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2333/P

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. 00.030.047
Solicitud de patente a nombre de
Novartis AG

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 00-030047-00009-0000 Feb: 2006-05-11 14:29:27
Rep: 3020 NUEVAS CREACIONES
Tra: 2 PATENTES Ene 1 REGDEPOSITO
Mot 444 RESPUESTA REQUE Folios: 15

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 94-76, Of. 305, obrando como apoderada de la sociedad Novartis AG, domiciliada en Basilea, Suiza, solicitante de la patente de la referencia, en respuesta al oficio No. 1761 notificado por fijación en lista el 16 de febrero de 2006, relacionado con el concepto técnico No. 033, me permito acompañar los siguientes documentos solicitados por el examinador:

- K. Nalepa et al.: Journal fur praktische chemie, vol. 314, No. 5-6, 1972, pag. 851-856.
- F. Pochat: Tetrahedron Letters, vol. 22, No. 37, 1981, pag. 3595-3596.
- Y. Kamitori et al.: Heterocycles, vol. 39, No. 1, 1994, pag. 155-162.

Espero con esto haber dado cabal cumplimiento a lo solicitado por ese despacho y de conformidad con lo indicado en los artículos 3º, inciso 3, 35 inciso 2 y 59 inciso 2 del CCA, al analizar este memorial, atentamente solicito se traten todas las cuestiones planteadas con motivo del mismo.

Señor Superintendente,

Jimena Escobar Uribe
JIMENA ESCOBAR URIBE
C.C. 39.779.452 de Usaquen.
T.P. 68.228

Nuevas vías de acceso a las diaril-3,6 hidroxí-5 triazinas-1,2,4
a partir de los nitrilos α -tioeteres

Francis POCHAT

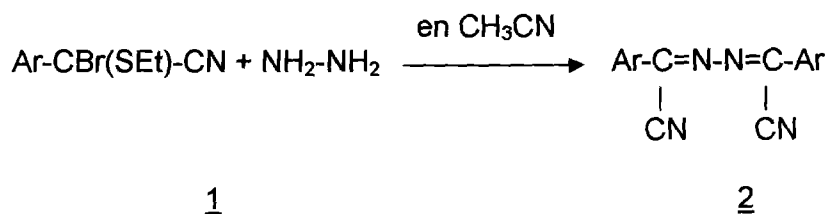
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$\text{Ar-C}(\text{CH})=\text{N-N}=\text{C}(\text{CH})-\text{Ar}$ y $\text{Ar-C}(\text{CN})=\text{NH-CO-Ar}$ ', fácilmente preparados a partir de derivados de bromo $\text{Ar-CBr}(\text{SEt})-\text{CN}$, permiten un buen rendimiento, mediante calentamiento en un medio básico, 3,6-diaