl and the optional substituents for cycloalkenyl are C₁₋₃ alkyl, halogen and cyano; carbocyclic rings are aryl, cycloalkyl and cycloalkenyl groups; and for substituted phenyl moieties, heterocyclyl and heteroaryl groups the substituents are independently selected from one or more of halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ haloalkylsulfinyl, C₁₋₆ alkylsulfonyl, C₁₋₆ haloalkylsulfonyl, C₂₋₆ alkenyl, C₂₋₆ haloalkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, nitro, cyano, CO₂H, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy carbonyl, R³²R³³N or R³⁴R³⁵NC(O) wherein R³², R³³, R³⁴ and R³⁵ are, independently, hydrogen or C₁₋₆ alkyl; and wherein dialkylamino substituents include those where the dialkyl groups together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further hetero atoms selected from O, N or S and which may be optionally substituted by one or two C₁₋₆ alkyl groups; and when heterocyclic rings are formed by joining two groups on an N atom, the resulting rings are pyrrolidine, piperidine, thiomorpholine and morpholine each of which may be substituted by one or two (C₁₋₆)alkyl groups.



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(Formalities and other matters)



Application No. 00 919 009.1-2117	Ref. PPD 50402/EPT	Date 04.02.2002
Applicant Syngenta Limited		

Communication pursuant to Article 96(2) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 78(2) and 83(2) and (4) EPC.

Amendments to the description, claims and drawings are to be filed where appropriate within the said period in three copies on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).



FRITZ M
Primary Examiner
for the Examining Division

Enclosure(s): 3 page/s reasons (Form 2906)

12

44
439

	Beschaid/Protokoll (Anlage)	Communication/Minutes (Annex)	Notification/Procès-verbal (Annexe)
	Datum Date 04.02.2002	Blatt Sheet Feuille 1	Annähe-Nr.: Application No.: Demande n°: 00 919 009.1

The examination is being carried out on the following application documents:

Text for the Contracting States:

AT BE CH LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE

Description, pages:

1-110 as originally filed

Claims, No.:

1-12 as originally filed

1. The following document (D1) is referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 95 31448 A (DOWELANCO) 23 November 1995 (1995-11-23)

2. The present application discloses compounds of the general formula (I) (claims 1-8), a process for the preparation thereof (claim 9), compositions thereof (claim 10) and a method of combating and controlling fungi (claim 11) or insects, acarines, nematodes and molluscs (claim 12) by applying the compounds of formula (I).

3. D1 discloses the compounds (1), (2) and (3) which are used both as insecticides and fungicides (cf. D1, p. 1, "field of the invention") the structure of which is comparable with the structure of the compounds (I) according to the present case. The compounds (I) according to the present case in which G designates (i) can be distinguished from the compounds (1) and (2) described in claim 1 of D1 insofar as the latter do not comprise a bridging moiety A. Furthermore the group Z in the compounds (1) and (2) according to D1 may be an aryl or heteroaryl rest, however it is not defined as a bicyclic aryl comprising a benzo moiety condensed with a 5-membered ring comprising at least 2 nitrogens in neighbouring positions (cf. the definition of the group Z in claim 1 of D1; p. 95, line 1 - p. 97, line 25). The compounds (I) according to the present case in which G designates (ii) can

17

442
440



Beschaid/Protokoll (Anlage)

Datum
Date
Date 04.02.2002

Communication/Minutes (Annex)

Blatt
Sheet
Feuille 2

Notification/Procès-verbal (Annexe)

Annonce-Nr.:
Application No.: 00 919 009.1
Demande n°:

be distinguished from the compounds (3) described in claim 1 of D1 by the meaning of the group Z.

In tables I, II and III displayed on p. 19 - p. 36 of D1 (which are exemplifying the compounds (1), (2), (3) described therein) in only one of 276 listed compounds the group Z is a bicyclic aromatic system (i.e. naphthyl in ex. 34) while in the other examples Z designates a (substituted) phenyl group.

Thus the subject-matter of claim 1 according to the present case is novel in the sense of Article 54 EPC.

4. The problem of the present application was to provide further compounds which can be used as both pesticides and insecticides.

This problem has been solved, as was can be seen in the description (cf. ex. 5 and 6).

Closest prior art is D1

Due to the structural differences outlined above the compounds (I) according to the present case cannot be considered obvious for a person skilled in the art

An inventive step in the sense of Article 56 EPC would therefore be acknowledged for the subject-matter of claims 1-12, if the terms "optionally substituted", "aryl", "heteroaryl", "heterocycl", "heterocyclyl", "acyl", "cycloalkyl", "cycloalkenyl" employed in claim 1 were precised in accordance with the definitions as given in the description on p. 5, lines 4 - p. 7, line 9 (Art. 6 PCT).

5. When filing amended claims the applicant should at the same time bring the description into conformity with the amended claims. Care should be taken during revision, especially of the introductory portion and any statements of problem or advantage, not to add subject-matter which extends beyond the content of the application as originally filed (Article 123(2) EPC).

11

443
441

	Beschuld/Protokoll (Anlage)		Communication/Minutes (Annex)		Notification/Procha-verbal (Annexe)	
	Datum	04.02.2002	Blatt	3	Anmelde-Nr.:	00 919 009.1
	Date		Sheet		Application No.:	
		Date		Fa.ille	Demande n°:	

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 123(2) EPC, the applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based.

If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

21

MEWBURN ELLIS
INTELLECTUAL PROPERTY
PATENTS-TRADE MARKS-DESIGNS

EUROPEAN PATENT OFFICE
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EPO - Munich
58

26. März 2001

Chartered Patent Agents
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22 March 2001

Dear Sirs

European Patent Application No. : 95904633.5
Applicant: SYNGENTA LIMITED
Our Ref: 5675004.EPG

It has been brought to our attention that there is a spelling mistake in the applicant's address.

The correct address is:- Fernhurst, Haslemere, Surrey GU27 3JE.

Please correct the address on all applications in the name of Syngenta Limited.

Thank you for your co-operation in this matter.

Kind regards.

Yours faithfully



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European Grant
MEWBURN ELLIS

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16

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Ligne directe:
2754

Zeichen / Référence / Reference

Datum / Date / Date
03.04.2001

Your letter of 22.03.2001
Your Ref: 5675004.EPG

Please be informed, that the address of the applicant
"Syngenta Limited" was corrected in all applications to read
"Fernhurst, Haslemere, Surrey GU27 3JE".


Maler R.P.
Formalities Officer

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17

PATENT COOPERATION TREATY

RECD 22 JAN 2001

PCT

WIPO

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PPD 50402/WO		FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEAM16)
International application No. PCT/GB00/01272	International filing date (day/month/year) 04/04/2000	Priority date (day/month/year) 20/04/1999		
International Patent Classification (IPC) or national classification and IPC C07D417/12				
Applicant ZENECA LIMITED et al.				
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 5 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.				
3. This report contains indications relating to the following items: - I ☒ Basis of the report - II ☐ Priority - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability - IV ☐ Lack of unity of invention - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement - VI ☐ Certain documents cited - VII ☐ Certain defects in the international application - VIII ☒ Certain observations on the international application				
Date of submission of the demand 07/09/2000		Date of completion of this report 18.01.2001		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2369 - 0 Tx: 523656 epnu d Fax: +49 89 2369 - 4465		Authorized officer Fritz, M  Telephone No. +49 89 2369 2792		

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/01272

1. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).;*

Description, pages:

1-110 as originally filed

Claims, No.:

1-12 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

19

448
446

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/01272

(Any replacement sheet containing such amendments must be referred to under Item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-12
	No: Claims
Inventive step (IS)	Yes: Claims 1-12
	No: Claims
Industrial applicability (IA)	Yes: Claims 1-12
	No: Claims

**2. Citations and explanations
see separate sheet**

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

22

449
447

INTERNATIONAL PRELIMINARY International application No. PCT/GB00/01272
EXAMINATION REPORT - SEPARATE SHEET

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: WO 95 31448 A (DOWELANCO) 23 November 1995 (1995-11-23) cited in the application

The present application discloses compounds of the general formula (I) (claims 1-8), a process for the preparation thereof (claim 9), compositions thereof (claim 10) and a method of combating and controlling fungi (claim 11) or insects, acarines, nematodes and molluscs (claim 12) by applying the compounds of formula (I).

D1 discloses the compounds (1), (2) and (3) which are used both as insecticides and fungicides (cf. D1, p. p, "field of the invention") the structure of which is comparable with the structure of the compounds (I) according to the present case.

The compounds (I) according to the present case in which G designates (I) can be distinguished from the compounds (1) and (2) described in claim 1 of D1 insofar as the latter do not comprise a bridging moiety A. Furthermore the group Z in the compounds (1) and (2) according to D1 may be an aryl or heteroaryl rest, however it is not defined as a bicyclic aryl comprising a benzo moiety condensed with a 5-membered ring comprising at least 2 nitrogens in neighbouring positions (cf. the definition of the group Z in claim 1 of D1; p. 95, line 1 - p. 97, line 25).

The compounds (I) according to the present case in which G designates (II) can be distinguished from the compounds (3) described in claim 1 of D1 by the meaning of the group Z.

In tables I, II and III displayed on p. 19 - p. 36 of D1 (which are exemplifying the compounds (1), (2), (3) described therein) in only one of 276 listed compounds the group Z is a bicyclic aromatic system (i.e. naphthyl in ex. 34) while in the other examples Z designates a (substituted) phenyl group.

Thus the subject-matter of claim 1 according to the present case is novel in the sense of Article 33(2) PCT.

The problem of the present application was to provide further compounds which can be

21

450

448

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/01272

used as both pesticides and insecticides.

This problem has been solved, as was can be seen in the description (cf. ex. 5 and 6).

Closest prior art is D1

Due to the structural differences outlined above the compounds (I) according to the present case cannot be considered obvious for a person skilled in the art

Thus an inventive step in the sense of Article 33(3) PCT can be acknowledged for the subject-matter of claims 1-12.

Re Item VIII

Certain observations on the International application

The meanings of the terms "optionally substituted", "aryl", "heteroaryl", "heterocycl", "heterocyclyl", "acyl", "cycloalkyl", "cycloalkenyl" employed in claim 1 should be pre-cised in accordance with the definitions as given in the description on p. 5, lines 4 - p. 7, line 9 (Art. 6 PCT). This can be done when entering the Regional/European Phase.

52

451
449

**TRATADO SOBRE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES**

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

(Artículo 36 y Regla 70 PCT)

No. de Expediente del Solicitante o Apoderado PPD 50402/WO	PROCEDIMIENTO POSTERIOR Véase comunicación sobre el envío del Informe de examen preliminar internacional (Formulario PCT/IPEA416)	
No. Solicitud Internacional PCT/GB00/01272	Fecha Internacional de Presentación (día/mes/año) 04/04/2000	Fecha de Prioridad (día/mes/año) 20/04/1999
Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC C07D 417/12		
Solicitante ZENECA LIMITED y colaboradores		

1. Este Informe de examen preliminar internacional fue elaborado por la Oficina Encargada del Examen Preliminar Internacional y se envía al solicitante según Artículo 36.																									
2. Este INFORME comprende un total de 5 hojas, inclusive esta portada ☐ Además se adjuntan ANEXOS al Informe; en este caso se trata de hojas con descripciones, reivindicaciones y/o dibujos, que se modificaron y que sirven de base a este Informe, y/o hojas con correcciones efectuadas por esta oficina (véase Regla 70.16 y Sección 607 de las Instrucciones administrativas al PCT). Estos anexos comprenden en total de hojas.																									
3. Este Informe contiene datos con respecto a los siguientes puntos: <table border="0"> <tr> <td>I</td> <td>☒</td> <td>Base del Informe</td> </tr> <tr> <td>II</td> <td>☐</td> <td>Prioridad</td> </tr> <tr> <td>III</td> <td>☐</td> <td>Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación industrial</td> </tr> <tr> <td>IV</td> <td>☐</td> <td>Uniformidad deficiente de la invención</td> </tr> <tr> <td>V</td> <td>☒</td> <td>Declaración justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración</td> </tr> <tr> <td>VI</td> <td>☐</td> <td>Ciertos documentos enumerados</td> </tr> <tr> <td>VII</td> <td>☐</td> <td>Ciertas deficiencias del registro internacional</td> </tr> <tr> <td>VIII</td> <td>☒</td> <td>Ciertas observaciones relacionadas con la solicitud internacional</td> </tr> </table>		I	☒	Base del Informe	II	☐	Prioridad	III	☐	Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación industrial	IV	☐	Uniformidad deficiente de la invención	V	☒	Declaración justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración	VI	☐	Ciertos documentos enumerados	VII	☐	Ciertas deficiencias del registro internacional	VIII	☒	Ciertas observaciones relacionadas con la solicitud internacional
I	☒	Base del Informe																							
II	☐	Prioridad																							
III	☐	Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación industrial																							
IV	☐	Uniformidad deficiente de la invención																							
V	☒	Declaración justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración																							
VI	☐	Ciertos documentos enumerados																							
VII	☐	Ciertas deficiencias del registro internacional																							
VIII	☒	Ciertas observaciones relacionadas con la solicitud internacional																							

Fecha de presentación de la petición 07/09/2000	Fecha de la preparación de este Informe 18.01.2001
Nombre y dirección postal de la autoridad que realiza el examen preliminar internacional: Oficina Europea de Patentes D - 80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Empleado Autorizado Fritz, M. Teléfono No. +49 89 2399 - 2792

Formulario PCT/IPEA/409 (hoja de portada) (Enero 2004)

23

452
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**INFORME DEL EXAMEN PRELIMINAR
INTERNACIONAL**

Solicitud Internacional No.

PCT/GB00/01272

I. Base para este informe.

1. Respecto a los elementos de la solicitud internacional (Las hojas de reemplazo que han sido entregadas a la oficina receptora en respuesta a una invitación bajo el Artículo 14 se referencian en éste informe como "entregadas originalmente" y nos anexadas a este informe ya que no contienen enmendaduras (Reglas 70.16 y 70.17)):

Descripción, páginas

1 - 110 como se entregaron originalmente

Reivindicaciones, No.:

1 - 12 como se entregaron originalmente

2. Respecto al idioma, todos los elementos anteriormente marcados estaban disponibles o fueron suministrados a esta oficina en el idioma en el que se entregó la solicitud internacional, a menos que se diga lo contrario en este punto.

Estos elementos estaban disponibles o fueron entregados a esta oficina en el siguiente idioma
_____ los cuales son

- ☐ El idioma de la traducción entregada para propósitos de la búsqueda internacional (Regla 23.1 (b)).
- ☐ El idioma de publicación de la solicitud internacional (bajo la Regla 48.3 (b)).
- ☐ El idioma de la traducción entregada para propósitos del examen preliminar internacional (bajo las Reglas 55.2 y/o 55.3)

3. respecto a cualquier secuencia de nucleótido y/o aminoácidos divulgados en esta solicitud internacional, el examen preliminar internacional se realizó sobre la base de la secuencia:

- ☐ contenida en la solicitud en forma impresa
- ☐ entregada junto con la solicitud internacional en una forma legible en un computador
- ☐ suministrada subsiguientemente a esta oficina de forma escrita
- ☐ suministrada subsiguientemente a esta oficina en forma legible en un computador
- ☐ la declaración que la secuencia escrita suministrada no va más allá de lo divulgado en la solicitud internacional como se entregó ha sido suministrada
- ☐ La declaración que la información registrada en la forma legible a computador es idéntica a la secuencia escrita ha sido suministrada.

4. ☐ Las correcciones han resultado en la cancelación de:

- ☐ la descripción, páginas:
- ☐ las reivindicaciones, Nos:
- ☐ los dibujos, hojas:

5 ☐ Este informe ha sido admitido como si (algunas de) las enmendaduras no hubieran sido hechas, ya que se considera que estas van más allá de la divulgación preliminar, como se indica el Apartado Suplementario (Regla 70.2 (c)):

27

453
451

**INFORME DEL EXAMEN
PRELIMINAR INTERNACIONAL**

No de Solicitud Internacional PCT/GB00/01272

(Cualquier hoja de reemplazo que contenga dichas enmiendas debe ser referenciada bajo el asunto 1 y anexada a este informe.)

6. Observaciones adicionales, de ser necesarias:

V. Declaración concluyente bajo el Artículo 35(2) con respecto a la novedad, el nivel inventivo o la aplicabilidad industrial; las citas y explicaciones que sustentan dicha declaración

1. DECLARACIÓN

Novedad (N)	Si:	Reivindicaciones	1 – 12
	No:	Reivindicaciones	
Nivel Inventivo (IS)	Si:	Reivindicaciones	1 – 12
	No:	Reivindicaciones	
Aplicabilidad Industrial (IA)	Si:	Reivindicaciones	1 – 12
	No:	Reivindicaciones	

2. CITAS Y EXPLICACIONES

VIII. Ciertas observaciones sobre la solicitud Internacional

Se hacen las siguientes observaciones sobre la claridad de las reivindicaciones, descripción, y dibujos o sobre la pregunta si las reivindicaciones están completamente sustentadas por la descripción:

Ver hoja aparte

454
452

INFORME DEL EXAMEN

Solicitud internacional No. PCT/GB00/01272

PRELIMINAR INTERNACIONAL – HOJA APARTE

Re Item V

Declaración justificada bajo la Regla 66.2(a)(ii) respecto a la novedad, altura inventiva o aplicabilidad industrial; citas y explicaciones que sustentan tal declaración.

D1: WO 95 31448 A (DOWLANANCO) 23 de noviembre de 1995 (1995-11-23) citado en la solicitud.

La presente solicitud divulga compuestos de fórmula general (I) (reivindicaciones 1 – 8), un proceso para la preparación de los mismos (reivindicación 9), composiciones de los mismos (reivindicación 10) y un método para combatir y controlar hongos (reivindicación 11) o insectos, ácaros, nemátodos, y moluscos (reivindicación 12) aplicando los compuestos de la fórmula (I).

D1 divulga los compuestos (1), (2), y (3) los cuales se utilizan tanto como insecticidas y fungicidas (ver D1, pp "campo de la invención") la estructura de los cuales es comparable con la estructura de los compuestos (I) de acuerdo con el presente caso.

Los compuestos (I) de acuerdo con el presente caso en los cuales G representa (i) pueden diferenciarse de los compuestos (1) y (2) descritos en la reivindicación 1 de D1 ya que estos últimos comprenden una mitad de puente A. Más aun, el grupo Z en los compuestos (1) y (2) de acuerdo con D1 pueden ser un anillo o heteroanillo, sin embargo no se define como un compuesto bicíclico que comprende una mitad benzo condensada con un anillo de 5 miembros que comprende al menos 2 nitrógenos en posiciones vecinas (ver la definición del grupo Z en la reivindicación 1 de D1; p. 95, línea 25).

Los compuestos (I) de acuerdo con el presente caso en el cual G significa (ii) puede diferenciarse de los compuestos (3) descritos en la reivindicación 1 de D1 por el significado del grupo Z.

En las tablas I, II y III mostrados en la p. 19 – p. 36 de D1 (los cuales son los compuestos ejemplificantes (1), (2), (3) descritos aquí) en solamente uno de los 276 compuestos listados el grupo es un sistema aromático bicíclico (en otras palabras, naftilo en el ejemplo 34) mientras que en los otros ejemplos Z designa un grupo fenilo (sustituido).

Por lo tanto la materia de la reivindicación 1 de acuerdo con el presente caso es novedosa en el sentido del Artículo 33(2) del PCT.

El problema de la presente solicitud era el de proporcionar compuestos adicionales

26

455
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453

INFORME DEL EXAMEN Solicitud internacional No. PCT/GB00/01272
PRELIMINAR INTERNACIONAL – HOJA APARTE

que pueden ser utilizados tanto como pesticidas e insecticidas.

Este problema ha sido resuelto, como podemos ver en la descripción (ver ejemplos 5 y 6).

El arte previo más cercano es D1.

Debido a las diferencias estructurales delimitadas arriba los compuestos (I) de acuerdo con el presente caso no pueden considerarse como obvios por la persona con habilidad en el arte.

Por lo tanto puede reconocerse la altura inventiva en el sentido de Artículo 3383) del PCT para la materia de las reivindicaciones 1 – 12.

Re Item VIII

Ciertas observaciones sobre la solicitud internacional.

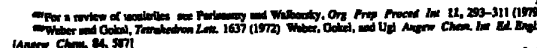
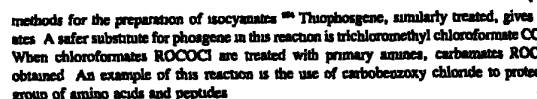
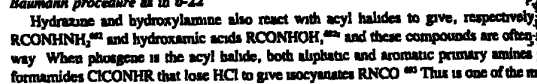
El significado de los términos "opcionalmente sustituido", "arilo", heteroarilo", heterociclo", "heterociclillo", "acilo", "cicloalquilo", "cicloalquenilo" empleado en la reivindicación 1 deben precisarse de acuerdo con las definiciones como se dan en la descripción en la página 5, línea 4 – página 7, línea 9 (Artículo 6 del PCT). Esto se puede hacer cuando se ingrese a la fase Regional/Europea.

2X

groups in general are often protected by conversion to amides. The treatment of acyl halides with nitride gives N,N-diacyl amides (triacylamines).⁶⁶



0-54 Acylation of Amines by Acyl Halides



¹⁰For a review, see Beckwith, in Zabicky Ref 455, pp. 73-185

²²For an improved method, see Ando and Tamaki, *Synth. Commun.* 13, 1033 (1983).

²²For reviews of the preparation and reactions of isocyanates and isothiocyanates see respectively the work of Ulich, pp. 619-818, and Drehsien Kristján and Augustin pp. 1003-1221, in Patai 'The Chemistry of the Carbonyl Group' 2, Wiley New York, 1977.

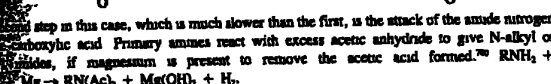
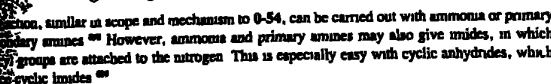
²⁰For examples, see Ozeki, *Chem. Rev.* 72, 457-496 (1972) pp. 457-460. For a review of the industrial importance of this reaction see Twitchett, *Chem. Soc. Rev.* 3, 209-230 (1974).

⁶⁰⁰Kurita and Iwakura, *Org. Synth.* 59, 195.
$$3\text{RCOCl} + \text{Li}_3\text{N} \longrightarrow (\text{RCO})_3\text{N}$$
reactions proceed by the tetrahedral mechanism.¹⁰

99, 165, II, 76, 208, 278, 328, 453, III, 167, 375, 415, 488, 490 613, IV, 339, 411, 780: V, 201, 336, 54, 88, 89, 195, 60, 72, 61, 17 See also OS 61, 71

Acidation of Amines by Anhydrides

Similar to a vowel substitution



though formic anhydride is not a stable compound (see p 487), amines can be formylated with the mixed anhydride of acetic and formic acids $\text{HCOOCOMe}^{\text{TM}}$ or with a mixture of formic and acetic anhydride. Acetamides are not formed with these reagents. Secondary amines can be formylated in the presence of a primary amine by conversion to their salts and addition of 18

The crown ether complexes the primary ammonium salt, preventing its acylation, while secondary ammonium salts, which do not fit easily into the cavity, are free to be acylated.

11, 437, II, II, III, 151, 436, 661, 813, IV, 3, 42, 106, 637, V, 27, 313, 636, 244, 313

Oxidation of Amines by Acids

Amination of Amino Acids by Amino-dehydrogenation



Carboxylic acids are treated with ammonia or amines, salts are obtained. The salts of ammonia

Blalock, Blanchard, and Koenig, *J. Org. Chem.* **30**, 671 (1965)

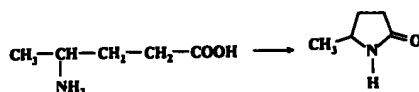
For a review, see Backlund in Zabicky, Ref. 455 pp. 84-96. For a review of peptide syntheses by treatment of

with a mixed anhydride of another amino acid, see Albertson, *Org. React.* 12, 137-233 (1966).
For reviews of ladders, see Wheeler and Rando, in Zabicky Ref. 455, pp. 335-381 Hargreaves, Pritchard, and Dev

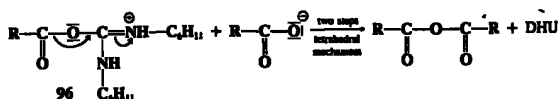
Boyer, Noida, Thomson, and Lawson, *Bull. Soc. Chim. Belg* 87, 621 (1978)

For the formulation of emulsions with the mixed anhydride of formic and transacetic acids, see Vachon, *J. Pharm. Med.*, 1961, 1, 108-11.

or primary or secondary amines can be pyrolyzed to give amides,⁷⁰ but the method is less convenient than 0-54, 0-55, and 0-57⁷⁰ and is seldom of preparative value. Lactams are produced fairly easily from γ - or δ -amino acids,⁷⁰ e.g.,



Although treatment of acids with amines does not directly give amides, the reaction can be made to proceed in good yield at room temperature or slightly above by the use of coupling agents,⁷⁰ the most important of which is dicyclohexylcarbodiimide. This is very convenient and is used⁷⁰ to great deal in peptide synthesis.⁷⁰ The mechanism is probably the same as in 0-24 up to the formation of 96. This intermediate is then attacked by another molecule of RCOO^- to give the anhydride ($\text{RCO})_2\text{O}$, which is the actual species that reacts with the amine



The anhydride has been isolated from the reaction mixture and then used to acylate an amine.⁷⁰ Other promoting agents⁷⁰ are $\text{N,N}'$ -carbonyldiimidazole (97, p. 350),⁷⁰ which behaves as in reaction 0-24 and has been used for peptide synthesis,⁷¹ POCl_3 ,⁷² TiCl_4 ,⁷² sulfonyl chloride fluoride SO_2ClF ,⁷³ chlorosulfonyl isocyanate,⁷⁴ P_2I_4 ,⁷⁵ pyridinium salts- Bu_3N ,⁷⁶ and a mixture of Bu_3P and PhCNO .⁷⁷ Certain dicarboxylic acids form amides simply on treatment with primary aromatic amines. In these cases the cyclic anhydride is an intermediate and is the species actually attacked by the amine. Acids can also be converted to amides by heating with amides of carboxylic acids (exchange).

⁷⁰For example, see Mitchell and Reid, *J. Am. Chem. Soc.* 83, 1879 (1931).

⁷¹For a review of amide formation from carboxylic acids, see Beckwith, in Zubecky, Ref. 453 pp. 105-109.

⁷²See, for example, Black-Pont, *Tetrahedron Lett.* 21, 2443 (1980).

⁷³For reviews of peptide synthesis with dicyclohexylcarbodiimide and other coupling agents, see Albertson, Ref. 205-211; Klammer and Bodansky, *Synthetic* 453-463 (1972).

⁷⁴It was first used this way by Shostak and Hens, *J. Am. Chem. Soc.* 77, 1067 (1955).

⁷⁵For a review on peptide synthesis, see Gross and Melnikoff, "The Peptides," 3 vols., Academic Press, New York, 1979-1981.

⁷⁶Schmider and Zehn, *Chem. Ber.* 96, 1076 (1962); Rehak and Foltz, *J. Am. Chem. Soc.* 96, 1606 (1974). They evidence that some of the 96 is converted to products by another mechanism. See Rehak and Foltz, *J. Am. Chem. Soc.* 96, 4052 (1974).

⁷⁷For some other methods, see Boland and Melnik, *J. Am. Chem. Soc.* 96, 1651 (1968); Tan, Olin, and Isom, *Synthetic* 714 (1973); Alper and Marquardt, *Tetrahedron Lett.* 3325 (1978); Neumannschneider, Foltz, and Liebsch, *Helv. Chim. Acta* 61, 2437 (1978); Isomata, Kinoshita, Foltz, Tanaka, and Kotaka, *Bull. Chem. Soc. Jpn.* 51, 1866 (1978), and references listed in Ref. 717.

⁷⁸Paul and Anderson, *J. Am. Chem. Soc.* 82, 4596 (1960).

⁷⁹Klein, *J. Prakt. Chem.* [4]19, 45 (1963).

⁸⁰Wheeler and Wolgarson, *Can. J. Chem.* 48, 983 (1970).

⁸¹Okah, Noriyo, and Gurole-Luna, *Synthetic* 661 (1980).

⁸²Suzuki, Tanji, Hiroi, Sato, and Otsuka, *Chem. Lett.* 449 (1983).

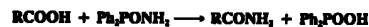
⁸³Bald, Selgo, and Mukaiyama, *Chem. Lett.* 1163 (1975). See also Mukaiyama, Alkawa, and Kobayashi, *Chem. Lett.* 57 (1976).

⁸⁴Grice, Clark, and Withers, *J. Org. Chem.* 44, 2945 (1979).

⁸⁵Higuchi, Mitsu, Shah, and Hard, *J. Am. Chem. Soc.* 85, 3635 (1963).

⁸⁶For example, see Schindler, *Monatsh. Chem.* 99, 1799 (1968).

sulfonic acids, or phosphoric acids, e.g.,⁷⁰



or by treatment with trialkylaminoboranes $[\text{B}(\text{NHR}')_3]$ or trialkylaminoboranes $[\text{B}(\text{NR}'')_3]$ ⁷²



An important technique, discovered by R. B. Merrifield in 1963⁷² and since used for the synthesis of many peptides,⁷² is called *solid phase synthesis* or *polymer-supported synthesis*.⁷² The reactions used are the same as in ordinary synthesis, but one of the reactants is anchored onto a solid polymer. For example, if it is desired to couple two amino acids (to form a dipeptide), the polymer selected might be polystyrene with CH_2Cl side chains (Fig. 1-99). One of the amino acids, protected by a *t*-butoxycarbonyl group (Boc), would then be coupled to the side chains (step A). It is not necessary that all the side chains be converted, but a random selection of them will be. The Boc group is then removed by hydrolysis with trifluoroacetic acid in CH_2Cl_2 (step B) and the second amino acid is coupled to the first, using DCC or some other coupling agent (step C). The second Boc group is removed (step D), resulting in a dipeptide that is still anchored to the polymer. If this dipeptide is the desired product, it can be cleaved from the polymer with HF (step E). If a longer peptide is wanted, additional amino acids can be added by repeating steps C and D.

The basic advantage of the polymer support techniques is that the polymer (including all chains attached to it) is easily separated from all other reagents, because it is insoluble in the solvents used. Excess reagents, other reaction products (such as DHU), side products, and the solvents themselves are quickly washed away. Purification of the polymeric species (such as 100, 101, and 102) is rapid and complete. In some cases the process can even be automated,⁷² to the extent that 10 or more amino acids can be added to a peptide chain in one day. Commercial automated peptide synthesizers are now available.

Although the solid phase technique was first developed for the synthesis of peptide chains and has seen considerable use for this purpose, it has also been used to synthesize chains of polysaccharides and polynucleotides. The technique has been applied less often to reactions in which only two molecules are brought together (nonrepetitive syntheses), but many examples have been reported.⁷²

OS I, 3, 82, 111, 172, 327, II, 65, 562, III, 95, 328, 475, 590, 646, 656, 768, IV, 6, 62, 113, V, 670, 1070. Also see OS III, 360, 56, 88.

⁷²Zimmerman, Voloshinova, and Krasnov, *J. Gen. Chem. USSR* 29, 2052 (1959). See also Kopecký and Šmejkal, *Chem. Ind. (London)* 1529 (1966); Liu, Chan, and Lee, *Synth. Commun.* 9, 31 (1979).

⁷³Palmer, Levin, and Nelson, *Tetrahedron* 26, 1539 (1970); Palmer and Levin, *Tetrahedron* 26, 1545, 1899 (1970).

⁷⁴Merrifield, *J. Am. Chem. Soc.* 85, 2149 (1963).

⁷⁵For reviews of solid phase peptide synthesis, see Barany and Merrifield, pp. 1-284 and Fridkin, pp. 333-363 in vol. 2 of Ref. 708; Erickson and Merrifield, in Neumaier, Hill, and Boster, "The Proteases," 3d ed., vol. 2, pp. 255-327, Academic Press, New York, 1976.

⁷⁶For monographs on solid phase synthesis in general, see Mather, Narang, and Williams, "Polymers as Aids in Organic Chemistry," Academic Press, New York, 1980; Hodge and Sherrington, "Polymer-Supported Reactions in Organic Synthesis," Wiley, New York, 1980. For reviews, see Sheppard, *Chem. Rev.* 402-416 (1983); Foltz and Mather, *Top. Curr. Chem.* 106, 115-175 (1982); Alkhalil and Sherrington, *Chem. Rev.* 81, 557-587 (1981); Alkhalil, *Synthetic* 413-438 (1981); Rehak, *Tetrahedron* 35, 723-731 (1979); McKillop and Young, *Synthetic* 401-422, 481-500 (1979); Neumaier, *Chemtech* 108-116 (Feb. 1978); Crowley and Rapoport, *Acc. Chem. Res.* 9, 135-144 (1976); Panchanik and Krasa, *Pure Appl. Chem.* 43, 325-326 (1975).

⁷⁷This was first reported by Merrifield, Stewart, and Jernberg, *Anal. Chem.* 38, 1905 (1966).

⁷⁸For reviews, see Fridkin, *Tetrahedron* 37, 663-683 (1981); Fridkin, in Hodge and Sherrington, Ref. 724, pp. 293-304; Lazzotti, *Acc. Chem. Res.* 11, 327-333 (1978); *Chem. Soc. Rev.* 3, 64-85 (1974).

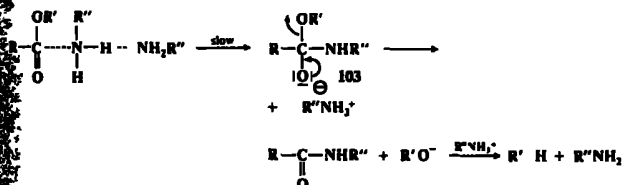
0-57 Acylation of Amines by Esters
Amino-de-alkoxylation

The conversion of esters to amides is a useful reaction, and unsubstituted *N*-substituted, and *N,N*-disubstituted amides can be prepared this way from the appropriate amine.⁷²² Both *R* and *R'* may be alkyl or aryl. An especially good leaving group is *p*-nitrophenyl. The reaction is particularly useful because many esters are readily available or easy to prepare even in cases where the corresponding acyl halide or anhydride is not. In another procedure esters are treated with di-*n*-butylaluminum amides $\text{Me}_2\text{AlNRR}'$ to give good yields of amides under mild conditions.⁷²³ The reagents are easily prepared from Me_2AlI and NH_3 or a primary or secondary amine or their salts.

As in 0-54 hydrazides and hydroxamic acids can be prepared from esters, with hydrazine and hydroxylamine, respectively. Both hydrazine and hydroxylamine react more rapidly than ammonia or primary amines (the alpha effect, p. 310). Phenylhydrazides, prepared with phenylhydrazine, are often used as derivatives for esters. The formation of hydroxamic acids, which form colored complexes in the presence of ferric ions, is often used as a test for esters. Imidates $\text{RC(=NH)OR}'$ give amides RC(=NH)NH_2 (see 0-36). Lactones, when treated with ammonia or primary amines, give lactams. Lactams are also produced from γ - and δ -amino esters in an internal example of this reaction. Isopropenyl formate is a useful compound for the formylation of primary and secondary amines.⁷²⁴



Although more studies have been devoted to the mechanism of the acylation of amines with esters than with other reagents, the mechanistic details are not yet entirely clear.⁷²¹ In its broad outlines, the mechanism appears to be essentially $\text{BAC}2$.⁷²² Under the normal basic conditions, the reaction is general base-catalyzed,⁷²³ indicating that a proton is being transferred in the rate-determining step and that two molecules of amine are involved.⁷²⁴



⁷²¹For a review, see Beckwith, Ref. 691 pp. 96-103.

⁷²²Becker, Lipson, and Widenberg, *Tetrahedron Lett.* 4171 (1977); *Org. Synth.* 59, 49; Levin, Turco, and Widenberg, *Synth. Commun.* 12, 989 (1982).

⁷²³For a review, see Smalley and Kato, Ref. 176, pp. 217-222 (1972).

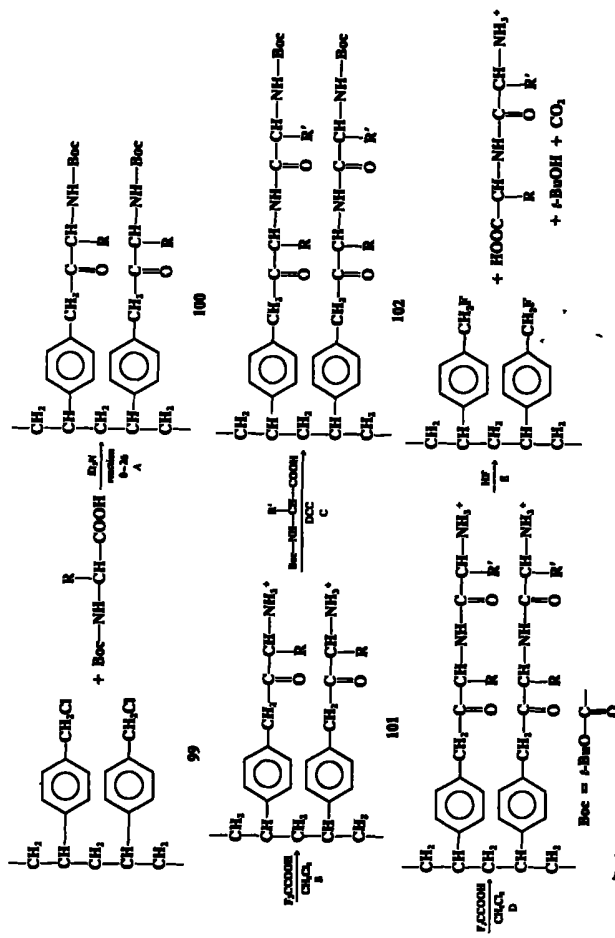
⁷²⁴Even Melick and Wolters, *Synth. Commun.* 1, 83 (1972).

⁷²⁵For a discussion of the mechanism, see Seachall and Seachall, Ref. 180, pp. 410-431.

⁷²⁶Bennett and Davis, *J. Am. Chem. Soc.* 82, 645 (1960); Bruno, Dumas, Hoffman, and Butler, *J. Am. Chem. Soc.* 89, 106 (1967).

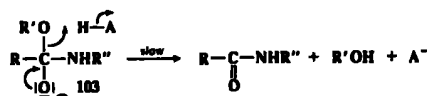
⁷²⁷Bennett and Davis, Ref. 732, Jacobs and Carrasco, *J. Am. Chem. Soc.* 82, 675 (1960); Brucke and Mayrath, *J. Am. Chem. Soc.* 82, 3667 (1960).

⁷²⁸Blackburn and Jacobs, *J. Am. Chem. Soc.* 90, 2638 (1968); Brucke and Felson, *J. Am. Chem. Soc.* 91, 2799 (1969); Adams and Brucke, *J. Am. Chem. Soc.* 91, 6721 (1969).



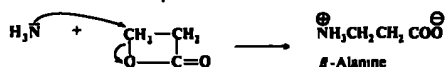
Reaction scheme showing the acylation of amines by esters, specifically focusing on the formation of amides from esters and amines.

Alternatively, another base, such as H_2O or OH^- , can substitute for the second molecule of amine. With some substrates and under some conditions, especially at low pH, the breakdown of 103 may become rate-determining.⁷²³ The reaction also takes place under acidic conditions and is generally acid-catalyzed, so that breakdown of 103 is rate-determining and proceeds as follows.⁷²⁴



HA may be $\text{R}'\text{NH}_3^+$ or another acid. 103 may or may not be further protonated on the nitrogen. Even under basic conditions, a proton donor may be necessary to assist leaving-group removal. Evidence for this is that the rate is lower with NR_2^- in liquid ammonia than with NHR_2 in water, apparently owing to the lack of acids to protonate the leaving oxygen.⁷²⁵

In the special case of β -lactones, where small-angle strain is an important factor, alkyl-oxygen cleavage is observed (BAL2 mechanism, as in the similar case of hydrolysis of β -lactones, 0-11), and the product is not an amide but a β -amino acid.



A similar result has been found for certain sterically hindered esters.⁷²⁶ This reaction is similar to reaction 0-45, with OCOR as the leaving group.

OS I, 153, 179, II, 67, 85, III, 10, 96, 108, 404, 440, 516, 536, 751, 765, IV, 80, 357, 441, 486, 532, 566, 819; V, 168, 301, 645, 51, 121, 53, 25, 59, 49, 183, 60, 66; 61, 24. Also see OS I, 5, V, 582.

0-58 Acylation of Amines by Amides Alkylamino-de-amination



This is an exchange reaction and is usually carried out with the salt of the amine. The leaving group is usually NH_3 rather than NHR or NR_2 and primary amines (in the form of their salts) are the most common reagents. BF_3 can be added to complex with the leaving ammonia. The reaction is often used to convert urea to substituted ureas. $\text{NH}_2\text{CONH}_2 + \text{RNH}_2 \rightarrow \text{NH}_2\text{CONHR} + \text{NH}_3$. Dimethylformamide can be converted to other formamides by prolonged heating with a primary or secondary amine.⁷²⁷ N-R-Substituted amides are converted to N-R'-substituted amides by treatment with N_2O , to give an N-nitroso compound, followed by treatment of this with a primary amine $\text{R}'\text{NH}_2$.⁷²⁸ Lactams can be converted to ring-expanded lactams if a side chain containing an amino group is present on the nitrogen. A strong base is used to convert the NH_2 to NH^- , which

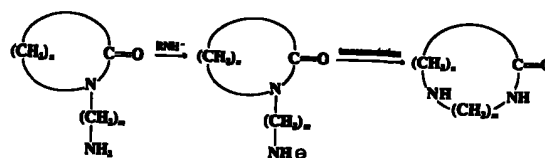
⁷²³Hansen, *Acta Chem. Scand.* 17, 1307 (1963); Satterthwaite and Jencks, *J. Am. Chem. Soc.* 96, 7018, 7031 (1974); Blackburn and Jencks, Ref. 734; Gresser and Jencks, *J. Am. Chem. Soc.* 99, 6963-6970 (1977).

⁷²⁴Blackburn and Jencks, Ref. 734.

⁷²⁵Barnett and Davis, Ref. 732.

⁷²⁶Zweig, Helgren, and Schaefer, *J. Org. Chem.* 28, 2617 (1963). See also Weststrate and Turrell, *J. Org. Chem.* 2470 (1965); Harada and Kinschtein, *Bull. Chem. Soc. Jpn.* 40, 2706 (1967).

⁷²⁷Kress, *Synthesis* 361 (1973). See also Oguni, Matsumura, and Imoto, *Bull. Chem. Soc. Jpn.* 41, 1485 (1968); Oguni and Matsumura, *Synthesis* 264 (1982).



then acts as a nucleophile, expanding the ring by means of a transamidation.⁷²⁹ The discoverers call it the Zip reaction, by analogy with the action of zippers.

OS I, 302 (but see V, 589), 450, 453, II, 461, III, 151, 404, IV, 52, 361.

0-59 Acylation of Amines by Other Acid Derivatives

Acid derivatives that can be converted to amides include thiol acids RCOSH , thiol esters RCOSR , methylselenol esters RCOSeMe ,⁷³⁰ acyloxyboranes RCOB(OR')_2 ,⁷³¹ silicic esters $(\text{RCOO})_2\text{Si}$, 1,1,1-trifluoro ketones RCOCF_3 , α -keto nitriles, acyl azides, and nonenolizable ketones (see the Hantzsch reaction 2-32).

OS III, 394, IV, 6, 569, V, 160, 166, 56, 122.

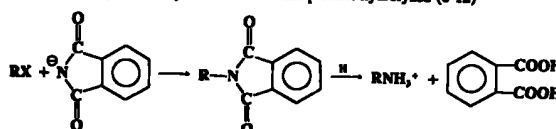
Attack by NHCOR

0-60 N-Alkylation of Amides and Imides Acylamino-de-halogenation



Amides are very weak bases, far too weak to attack alkyl halides, so that they must first be converted to their conjugate bases. By this method, unsubstituted amides can be converted to N-substituted, or N-substituted to N,N-disubstituted, amides.⁷³² Esters of sulfonic or sulfuric acids can also be substrates. Tertiary substrates give elimination. O-Alkylation is at times a side reaction.⁷³³ Both amides and sulfonamides have been alkylated under phase transfer conditions.⁷³⁴

The Gabriel synthesis⁷³⁵ for converting halides to primary amines is based on this reaction. The halide is treated with potassium phthalimide and the product hydrolyzed (0-12).



⁷²⁹Kramer, Guggenberger, Henze, and Schmid, *Angew. Chem. Int. Ed. Engl.* 16, 861 (1977); *Angew. Chem.* 89, 899; *Helv. Chim. Acta* 61, 1342 (1978); Hentschberger, Guggenberger, Stephenson, and Henze, *Helv. Chim. Acta* 64, 299 (1981). For a carbon atom, see Nakashima and Henze, *Helv. Chim. Acta* 66, 845 (1983).

⁷³⁰Kosharevskii and Amos, *J. Org. Chem.* 43, 2735 (1978).

⁷³¹The best results are obtained when the acyloxyboranes are made from a carboxylic acid and catecholborane (p. 552).

⁷³²Amos, Chen, and Gresser, *J. Org. Chem.* 43, 4393 (1978).

⁷³³The procedures are Loh and Pang, *Synth. Commun.* 9, 757 (1979); Kosharevskii and Zverevskii, *Synthesis* 527 (1979); Dajda, Kosharevskii, and Zverevskii, *Synthesis* 549 (1979); Yanagawa, Ando, and Harashina, *Chem. Lett.* 1143 (1981).

⁷³⁴For a review of alkylation of amides, see Challa and Challa, Ref. 455, pp. 734-754.

⁷³⁵Ogden and Zverevskii, *Synthesis* 1005 (1981).

⁷³⁶For a review, see Filtham and Brackman, *Synthesis* 1005 (1981).

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The Conversion of Secondary into Tertiary Amides Using Benzotriazole Methodology

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N-Alkyl-*N*-[1-(benzotriazol-1-yl)alkyl]amides, easily prepared from benzotriazole, an aldehyde, and a secondary amide, react readily with organosilic reagents to give tertiary amides in moderate to good yields. They are also reduced by LiAlH_4 to afford tertiary amines.

Introduction

The tertiary amide moiety is an important constituent of many biologically significant compounds,¹ and tertiary amides have frequently been used as precursors to unsymmetrical tertiary amines having different substituents.² Tertiary amides have usually been prepared by acylation of a secondary amine or by alkylation of a secondary amide. The alkylation of primary and secondary amides has been well investigated and reviewed;³ it has been carried out under neutral, acidic, and basic conditions. Under neutral conditions, only reactive electrophiles such as alkyl sulfates,^{4a} oxonium salts,^{4b} and diazoalkanes^{4c} are synthetically useful, and mixtures of the *O*- and *N*-alkylated products are frequently obtained.^{4d} Alkylation of amides under acidic conditions is rare, but has been reported for some alcohols^{5a} and acetals.^{5b} The alkylations under basic conditions are synthetically the most important. A variety of electrophilic species usually react predominantly at the amide nitrogen atom,⁶ and intramolecular alkylation yields lactams and other heterocyclic nitrogen compounds.⁷ However, strongly basic conditions are required such as KOH in DMSO^{8a} or in EtOH,^{8b} lithium amide in toluene,⁹ and sodium hydride in THF,^{10a} in *p*-xylene,^{10b} in toluene,^{10c} or in DMF,^{10d} often with phase-transfer reagents.^{11a-d} Such alkylations with *sec*-alkyl halides proceed with difficulty and with *tert*-alkyl halides not at all.¹² The strong basic conditions required along with the limitations for the alkylating reagents sometimes preclude this classical *N*-alkylation of *sec*-amides. The more general electroreductive *N*-alkylation of amides¹³ is not convenient in many laboratories.

Previous work from our group has demonstrated the versatility of benzotriazole as a synthetic auxiliary in synthesis.¹⁴ The benzotriazole anion is a good leaving group and can be used in place of a halogen or other substituent in many transformations. In particular, primary amides RCONH_2 are readily converted by treatment with benzotriazole and an aldehyde into intermediates $\text{RCONHCHR}^+\text{Bt}$ which react smoothly with Grignard reagents or NaBH_4 to give secondary amides and with LiAlH_4 to give secondary amines.^{15,16} These same $\text{RCONHCHR}^+\text{Bt}$ intermediates have also been shown to be effective amidalkylating reagents: they react readily with active aromatic compounds,¹⁷ CH acids,¹⁸ thiols,¹⁹ and alcohols²⁰ to give the corresponding amidalkylated products. The original procedure is also applicable to effect similar transformations with primary thioamides^{21a} and with primary sulfonamides.²² However, no successful reactions were reported for secondary amides. Indeed, compounds of type RCONHR' , in which neither R nor R' are hydrogen, do not condense with an aldehyde and benzotriazole under the procedure previously reported (i.e., refluxing in dry toluene with azeotropic removal of water). However, we have recently achieved condensations of *sec*-secondary amides by the use of catalytic amounts of *p*-toluenesulfonic acid in toluene or by carrying out the reactions in acetic acid. This has led to a significant expansion of the range of applicability of our published procedure in the form of a two-step convergent method commencing with the condensation of a secondary amide

(1) (a) Reisman, J. E.; Byerrum, R. U. *Biological Formation and Reactions of the Amide Group*. In *The Chemistry of Amides*; Zabicky, J. Ed.; Interscience Publishers: London, 1970; p 601. (b) *Tetrahedron Symposia in Print*, No. 10; Baldwin, J. E., Ed.; *Tetrahedron* 1983, 39, 2445-2608.

(2) (a) Khanna, J. M.; Dixit, V. M.; Anand, N. *Synthesis* 1975, 607. (b) Holland, H. L.; Johnson, G. B. *Tetrahedron Lett* 1978, 3395.

(3) Challa, B. C.; Challa, J. A. *Reactions of the Carboxamide Group*. In *The Chemistry of Amides*; Zabicky, J. Ed.; Interscience Publishers: London, 1970; p 731.

(4) (a) Benson, R. E.; Cairns, T. L. *J. Am. Chem. Soc.* 1948, 70, 2118. (b) Borch, R. F. *Tetrahedron Lett* 1968, 61. (c) Rella, J. W. *J. Org. Chem.* 1961, 26, 68. (d) Gompper, R.; Christmann, O. *Chem. Ber* 1969, 92, 1936.

(5) (a) Bredereck, H.; Gompper, R.; Rempfer, H.; Klemm, K.; Keck, H. *Chem. Ber* 1969, 92, 323. (b) Johnson, H. E.; Crosby, D. G. *J. Org. Chem.* 1962, 27, 2205.

(6) Levine, R. *Chem. Rev.* 1964, 54, 467. (7) (a) Fletcher, S. R.; Kay, I. T. *J. Chem. Soc., Chem. Commun.* 1978, 903. (b) Napolitano, E.; Finchi, R.; Marzilli, A. *Tetrahedron Lett* 1983, 24, 1319.

(8) (a) Ippa, G. L.; Luntzringham, A. *Synthesis*, 1971, 268. (b) Berti, G. *Gazz. Chim. Ital.* 1951, 81, 568.

(9) Kaye, I. A.; Parria, C. L.; Weiner, N. *J. Am. Chem. Soc.* 1963, 75, 744.

(10) (a) Jones, K.; Thompson, M.; Wright, C. *J. Chem. Soc., Chem. Commun.* 1986, 115. (b) Bertoloni, M.; Bloch, R.; Conia, J. M. *Tetrahedron Lett* 1977, 2389. (c) Amstutz, R.; Ringdahl, B.; Karlen, R.; Rock, M.; Janda, D. J. *J. Med. Chem.* 1985, 28, 1790. (d) Hartwell, J. A.; Hodge, P.; Maughan, W.; Wildsmith, E. *Synthesis* 1984, 941.

(11) (a) Rouschling, D.; Pletsch, H.; Linker, A. *Tetrahedron Lett* 1978, 613. (b) Cromble, L.; Jones, R. C. F.; Osborn, S.; Mat-Ein, A. H. *J. Chem. Soc., Chem. Commun.* 1983, 869. (c) Cromble, L.; Jones, R. C. F.; Mat-Ein, A. H.; Osborn, S. *J. Chem. Soc., Chem. Commun.* 1983, 869. (d) Ayyangar, N. R.; Choudhary, A. R.; Kalkote, U. R.; Natta, A. *Synth. Commun.* 1988, 18 (16 & 17), 2011.

(12) Gajda, T.; Zwiernak, A. *Synthesis* 1981, 1005.

(13) Shono, T.; Koshimura, S.; Nogura, H. *Chem. Lett.* 1983, 451.

(14) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron Lett* 1977, 2683 and the references cited therein.

(15) Katritzky, A. R.; Drowniak, M. *J. Chem. Soc., Perkin Trans. 1* 1988, 2239.

(16) Katritzky, A. R.; Drowniak, M.; Luo, P. *J. Org. Chem.* 1992, 57, 5554.

(17) Katritzky, A. R.; Jernak, J.; Fan, W.-Q. *Synthesis* 1991, 881.

(18) Katritzky, A. R.; Jernak, J.; Fan, W.-Q.; Szczeniowski, F. *J. Org. Chem.* 1991, 56, 445.

(19) Katritzky, A. R.; Jernak, J.; Fan, W.-Q.; Parnak, J. *Synthesis* 1991, 1147.

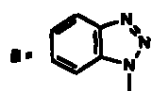
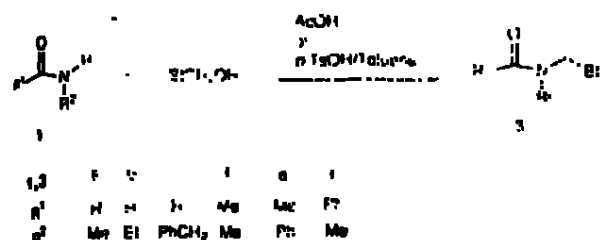
(20) Katritzky, A. R.; Jernak, J.; Fan, W.-Q.; Black, M.; Parnak, J. *J. Org. Chem.* 1993, 57, 547.

(21) Katritzky, A. R.; Jernak, J.; Fan, W.-Q.; Black, M.; Parnak, J. *J. Org. Chem.* 1993, 57, 547.

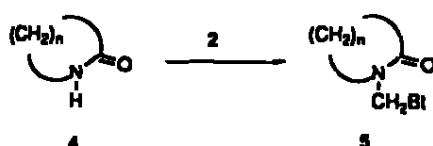
(22) Katritzky, A. R.; Jernak, J.; Fan, W.-Q.; Black, M.; Parnak, J. *J. Org. Chem.* 1993, 57, 547.

32

Scheme I



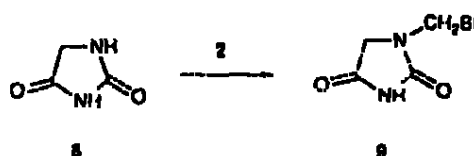
Scheme II



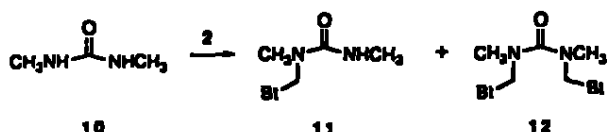
4,5	a	b	c
n	2	3	5



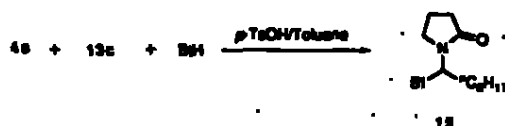
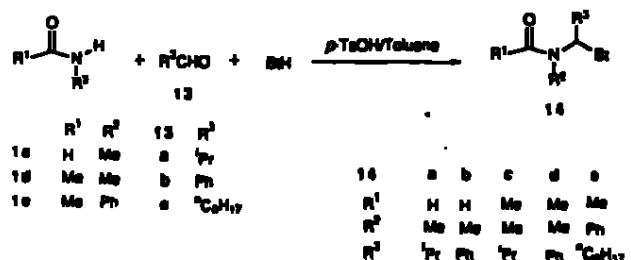
Scheme III



Scheme IV



Scheme V



with benzotriazole and an aldehyde followed by displacement of the benzotriazolyl group in the resulting adducts by organozinc reagents to afford tertiary amides or by reduction with LiAlH₄ to give tertiary amines.

Results and Discussion

Preparation of Secondary Amide-Benzotriazole Adducts (3, 5, 7, 9, 11, 12, 14, 15, 17, 19, and 21). Heating a mixture of *N*-alkylformamides 1a-c with 1-(hydroxymethyl)benzotriazole (2) in toluene in the presence of *p*-toluenesulfonic acid under reflux for an appropriate time, with azeotropic removal of water by a Dean-Stark trap, gave the *N*-alkyl-*N*-(benzotriazol-1-ylmethyl)amides 3a-c in good yields (Scheme I). Use of acetic acid as both the solvent and the acid catalyst was also investigated and it was found to afford comparable yields of the desired products. This procedure succeeded with the other secondary amides 1d-f and with cyclic secondary amides 4 and 6 (Schemes I, II). However, further extension to imides such as phthalimide and succinimide failed, probably due to their lower nucleophilicity. This limitation was also demonstrated by the reaction of hydantoin (8) with 2 where only the 3-monoalkylated hydantoin product 9 was obtained (Scheme III). The product of the reaction of dimethylurea with 2 depends on the number of equivalents of 2 used. With 1 equiv of 2, the monoalkylated urea 11 was obtained in 60% yield, and the disubstituted product 12 was not observed. A mixture of 11 and 12 was obtained in 62% and 11% yields, respectively, when 2 equiv of 2 was used. With 4 equiv of 2, only the disubstituted product 12 was obtained in 40% yield (Scheme IV).

We examined similar condensations with benzotriazole and aldehydes other than formaldehyde. We found that heating a mixture of a secondary amide, an aldehyde (13; R³ ≠ H) and benzotriazole with a catalytic amount of *p*-toluenesulfonic acid in toluene afforded the desired derivatives 14 and 15 in 29-73% yields (Scheme V). Both aliphatic (13; R³ = ⁱPr, ⁿC₆H₁₇) and aromatic (13; R³ = Ph) aldehydes were employed. The yields were lower than for the products from 2 probably in part because side reactions occurred between the aldehydes. We also examined similar reactions with the secondary thioamides, thioacetanilide (16), and thiohydantoin (18) and with the secondary *N*-methylbenzenesulfonamide (20) and found that the desired products 17, 19, and 21 were obtained in good to excellent yields in condensations with 2 (Scheme VI). Again, the reaction of the thiohydantoin (18) gave only the monoalkylated product 19. The preparative data and NMR spectral data of the products are given in Tables I-III.

The new benzotriazole derivatives were characterized by their ¹H and ¹³C NMR spectra and elemental analysis. The four characteristic multiplets between 7.3 and 8.1 ppm (¹H NMR) and the six characteristic carbon signals between 108 and 146 ppm show that they are all benzotriazole-1 isomers.²³ This is in accord with the benzotriazole derivatives from primary amides.¹⁵ For the derivatives of *N*-alkylformamide 3a-c and 14a,b, two sets of signals were observed in both the ¹H and ¹³C NMR spectra. This is expected for the rotational isomers which slowly interconvert at room temperature due to the well-established partial double bond character of the C-N bond

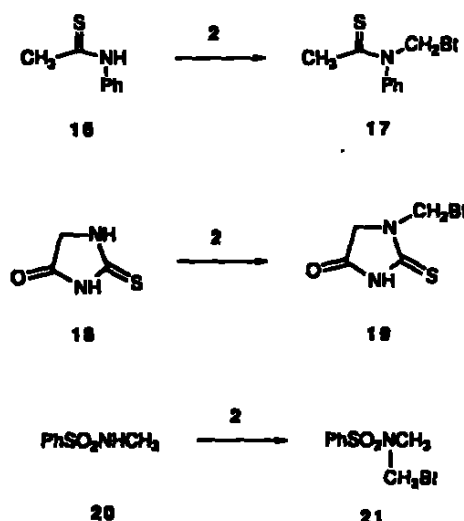
37

Table I. Preparation of Condensation Products 2, 5, 7, 9, 11, 12, 14, 15, 17, 19, and 21

compd	solvent	time (h)	yield (%)	mp (°C)	molecular formula	calcd/found			purification ^a
						C	H	N	
3a	toluene	6	62	84-86	C ₉ H ₁₀ N ₄ O	56.84/57.21	5.28/5.30	28.47/29.89	Et ₂ O
3b	toluene	8	60	oil	C ₁₀ H ₁₂ N ₄ O	MS (HR): 304.1011/104.1006 (calcd/found)			Et ₂ O
3c	toluene	12	73	109-10	C ₁₈ H ₁₄ N ₄ O	67.67/67.36	5.36/5.21	21.05/21.09	Et ₂ O
3d	HOAc	24	77	76-8	C ₁₀ H ₁₂ N ₄ O	59.01/58.61	5.89/5.87	27.30/27.52	hexane-EtOAc ^b
3e	HOAc	96	80	134-5	C ₁₈ H ₁₄ N ₄ O	67.65/67.70	5.30/5.32	21.04/21.29	hexane-EtOAc (1:1)
	toluene	48	77						
3f	HOAc	48	80	111-2	C ₁₈ H ₁₄ N ₄ O	67.65/67.65	5.30/5.24	21.04/21.25	Et ₂ O
5a	toluene	48	43	94-5	C ₁₀ H ₁₀ N ₄ O	59.40/58.98	4.98/4.94	27.71/28.04	hexane-EtOAc (1:4)
5b	HOAc	24	96	78-80	C ₁₁ H ₁₂ N ₄ O	61.10/61.33	5.59/5.63	25.91/26.25	hexane-EtOAc (1:2)
5c	HOAc	96	62	74-5	C ₁₂ H ₁₂ N ₄ O	63.92/64.07	6.60/6.73	22.93/22.85	-
7	HOAc	48	95	178-80	C ₁₈ H ₁₂ N ₄ O	68.18/68.23	4.58/4.54	21.20/21.23	hexane-EtOAc (1:2)
9	HOAc	96	76	235-6	C ₁₀ H ₈ N ₄ O ₂	51.95/51.68	3.92/3.91	30.29/30.37	HOAc ^c
11	toluene	24	60	101-2	C ₁₀ H ₁₂ N ₄ O	54.78/54.72	5.98/5.93	31.94/32.32	acetone
12	toluene	24	80 ^d	143-4	C ₁₇ H ₁₈ N ₄ O	58.28/58.18	5.18/5.15	31.98/32.30	Et ₂ O ^e
14a	toluene	12	73	86-88	C ₁₂ H ₁₀ N ₄ O	62.06/61.69	6.94/6.96	24.12/23.84	CHCl ₃
14b	toluene	24	33	112-5	C ₁₃ H ₁₄ N ₄ O	67.65/67.77	5.30/5.31	21.04/21.21	CHCl ₃
14c	toluene	24	67	123-5	C ₁₂ H ₁₂ N ₄ O	63.39/63.59	7.37/7.44	22.75/23.08	hexane-EtOAc (4:1)
14d	toluene	24	34	106-110	C ₁₀ H ₁₀ N ₄ O	68.55/68.62	5.75/5.76	19.99/20.15	hexane-EtOAc (6:1)
14e	toluene	72	29	oil	C ₂₀ H ₂₀ N ₄ O	72.98/72.98	7.99/8.11	14.80/14.77	hexane-EtOAc (1:1)
15	toluene	72	67	84-5	C ₁₉ H ₂₀ N ₄ O	69.48/69.56	8.59/8.65	17.08/16.99	Et ₂ O-CH ₂ Cl ₂ (1:1)
17	toluene	72	42	96-97	C ₁₉ H ₁₄ N ₄ S	63.81/63.52	5.00/4.92	19.84/19.79	hexane-Et ₂ O (1:1)
19	HOAc	20	61	266-8	C ₁₀ H ₈ N ₄ OS	48.57/48.52	3.67/3.67	28.32/28.18	HOAc ^c
21	toluene	16	94	97-8	C ₁₂ H ₁₄ N ₄ O ₂ S	55.62/55.94	4.67/4.67	18.53/18.67	Et ₂ O ^f

^a Eluent used for column chromatography. ^b Recrystallization solvent. ^c Four equivalents of 2 was used. When 2 equiv of 2 was used, mixture of 11 and 12 was obtained in 52 and 14%, respectively. The mixture was separated by column chromatography with Et₂O.

Scheme VI



of amides^{24a-d} and of thioamides.^{24e-g} For products from other secondary amides, only one preferred rotational isomer is observed in the NMR spectra due to steric hindrance which increases the energy of the other. ¹³C NMR spectra show the amide carbonyl for formamide in the region of 162.2-163.8 ppm and other open-chain carbonyl resonances in the region of 170.7-172.1 ppm and for the cyclic amide carbonyl in the region of 175.0-176.3 ppm except for strained ring 5a at 167.6 ppm. The ¹³C resonances for the thioamide are observed for 17 and 19 at 205.0 and 183.3 ppm, respectively. No significant changes were observed for the carbonyl resonances as

compared with those of the starting amides. For formaldehyde derivatives, the methylene groups directly attached to the amide nitrogen atom resonated between 5.95-6.52 ppm for protons and between 51.0-61.6 ppm for carbons. While no significant differences are observed for the ¹H shifts, the ¹³C shifts for strained rings, 5a, b, 7, and 9, are in the region 51.0-53.7 ppm, which is upfield compared to the corresponding open-chain derivatives due to the ring strain. The methylene carbons for the thio derivatives 17 and 19 are downfield compared to their oxygen analogues 3e and 9. For derivatives of other aldehydes, the ¹H and ¹³C chemical shifts of the methine groups are in the region 5.78-6.67 and 63.2-77.2 ppm, respectively, due to additional group.

Preparation of Tertiary Amides. We have previously demonstrated that the benzotriazole group in 1-(benzotriazol-1-yl)alkyl esters can be displaced by organozinc reagents to give esters without attack at the carbonyl group.²⁵ We have now found that the *N*-(benzotriazol-1-yl)-*N*-alkylamides obtained above react similarly with organozinc reagents to give the desired tertiary amides in moderate to good yields. Thus, a mixture of the benzotriazole adduct (dissolved in THF before addition) and the appropriate organozinc reagent in toluene is refluxed for the appropriate time. THF was essential for a satisfactory suspension, otherwise solids stuck to the bottom of the flask and failed to react. The reactions and results are shown in Scheme VII and Table IV, respectively. The benzotriazole byproduct is easily removed with dilute alkali during workup. This makes the isolation and purification of the desired products very simple.

The reaction worked successfully with both aromatic and aliphatic carbanions from organozinc reagents (R¹ = Ph, PhCH₂, PhC≡C) with benzotriazole derivatives from both formaldehyde and other aldehydes (R² = H, ⁱPr, Ph) as shown in Scheme VII. In this way, the H atom in the secondary amide NH was replaced with a R³R⁴CH group where R³ was derived from the aldehyde in the condensation and R⁴ from the organozinc reagent. Since various

(24) (a) Franconi, C. *SIPS (Soc. Ital. Progr. Sci.), Sci. Tec.* 1980, 4, 183. (b) Franconi, C.; Ogg, Jr.; R. A.; Fraenkel, G. *Arch. Sci. (Geneva)* 1960, 13, 543. (c) Yoder, C. H.; Gardner, R. D. *J. Org. Chem.* 1961, 46, 64. (d) Robin, M. B.; Bovey, F. A.; Basch, H. *Molecular and Electronic Structure of the Amide Group*. In *The Chemistry of Amides*; Zabicky, J. Ed.; Interscience Publishers: London, 1970; p 1. (e) Walter, W.; Imbert, J. P. *J. Mol. Struct.* 1975, 29, 253. (f) Walter, W.; Scheumann, E.; Voss, J. *Org. Mag. Res.* 1971, 3, 733. (g) Walter, W.; Maerten, G. *Liebigs Ann. Chem.* 1963, 712, 58.

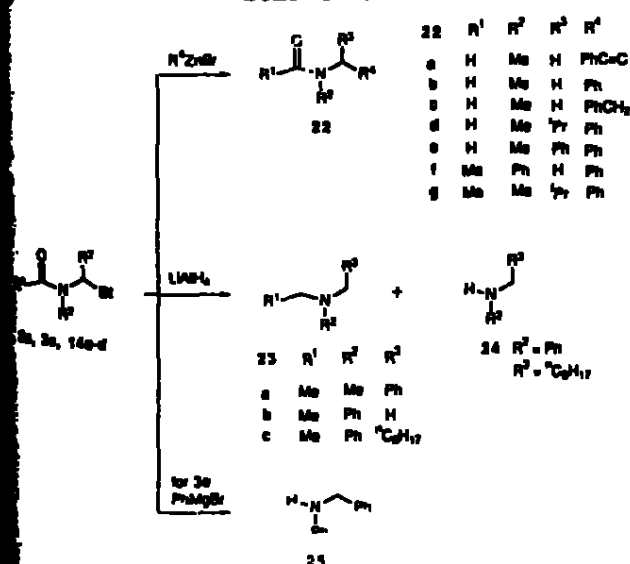
(25) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Synthesis* 1991, 8

Table II. ¹H NMR Spectral Data of Compounds 3, 5, 7, 9, 11, 12, 14, 15, 17, 19, and 21 (δ, ppm)

compd	benzotriazolyl ^a				NCH ₂ Bt or NCHBt	other groups
	4	5	6	7		
3a ^b	8.11 (8.07) (d, 8.3)	7.4-7.9 (m)	7.4-7.9 (m)	7.4-7.9 (m)	6.37 (6.39) (s, 2 H)	2.76 (2.96) (s, 3 H), 8.23 (8.79) (s, 1 H)
3b ^b	8.10 (8.13) (d, 8.3)	7.44 (7.47) (t, 7.9)	7.60 (7.64) (t, 7.4)	7.93 (8.03) (d, 8.3)	6.22 (6.36) (s, 2 H)	0.79 (1.08) (t, 3 H, J = 7.0), 3.23 (3.34) (q, 2 H, J = 7.0), 8.36 (8.71) (s, 1 H)
3c ^b	8.02 (8.08) (d, 8.4)	d	d	7.86 (7.89) (d, 8.4)	6.03 (5.95) (s, 2 H)	4.36 (4.43) (s, 2 H), 8.38 (8.79) (s, 1 H) 7.26-7.55 (m, 8 H)
3d	8.01 (d, 8.3)	7.39 (t, 7.9)	7.49 (t, 7.9)	7.90 (d, 8.3)	6.20 (s, 2 H)	2.13 (s, 3 H), 3.11 (s, 3 H)
3e	8.05 (d, 8.3)	d	7.54 (t, 7.1)	7.97 (d, 8.3)	6.50 (s, 2 H)	1.88 (s, 3 H), 6.84-6.87 (m, 2 H), 7.27-7.43 (m, 4 H)
3f	8.06-8.09 (m)	d	d	8.06-8.09 (m)	6.40 (s, 2 H)	3.05 (s, 3 H), 7.39-7.44 (m, 7 H)
3g	8.06 (d, 8.3)	7.43 (d, 8.3)	7.55 (t, 7.1)	7.83 (d, 8.3)	5.97 (s, 2 H)	3.00 (t, 2 H, J = 4.3), 3.32 (t, 2 H, J = 4.3)
5b	8.04 (d, 8.3)	7.41 (t, 7.1)	7.51 (t, 7.1)	7.86 (d, 8.3)	6.10 (s, 2 H)	1.96-2.10 (m, 2 H), 2.41 (t, 2 H, J = 8.0), 3.46 (t, 2 H, J = 7.2)
5c	8.04 (d, 8.3)	7.40 (t, 7.1)	7.50 (t, 7.1)	7.92 (d, 8.3)	6.23 (s, 2 H)	1.20-1.38 (m, 2 H), 1.59-1.61 (m, 4 H), 2.48-2.61 (m, 2 H), 3.56-3.69 (m, 2 H)
7	8.02 (d, 8.3)	d	d	7.92 (d, 8.3)	6.52 (s, 2 H)	3.60 (s, 2 H), 7.06 (t, 1 H, J = 6.7), 7.21 (d, 1 H, J = 7.4), 7.23-7.50 (m, 4 H)
9	8.09 (d, 8.3)	7.46 (t, 7.4)	7.62 (t, 7.4)	7.94 (d, 8.3)	6.21 (s, 2 H)	4.06 (s, 2 H), 11.20 (s, 1 H)
11	7.97-8.03 (m)	7.28-7.50 (m, 2 H)		7.97-8.03 (m)	6.19 (s, 2 H)	2.85 (d, 3 H, J = 4.6), 2.99 (s, 3 H), 4.85 (s, br, 1 H)
12	8.06 (d, 8.3, 2 H)	7.38-7.46 (m, 4 H)		7.91 (d, 8.2, 2 H)	6.10 (s, 4 H)	2.94 (s, 6 H)
14a ^b	8.06 (8.11) (d, 8.3)	7.40-7.50 (m)	7.50-7.60 (m)	7.79 (d, 8.3)	6.72 (5.78) (d, 1 H, J = 11.0)	0.91 (0.93) (d, 3 H, J = 6.5), 1.16 (1.17) (d, 3 H, J = 6.5), 2.92 (2.88) (s, 3 H), 3.29-3.33 (3.39-3.41) (m, 1 H), 8.13 (8.59) (s, 1 H)
14b ^b	8.10-8.20 (m)	d	d	d	8.29 (7.80) (s, 1 H)	3.06 (3.97) (s, 3 H), 7.15-7.64 (m, 8 H), 8.39 (8.65) (s, 1 H)
14c	8.04 (d, 8.3)	7.38 (t, 7.3)	7.50 (t, 7.3)	7.82 (d, 8.3)	7.00 (d, 1 H, J = 11.0)	0.89 (d, 3 H, J = 6.5), 1.12 (d, 3 H, J = 6.5), 2.11 (s, 3 H), 2.99 (s, 3 H), 3.2-3.3 (m, 1 H)
14d	8.09 (d, 8.3)	d	7.48 (t, 7.1)	7.67 (d, 8.3)	8.67 (s, 1 H)	2.20 (s, 3 H), 3.10 (s, 3 H), 7.1-7.2 (m, 2 H), 7.3-7.4 (m, 4 H)
14e	8.06 (d, 8.3)	7.52-7.65 (m, 2 H)		7.97 (d, 8.3)	5.9-6.0 (m, 1 H)	0.82-1.00 (m, 3 H), 1.20-1.60 (m, 12 H), 1.79 (s, 3 H), 2.20-2.36 (m, 1 H), 2.42-2.80 (m, 1 H) 7.02-7.52 (m, 8 H)
15	8.04 (d, 8.3)	7.37 (t, 6.9)	7.49 (t, 6.9)	7.83 (d, 8.3)	6.78 (t, 1 H, J = 7.7)	0.82-1.00 (m, 3 H), 1.20-1.55 (m, 12 H), 1.80-2.15 (m, 2 H), 2.24-2.78 (m, 4 H), 3.2-3.4 (m, 1 H), 3.6-3.7 (m, 1 H)
17	8.01-8.06 (m)	d	d	8.01-8.06 (m)	6.77 (d, 2 H, J = 7.8)	2.39 (s, 3 H), 7.21-7.33 (m, 7 H)
19	8.11 (d, 8.3)	7.46 (t, 7.3)	7.62 (t, 7.3)	8.07 (d, 8.3)	6.59 (s, 2 H)	4.27 (s, 2 H), 12.10 (s, br, 1 H)
21	8.06 (d, 8.2)	d	d	8.01 (d, 8.2)	6.03 (s, 2 H)	2.88 (s, 3 H), 7.41-7.61 (m, 3 H), 7.56-7.61 (m, 2 H), 7.72-7.75 (m, 2 H)

^aThe data in the brackets indicates multiplicity and coupling constant, J. Each represents one proton unless stated otherwise. ^bMixtures of two rotamers and signals appear in pairs. The numbers in the brackets are the chemical shifts for another rotamer. ^cDMSO-d₆ solvent. ^dOverlapped with the phenyl signals.

Scheme VII



previous procedures for alkylation under basic conditions, the R³R⁴CH group introduced by the present method corresponds to primary alkyl halides when R³ = H and to secondary halides when R³ ≠ H. It is in respect of secondary alkyl groups that our new method shows great advantages.¹²

The tertiary amides 22a-g thus prepared all appear to be novel: compound 22e was mentioned in the literature^{24c} for calculation of its rotational barrier, but no physical data is available. Structures 22a-g were confirmed by their ¹H and ¹³C NMR spectra and by elemental analysis or high resolution MS data. The chemical shifts and assignments are listed in Table V and VI. Chemical shifts for the amide carbonyl and the carbons of R¹, R², and R³ groups were as expected. The principal differences from the precursors were in the chemical shifts of the characteristic C-α which, in the absence of the electron-withdrawing benzotriazole residue, has shifted upfield by about 7 ppm to 33.7-69.4 ppm. The protons were also shifted upfield to the region 3.98-6.82 ppm. Two sets of signals derived from the two rotational isomers were observed for formamide derivatives 22a-e. Such rotational

and R⁴ groups could be used, this method is general for the preparation of tertiary amides. Compared to the

35

Table III. ^{13}C NMR Spectral Data of Compounds 3, 4, 7, 9, 11, 12, 14, 15, 17, 19, and 21 (4, ppm)

compd	benzotriazolyl				3a	7a	C(=O)	NCH ₂ Et or NCH ₂ Et	other groups
	4	5	6	7					
2a ^a	119.2 (119.5)	124.3 (124.4)	127.7 (128.1)	110.9 (110.3)	145.2 (145.4)	132.2 (132.3)	163.7 (163.3)	54.5 (50.7)	28.5 (32.0)
2b ^a	119.2 (119.5)	124.4 (124.5)	127.8 (128.1)	111.0 (110.4)	144.3 (145.5)	132.1 (132.2)	163.8 (163.1)	52.5 (50.2)	14.3 (12.2), 40.3 (36.6)
2c ^a	119.6 (120.2)	124.4 (124.5)	128.0 (127.9)	110.5 (108.7)	145.9 (146.0)	134.3 (134.4)	162.9 (162.2)	51.7 (50.6)	40.6 (44.6), 128.2 (128.4), 128.5 (128.5), 128.9 (128.7), 134.3 (134.4)
2d	119.0	122.9	127.4	110.7	145.6	131.9	171.2	57.1	21.2, 34.5
2e	119.5	124.1	127.8	110.8	145.9	132.2	171.1	56.5	22.4, 127.9, 128.9, 129.9, 140.2
3f	119.7	124.4	127.0	111.0	146.1	132.4	172.1	56.0	26.2, 128.0, 128.5, 130.4, 134.5
5a	119.8	124.5	128.2	108.7	145.1	131.9	167.8	52.4	27.5, 38.9
5b	119.5	124.4	127.9	110.4	145.9	132.1	175.5	53.7	17.4, 30.3, 45.7
5c	119.3	124.1	127.7	110.8	145.5	131.9	175.3	57.9	22.9, 27.3, 29.2, 36.4, 47.3
7	119.8	124.4	128.2	110.4	146.0	132.1	175.0	51.0	26.5, 100.9, 123.41, 123.43, 128.5, 132.3, 142.1
9	119.2	124.3	127.8	110.7	145.3	132.3	157.0	53.5	50.1, 171.0
11	119.3	124.2	127.7	111.2	146.0	132.3	157.9	56.8	27.4, 33.1
12	120.0	124.6	128.2	111.2	146.5	132.9	162.8	61.6	26.3
14a	119.6 (120.4)	124.4 (124.5)	127.8 (128.2)	110.2 (108.6)	145.4 (145.9)	132.3 (132.5)	162.4 (162.0)	58.2 (77.3)	18.2 (19.0), 18.9 (19.2), 27.5 (25.7), 29.5 (26.7)
14b	119.8 (120.4)	124.4 (124.5)	127.9 (128.1)	109.9 (108.8)	145.1 (146.1)	132.1 (132.4)	163.5 (162.0)	55.1 (74.3)	21.2 (25.5), 127.2 (128.2), 128.9 (129.0), 129.2 (129.5), 132.9 (132.8)
14c	119.2	124.1	127.5	110.3	145.1	133.2	171.5	59.5	18.2, 18.8, 21.7, 25.1, 28.7
14d	119.5	124.1	127.8	109.9	145.0	133.2	171.9	59.5	21.7, 22.4, 128.9, 129.5, 129.8, 134.3
14e	119.3	123.8	127.4	110.4	145.3	132.8	170.7	64.8	12.7, 22.1, 22.7, 25.1, 28.7, 28.9, 31.0, 31.3, 128.2, 129.2, 129.5, 129.8
15	119.5	124.3	127.7	110.3	145.6	132.5	175.3	63.2	14.0, 17.7, 22.5, 25.2, 28.2, 28.9, 29.2, 30.3, 30.8, 31.7, 42.0
17	119.8	124.3	128.0	111.0	145.8	132.2	205.0	64.1	24.7, 128.4, 129.4, 130.1, 140.8
19	119.2	124.3	127.7	111.2	145.2	132.4	183.3	56.2	22.5, 171.6
21	119.8	124.5	127.0	110.5	146.1	132.2	-	61.4	24.1, 128.9, 128.2, 129.2, 137.7

^a Mixtures of two rotamers and signals appear in pairs. The numbers in the bracket are the chemical shifts for another rotamer. ^b DMSO-*d*₆ solvent. ^c Exchangeable signals.

Table IV. Preparation of Compounds 22-24

compd	substrate	reagent ^a	time (h)	yield (%)	mp (°C)	molecular formula	calcd/found			purification ^b
							C	H	N	
22a	3a	PhO=CZnBr	16	55	oil	C ₁₁ H ₁₁ NO	MS (HR): 173.0641/173.0638			Et ₂ O
22b	3a	PhZnBr	16	30	oil	C ₉ H ₁₁ NO	MS (HR): 149.0641/149.0639			Et ₂ O
22c	3a	PhCH ₂ ZnBr	16	41	oil	C ₁₀ H ₁₃ NO	MS (HR): 163.0987/163.1001			Et ₂ O
22d	14a	PhZnBr	19	43	65-69	C ₁₂ H ₁₃ NO	75.25/75.61	8.98/9.07	7.32/7.32	hexane-Et ₂ O (1:1)
22e	14b	PhZnBr	19	52	82-86	C ₁₀ H ₁₅ NO	79.97/79.87	6.71/6.89	6.22/6.31	hexane-Et ₂ O (1:1)
22f	3c	PhZnBr	96	64	oil	C ₁₀ H ₁₃ NO	79.97/79.88	6.71/6.78	6.22/6.19	hexane-EtOAc (1:1)
22g	14c	PhZnBr	16	44	61-63	C ₁₂ H ₁₅ NO	76.06/76.07	9.39/9.41	6.82/6.79	Et ₂ O
22a	14d	LiAlH ₄	15	82	oil	C ₁₀ H ₁₃ N	lit. ²⁸ bp 103.5 °C/36 mm			hexane-EtOAc 1)
22b	3c	LiAlH ₄	24	96	oil	C ₉ H ₁₁ N	lit. ²⁸ bp 202.5 °C			hexane
22c	14e	LiAlH ₄	24	40	oil	C ₁₇ H ₂₅ N	82.53/82.43	11.61/11.81	5.69/5.63	hexane
24	14e	LiAlH ₄	24	37	oil	C ₁₅ H ₂₃ N	lit. ²⁸ bp 178 °C/9 mm			hexane

^a The reactions were carried out in toluene except for 22a where THF was used as solvent. ^b Eluent for column chromatography.

isomers were also observed in the case of acetamide 22g, but not in the more sterically hindered *N*-phenylacetamide 22f.

Preparation of Tertiary Amines. We previously demonstrated that *N*-(benzotriazolylalkyl)amides derived from primary amides react with LiAlH₄ or NaBH₄ to give secondary amines and secondary amides respectively in good yields.¹⁵ We have now shown that the benzotriazole group in *N*-alkyl-*N*-(benzotriazolylalkyl)amides derived from secondary amides is also removed by LiAlH₄, with the concomitant reduction of the carbonyl to a methylene group. Thus, heating a mixture of the benzotriazole derivative and an excess of LiAlH₄ in THF or toluene under reflux gave the desired tertiary amines 22a-c in good yields. In the case of 3c, the expected product 22c was accompanied by the secondary amine 24 derived from the removal rather than reduction of the amido group.

The isolation of the amines was simple since the benzotriazole byproduct was easily extracted in aqueous alkaline solution. The reactions are shown in Scheme VII and the preparative data along with the ¹H and ¹³C NMR data are given in Tables IV-VI. These conversions are believed to involve initial reduction of the amide group to a methylene group. The resulting intermediate reacts readily with LiAlH₄ to remove the benzotriazole and give tertiary amines as previously described.²⁸

The structures of the tertiary amines 23 obtained were confirmed by the NMR spectra, by elemental analysis (for 22c), or by comparison with literature data. The C- groups now appear upfield due to the loss of the electron withdrawing benzotriazole group, in the regions of 2.89

(28) Katritzky, A. R.; Rachwal, S.; Rachwal, B. J. Chem. Soc., Perkin Trans. 1 1987, 805.

34

Table V. ¹H NMR Spectral Data of Compounds 22-24 (δ, ppm)

compd	R ¹	R ²	R ³	R ⁴	NCH ₂ R ¹ or NH	NCH ₂ R ⁴ or NCH ₂ R ³
22 ^a	8.04 (8.14) (s, 1 H)	2.99 (3.05) (s, 3 H)	-	7.3-7.4 (m, 5 H)	-	4.21 (4.38) (s, 2 H)
22 ^b	8.10 (8.22) (s, 1 H)	2.72 (2.78) (s, 3 H)	-	7.3-7.4 (m, 5 H)	-	4.33 (4.48) (s, 2 H)
22 ^c	7.77 (7.98) (s, 1 H)	2.81 (2.87) (s, 3 H)	-	2.81-2.87 (m, 2 H)	-	3.44 (3.55) (t, 2 H, J = 7.6)
22 ^d	8.05 (8.32) (s, 1 H)	2.68 (2.65) (s, 3 H)	0.85-0.95 (m, 3 H), 1.00-1.05 (m, 3 H), 2.4-2.6 (m, 1 H)	7.11-7.32 (m, 5 H) 7.3-7.4 (m, 5 H)	-	5.20 (3.98) (d, 1 H, J = 11.0)
22 ^e	8.20 (s, 1 H)	2.71 (2.68) (s, 3 H)	7.1-7.3 (m, 10 H)	see R ²	-	5.79 (6.82) (s, 1 H)
22 ^f	1.57 (s, 3 H)	6.96-7.00 (m, 2 H) 7.17-7.31 (m, 8 H)	-	see R ²	-	4.88 (s, 2 H)
22 ^g	2.08 (2.32) (s, 3 H)	2.70 (2.71) (s, 3 H)	0.85-0.95 (m, 3 H), 0.97-1.05 (m, 3 H), 2.3-2.5 (m, 1 H)	7.2-7.4 (m, 5 H)	-	5.52 (4.38) (d, 1 H, J = 11.4)
22 ^h	1.01 (t, 3 H, J = 7.2)	2.10 (s, 3 H)	7.1-7.3 (m, 5 H)	-	2.35 (q, 2 H, J = 7.2)	3.38 (s, 2 H)
22 ⁱ	1.05 (t, 3 H, J = 7.1)	6.69-6.72 (m, 3 H), 7.18-7.24 (m, 2 H)	-	-	3.36 (q, 2 H, J = 7.1)	3.89 (s, 3 H)
22 ^j	1.14 (t, 3 H, J = 7.0)	6.59-6.67 (m, 3 H), 7.16-7.22 (m, 2 H)	0.86-0.96 (m, 3 H), 1.20-1.60 (m, 14 H)	-	3.34 (q, 2 H, J = 7.0)	3.22 (t, 2 H, J = 7.7)
24	-	6.57-6.69 (m, 3 H), 7.12-7.18 (m, 2 H)	0.86-0.96 (m, 3 H), 1.20-1.62 (m, 14 H)	-	3.50 (s, br, 1 H)	3.08 (t, 2 H, J = 7.5)

^a Mixtures of two rotamers and signals appear in pairs where the numbers in the bracket are the chemical shifts for another rotamer.

Table VI. ¹³C NMR Spectral Data of Compounds 22-24 (δ, ppm)

compd	R ¹	R ²	R ³	R ⁴	NCH ₂ R ¹	NCH ₂ R ⁴ or NCH ₂ R ³	C=O
22 ^a	-	33.66 (29.3)	-	82.7 (82.4), 85.2 (83.9), 121.9 (122.3), 128.15 (128.34), 128.7 (128.6), 131.6 (131.5)	-	33.68 (38.8)	161.9 (162.1)
22 ^b	-	28.9 (33.5)	-	127.1 (128.9), 127.5 (127.7), 128.2 (128.4), 136.6 (135.4)	-	47.2 (52.9)	162.1 (162.3)
22 ^c	-	28.5 (34.8)	-	33.0 (34.5), 126.2 (126.6), 128.3 (128.4), 128.46 (128.62), 128.4 (127.5)	-	45.8 (51.0)	162.3 (162.4)
22 ^d	-	27.0 (28.7)	19.5 (19.2), 20.2 (20.0), 25.9 (25.4)	127.9 (127.5), 128.0 (128.3), 128.6 (128.7), 127.3 (127.7)	-	69.4 (60.5)	162.3 (162.7)
22 ^e	-	29.0 (31.6)	127.9 (127.5), 128.3 (128.4), 128.6, 137.9 (137.5)	see R ²	-	68.4 (58.5)	163.4 (163.0)
22 ^f	22.5	127.1, 127.8, 128.1, 128.4, 128.6, 129.4, 137.3, 142.6	-	see R ²	-	52.6	170.1
22 ^g	22.13 (22.18)	28.5 (29.9)	19.2 (19.6), 20.1 (20.4), 28.0 (27.1)	127.2 (127.6), 128.2 (127.9), 128.54 (128.47), 128.9 (128.3)	-	61.4 (58.1)	170.5 (170.1)
22 ^h	12.4	41.6	128.5, 128.1, 129.0, 139.1	-	51.1	61.9	-
22 ⁱ	11.2	112.4, 116.0, 129.1, 149.1	-	-	46.7	37.3	-
22 ^j	12.3	111.7, 115.1, 129.2, 148.0	14.1, 22.7, 27.2, 27.5, 29.3, 29.5, 29.6, 31.9	-	44.8	50.4	-
24	-	112.6, 117.0, 129.1, 148.5	14.0, 22.6, 27.1, 29.2, 29.4, 29.5, 31.5	-	-	43.9	-

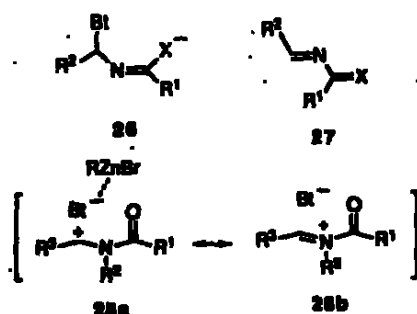
^a Mixtures of two rotamers and signals appear in pairs where the numbers in the bracket are the chemical shifts for another rotamer.

3.39 ppm for protons and 37.3-61.9 ppm for carbons. The newly formed methylene groups resonated at 2.35-3.36 and 44.8-51.1 ppm for protons and carbons, respectively.

Comparison of the Reaction Mechanisms of N-Benzotriazolylalkylated Primary and Secondary Amides. Reaction of N-(benzotriazol-1-ylalkyl)amides from primary amides with Grignard reagents and NaBH₄ gave secondary amides.^{18,19} Reaction of the present benzotriazole derivative with a Grignard reagent was also attempted: this succeeded, but simultaneous removal of the amido group was also observed; thus compound 3e with phenylmagnesium bromide in refluxing toluene gave the secondary amine 25 in 69% yield. The present compounds did not react with NaBH₄, which left the starting material unaffected even when the reaction was carried out in refluxing toluene for 3 days. These results

suggest that our derivatives from secondary amides react in a different manner to those from primary amides. It was previously postulated¹⁸ that for the primary amide derivatives, initial deprotonation of NH by Grignard reagents or NaBH₄ gave 26 from which the anion expelled benzotriazole anion to give 27. The second molecule of Grignard reagent or NaBH₄ then reacted with 27 to afford the desired secondary amides. In the reactions of secondary amide derivatives, the amide NH was not available and the reaction should go through initial ionization as shown by 28. Because the cation 25 is destabilized by the carbonyl group, the reaction requires an elevated temperature in refluxing toluene, much stronger conditions than for the corresponding primary amide derivatives in refluxing THF. Additionally, organozinc reagents need to be used which do not attack the amide carbonyl group.

37



Under refluxing toluene conditions with organosinc reagents, ionization was possible by the assistance of the free electron pair on the amide nitrogen and by the chelation of benzotriazole with the zinc atom (see 28a). Subsequent reaction with organosinc reagents gave tertiary amides. This reaction is similar in nature to that previously reported for esters.²⁵

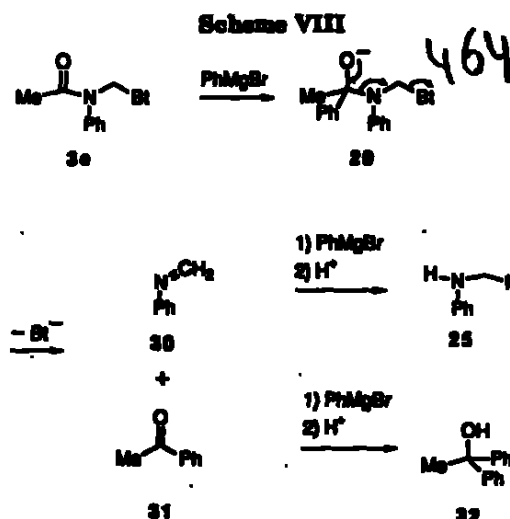
In the reaction with Grignard reagent, initial attack of the carbanion from the Grignard reagent on the amide carbonyl afforded anion 29 which activated the elimination of the benzotriazole group via the loss of acetophenone (31) to give 30. Further reactions of 30 and 31 with PhMgBr gave the secondary amine 25 and presumably the tertiary alcohol 32 (Scheme VIII). With the weak reducing reagent NaBH_4 , which is known not to reduce amides, no reaction was thus observed.

In summary, we have developed a general, two-step sequence for the N-alkylation of secondary amides to give tertiary amides. The method commences with easily available benzotriazole derivatives from a secondary amide, an aldehyde, and a benzotriazole. The overall result is the replacement of the H attached to the amide nitrogen by a $\text{R}^2\text{R}^1\text{CH}$ group where R^2 derives from an aldehyde and R^1 from an organosinc reagent. The sequence proceeds with both aliphatic and aromatic aldehydes and with various organosinc reagents. In addition, tertiary amines were obtained by the reaction of the benzotriazole adducts with LiAlH_4 . This method is also potentially useful for the alkylation of lactams and for the elaboration of secondary thioamides and sulfonamides. Compared to previous routes, which use strong basic conditions and are limited to primary alkyl halides, or use an inconvenient electroreductive method, our route, general in scope, employs easily accessible starting materials, mild reaction conditions, and a simple workup procedure and affords reasonable yields of tertiary amides. This work further demonstrates the utility of benzotriazole in organic synthesis.

Experimental Section

^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra²⁵ were recorded in CDCl_3 solutions unless otherwise stated.

N-Substituted-N-(Benzotriazol-1-yl)alkyl)amides (3, 5, 7, 9, 11, 12, 14, 15, 17, 19, and 21): General Procedure. A mixture of 1-(hydroxymethyl)benzotriazole (2) (2.98 g, 20 mmol) [or benzotriazole (2.38 g, 20 mmol) and an aldehyde (20 mmol) for 14 and 15] and the secondary amide (20 mmol) in acetic acid (30 mL) or in toluene (30 mL) with a catalytic amount of *p*-toluenesulfonic acid (0.19 g, 1.0 mmol) was refluxed for the time given in Table I. In the case of toluene solutions, water was removed with a Dean-Stark trap. The progress of the reaction was



monitored by TLC until it indicated the starting material had been consumed. The solvent was removed reduced pressure. For 3a-e and 14a,b, the crude products were purified by flash column chromatography with (3a-e) or chloroform (14a,b). Other products were up in CHCl_3 (100 mL), and washed with 5% NaOH solution (30 mL) and H_2O (30 mL). The CHCl_3 was dried (MgSO_4) and the solvent was evaporated. Residues were purified by column chromatography recrystallization as given in Table I.

Reactions of Compounds 3a, 3e, and 14a-c with Organosinc Reagents. Preparation of Tertiary Amides: General Procedure. A solution of zinc in dry Et_2O (10 mmol; 1.0 mmol/mL; 10 mL) prepared by addition of bromine to zinc powder (Et_2O) was added to a Et_2O solution of the Grignard (10 mmol; 1.0 mmol/mL; 10 mL) (prepared from appropriate organic halide and magnesium). $\text{PhC}\equiv\text{CH}$ was prepared by the exchange reaction of MeMgBr ($\text{PhC}\equiv\text{CH}$). The mixture was stirred at room temperature under N_2 for 30 min. Then a solution of the appropriate benzotriazole derivative (5.0 mmol) in THF (20 mL) was added followed by dry toluene (40 mL). The low solvents were distilled from the mixture and the toluene solution refluxed for the time given in Table I. The mixture was poured into water (30 mL) and adjusted to pH 5 with 2 N HCl. The aqueous layer was extracted with chloroform (3 $\times$ 40 mL). The combined extracts were washed with 2 N NaOH (30 mL) and H_2O (30 mL) with MgSO_4 , and concentrated in vacuo. The products were purified by flash column chromatography using the eluents given in Table IV to afford the amides.

Reaction of Compounds 3e and 14d,e with LiAlH_4 for Preparation of Tertiary Amines: General Procedure. To a solution of the benzotriazole derivative (5 mmol) in dry THF (40 mL) or in dry toluene (40 mL) (see Table I) under N_2 , was added LiAlH_4 (0.50 g, 13 mmol) portionwise. The resulting solution was heated under reflux until indicated that the starting material had been consumed. The reaction mixture was cooled, ice (5 g) added, and solvent evaporated. The residue was taken up in H_2O , the CHCl_3 layer was separated, and the aqueous layer extracted with CHCl_3 (3 $\times$ 60 mL). The CHCl_3 solution was washed with H_2O (30 mL) with MgSO_4 , the solvent removed to give the crude product. Compound 23a thus obtained was pure. Column

38

ography purification using eluents given in Table IV
 orded compounds 23b,c and 24.

Reaction of Compound 3e with PhMgBr: Preparation of *N*-Benzylaniline 25. To a Et₂O solution of MgBr (40 mmol; 2.0 mmol/mL; 20 mL) (freshly prepared from reaction of bromobenzene and magnesium) added a solution of 3e (1.33 g, 5 mmol) in THF (50 mL) dropwise. Et₂O was distilled off and the residual solution heated under reflux for 2 days. It was cooled and poured into H₂O (50 mL) and the solid filtered off. The organic layer was separated and the aqueous solution extracted with Et₂O (2 × 60 mL). The combined extracts were dried (MgSO₄) and the solvent was removed to give crude product. Purification by column chromatography (hexane-Et₂O = 10:1) afforded compound 25 (0.76 g, 9%); mp 34–35 °C (lit.²⁷ mp 37–39 °C); ¹H-NMR 3.97

(s, br, 1 H), 4.28 (s, 2 H), 6.56–6.70 (m, 3 H), 7.1–7.4 (m, 7 H); ¹³C-NMR 48.2, 112.7, 117.4, 127.1, 127.4, 128.5, 129.2, 139.4, 148.1.

Acknowledgment. We thank Dr. Marek Bernard for some of the early experimental work and in particular for the first preparation of compounds 14a and 14b. We also thank him and Dr. N. Malhotra for several helpful discussions during this work.

Supplementary Material Available: Copies of NMR spectra of 3b and 22a–c (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(27) Elch, J. J.; Kaska, D. D.; Peterson, C. J. *J. Org. Chem.* 1986, 51,

(28) Ohshiro, Y.; Komatsu, M.; Agawa, T. *Synthesis* 1971, 89.
 (29) Clowson, R. D.; Napolitano, J. P.; Eche, G. G.; Kohn, A. J. *J. Org. Chem.* 1987, 52, 646.
 (30) Foster, R.; Hammick, D. L. *J. Chem. Soc.* 1964, 2886.

31

468
466

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

Expediente N° 00-28953

IPC A01N43/56

CONCEPTO TÉCNICO N° 846

Realizado el estudio de fondo definitivo de la solicitud de patente de invención No. 00-28953 con fundamento en el artículo 48 de la Decisión 486 de la Comisión de la Comunidad Andina y teniendo en cuenta el memorial del interesado radicado bajo el mismo número del 16 de mayo de 2006, se notifica el siguiente Concepto Técnico:

1. DOCUMENTOS ESTUDIADOS

- ❖ Para el presente estudio se tuvo en cuenta el capítulo descriptivo, folios 6 a 152 presentados originalmente y las nuevas reivindicaciones 1 a 7, folios 425 a 427, las cuales fueron aceptadas dado que éstas no implican una ampliación de la solicitud originalmente presentada conforme lo establece el artículo 34 de la decisión 486 de la Comisión de la Comunidad Andina "art. 34.- *El solicitante de una patente podrá pedir que se modifique la solicitud en cualquier momento del trámite. La modificación no podrá implicar una ampliación de la protección que correspondería a la divulgación contenida en la solicitud inicial.*
- ❖ *Del mismo modo, se podrá pedir la corrección de cualquier error material".*
- ❖ Se acepta reivindicación de prioridad UK 9909062.3 del 20 de abril de 1999 y UK 0002039.6 del 28 de enero de 2000.

2. OBJETO DE LA INVENCION

- Título: Se recomienda precisar un poco más el título en el sentido de: **Compuestos químicos del tipo benzodiazoles o tiazoles y su proceso de obtención.**
- El objeto de la invención es un compuesto caracterizado por la fórmula (I) descrito en los folios 425 a 426.
- Un proceso para preparar el compuesto de fórmula (I) descrito en los folios 425 a 426 que comprende los pasos de:
 - a) En el caso que Y sea oxígeno; hacer reaccionar un compuesto amino de fórmula (II) definido en el folio 426 con un compuesto éster carboxílico de fórmula (III) descrito en el folio 426 y en el 427.
 - b) En el caso que Y sea azufre; se lleva a cabo la reacción del inciso a) y posteriormente, el producto se hace reaccionar con un agente tionizador tal como 2,4-bis-(4-metoxifenil)-1,3-ditio-2,4-difosfetan-2,4-disulfuro (reactivo de Lawesson); 2,4-bis(metilo)-1,3-ditio-2,4-difosfetan-2,4-disulfuro (metil reactivo de Davy); 2,4-bis-(para-tolil)-1,3-ditio-2,4-difosfetan-2,4-disulfuro (p-tolil reactivo de Davy) o pentasulfuro de fósforo.
- Una composición fungicida, insecticida, acaricida, molusquicida o nematocida caracterizada porque comprende en peso 0,0001 a 95% de un compuesto de fórmula (I) de acuerdo a la materia que se reclama y un vehículo o diluyente para el mismo.
- Un método para combatir y controlar insectos, ácaros, nemátodos o moluscos caracterizado porque comprende aplicar a una peste, a un lugar de una peste o a una planta susceptible de ser atacada por una plaga, una cantidad eficaz como insecticida, acaricida, nematocida o molusquicida de un compuesto pesticida.
- ❖ El problema técnico expuesto en esta solicitud es la necesidad de proporcionar productos pesticidas.
- ❖ La clasificación según la IPC correspondiente al objeto de la solicitud es A01N43/56.

3. CLARIDAD DE LA SOLICITUD

La descripción divulga la invención de manera clara y completa tal como lo establece el artículo 28 de la Decisión 486 de la Comisión de la Comunidad Andina cuando dice: *"La descripción deberá divulgar la invención de manera suficientemente clara y completa para su comprensión y para que una persona capacitada en la materia técnica correspondiente pueda ejecutarla. La descripción de la invención indicará el nombre de la invención e incluirá la siguiente información:*

- a) el sector tecnológico al que se refiere o al cual se aplica la invención;*
- b) la tecnología anterior conocida por el solicitante que fuese útil para la comprensión y el examen de la invención, y las referencias a los documentos y publicaciones anteriores relativas a dicha tecnología;*
- c) una descripción de la invención en términos que permitan la comprensión del problema técnico y de la solución aportada por la invención, exponiendo las diferencias y eventuales ventajas con respecto a la tecnología anterior;*
- d) una reseña sobre los dibujos, cuando los hubiera;*
- e) una descripción de la mejor manera conocida por el solicitante para ejecutar o llevar a la práctica la invención, utilizando ejemplos y referencias a los dibujos, de ser éstos pertinentes; y,*
- f) una indicación de la manera en que la invención satisface la condición de ser susceptible de aplicación industrial, si ello no fuese evidente de la descripción o de la naturaleza de la invención."*

Las reivindicaciones están acordes con el artículo 30 de la Decisión de la Comunidad Andina: *".- Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción.*

Las reivindicaciones podrán ser independientes o dependientes. Una reivindicación será independiente cuando defina la materia que se desea proteger sin referencia a otra reivindicación anterior. Una reivindicación será dependiente cuando defina la materia que se desea proteger refiriéndose a una reivindicación anterior. Una reivindicación que se refiera a dos o más reivindicaciones anteriores se considerará una reivindicación dependiente múltiple."

4.EVALUACIÓN DE UNIDAD DE INVENCION

La presente solicitud comprende una invención o grupo de invenciones relacionadas entre sí, de manera que se integra un único concepto inventivo conforme al artículo 25 de la Decisión de la Comunidad Andina: *"La solicitud de patente sólo podrá comprender una invención o un grupo de invenciones relacionadas entre sí, de manera que conformen un único concepto inventivo."*

5.ES UNA INVENCION

El objeto de la presente solicitud no se encuentra comprendido dentro del alcance del artículo 15 de la Comisión de la Comunidad Andina que establece: *"No se considerarán invenciones:*

- a) los descubrimientos, las teorías científicas y los métodos matemáticos;*
- b) el todo o parte de seres vivos tal como se encuentran en la naturaleza, los procesos biológicos naturales, el material biológico existente en la naturaleza o aquel que pueda ser aislado, inclusive genoma o germoplasma de cualquier ser vivo natural;*
- c) las obras literarias y artísticas o cualquier otra protegida por el derecho de autor;*
- d) los planes, reglas y métodos para el ejercicio de actividades intelectuales, juegos o actividades económico-comerciales;*
- e) los programas de ordenadores o el soporte lógico, como tales; y,*
- f) las formas de presentar información."*

6.PATENTABILIDAD DE LAS INVENCIONES

La presente solicitud no se encuentra bajo el alcance del artículo 20 de la Decisión de la Comisión de la Comunidad Andina: *"No serán patentables:*

470
468

a) las invenciones cuya explotación comercial en el territorio del País Miembro respectivo deba impedirse necesariamente para proteger el orden público o la moral. A estos efectos la explotación comercial de una invención no se considerará contraria al orden público o a la moral solo debido a la existencia de una disposición legal o administrativa que prohíba o que regule dicha explotación;

b) las invenciones cuya explotación comercial en el País Miembro respectivo deba impedirse necesariamente para proteger la salud o la vida de las personas o de los animales, o para preservar los vegetales o el medio ambiente. A estos efectos la explotación comercial de una invención no se considerará contraria a la salud o la vida de las personas, de los animales, o para la preservación de los vegetales o del medio ambiente sólo por razón de existir una disposición legal o administrativa que prohíba o que regule dicha explotación;

c) las plantas, los animales y los procedimientos esencialmente biológicos para la producción de plantas o animales que no sean procedimientos no biológicos o microbiológicos;

d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales."

8. EVALUACIÓN DE LOS REQUISITOS DE PATENTABILIDAD

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."*

En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

- ♦ La fecha a partir de la cual se realizó la búsqueda de anterioridades para las reivindicaciones 1 a 6 (folios 425 a 427) corresponde al 19 de abril de 1999.

1.0 Evaluación de la NOVEDAD

La Decisión 486 de la Comisión de la Comunidad Andina establece en su art. 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica."*

El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

Después de realizada la búsqueda de anterioridades en los archivos con que cuenta la Oficina, y no habiéndose encontrado alguna anterioridad que se anticipara a un compuesto de fórmula (I) y la composición que los contiene tal y como se define en las reivindicaciones 1 a 4 y 6 (folios 425 a 427), el proceso de preparación de dichos compuestos definido en la cláusula 5 (folios 426 a 427) se considera que la materia correspondiente a estas reivindicaciones es nueva.

1.0 Evaluación del NIVEL INVENTIVO

De acuerdo al art. 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."*, se conceptúa:

471
460

El compuesto de fórmula (I) definido en las reivindicaciones 1 a 4 tiene nivel inventivo puesto que su configuración química contiene un benzodiazol o benzotiazol unido a heterociclos con sustituciones específicas para conformar una estructura con actividad pesticida. Lo anterior no resulta obvio ni derivable del estado de la técnica para una persona versada en el arte. Así mismo también tiene nivel inventivo la composición que los contiene como componente activo de la reivindicación 6.

El proceso de preparación definido en la cláusula 5 tiene nivel inventivo debido a que presenta una reacción específica para la producción de los compuestos objeto de la presente solicitud.

Teniendo en cuenta lo anterior y en razón del cumplimiento del Art.14 de la Comisión de la Comunidad Andina, se recomienda conceder el privilegio solicitado para las reivindicaciones 1 a 6, folios 425 a 427.

EXAMINADOR TÉCNICO CÓDIGO 202001	JEFE DIVISIÓN NUEVAS CREACIONES	FECHA 2008-05-25
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**REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

RESOLUCION 17193

Por la cual se otorga una patente de invención

CERTIFICADO 28496

Rad. N° 00-28953

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
en ejercicio de sus facultades legales, en especial de las que se confirieron en el artículo
4, numeral 5 del decreto 2153 de 1992, y

CONSIDERANDO:

PRIMERO: Que mediante escrito radicado en esta Superintendencia con el número 00028953 del día 19 de abril del 2000, se solicitó conceder patente para la invención contenida en el expediente de la referencia.

SEGUNDO: Que efectuado el examen de forma y cumplidas las exigencias legales, se ordenó publicar el extracto sin que se hubieran presentado observaciones.

TERCERO: Que realizado el examen de fondo se requirió al solicitante en los términos del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, para que presentara respuesta a las observaciones de carácter técnico visibles a folios 419 a 422 del cuaderno administrativo, relacionadas con la patentabilidad o cumplimiento de los requisitos establecidos por esta Decisión, para la concesión de la patente.

CUARTO: Que el solicitante, mediante escrito radicado bajo el número 00-028953-00009-0000 del 15 de mayo del 2006, atendió oportunamente el requerimiento formulado, presentando nuevos folios 425 a 427, con el texto de las reivindicaciones que reemplazan las originalmente presentadas, atendiendo de esta manera las observaciones efectuadas en el examen de fondo. El capítulo en mención se acepta, como quiera que se ajusta a las prescripciones contenidas en el artículo 34 de la Decisión 486.

QUINTO: Que en virtud de lo dispuesto en el artículo 14 de la Decisión 486 expedida por la Comisión de La Comunidad Andina se otorgarán patentes "...para las invenciones sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial".

SEXTO: Que en el presente caso cumplen los requisitos indicados en el numeral anterior las reivindicaciones 1 a 6 contenidas en los folios 425 a 427, razón por la cual este Despacho encuentra procedente conceder para las mismas el privilegio solicitado.

RESUELVE:

**REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

RESOLUCIÓN 17193

Por la cual se otorga una patente de invención

CERTIFICADO 28496

Rad. N° 00-28953

ARTICULO PRIMERO: Otorgar privilegio de patente de invención a la creación denominada:

**" COMPUESTOS QUIMICOS DEL TIPO BENZODIA – O TIAZOLES Y SU PROCESO
DE OBTENCION "**

Clasificación IPC: A 01 N 43/56.

Reivindicación(es): 1 a 6 **Folio(s):** 425 a 427.

Titular(es): SYNGENTA LIMITED.

Domicilio(s): Guildford, Surrey, Reino Unido.

Inventor(es): Sarah Armstrong, Nigel John Barnes, Susan Patricia Barnett, Eric Daniel Clarke, Patrick Jelf Crowley, Torquil Eoghan Macleod Fraser, David John Hughes, Alan John Whittle, Christopher John Mathews, Brian Leslie Pilkington, Roger Salmon, Stephen Christopher Smith, Russell Viner, William Guy Whittingham y John Williams.

Prioridad N°: 9909062.3 **Fecha:** 20 de abril de 1999 **País:** UK.
0002039.6 28 de enero del 2000 UK.

Vigente desde: 19 de abril del 2000 **Hasta:** 19 de abril del 2020

ARTICULO SEGUNDO: El titular tendrá los derechos y las obligaciones establecidos en la Decisión 486 de la Comisión de la Comunidad Andina y su privilegio caducará en las condiciones prescritas por las disposiciones legales vigentes sobre propiedad Industrial.

ARTICULO TERCERO: Entregar al titular copia auténtica de esta resolución y el certificado

472

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION No. 17193

Por la cual se otorga una patente de invención

CERTIFICADO 28496

Rad. N° 00-28953

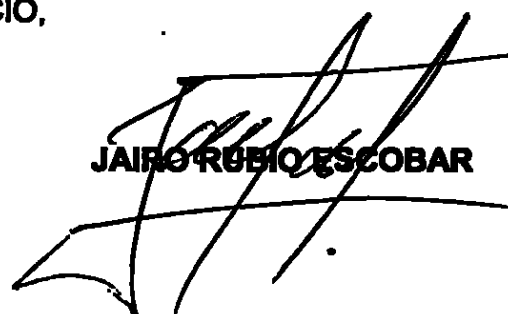
de patente, previas las anotaciones en los libros de registro.

ARTICULO CUARTO: Notificar el contenido de la presente resolución al doctor Juan Pablo Cadena Sarmiento, o a quien haga sus veces, en su calidad de apoderado de Syngenta Limited., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición ante el Superintendente de Industria y Comercio, del cual podrá hacer uso al momento de la notificación o dentro de los cinco 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los **29 JUN. 2005**

APORTE EFECTUADO POR VALOR DE
\$ 7.100 POR CONCEPTO
DE DERECHOS ADMINISTRATIVOS

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIME RUBIO ESCOBAR

Doctor
JUAN PABLO CADENA SARMIENTO
Carrera 7 N° 16 – 56.
Bogotá, D.C. bms

202021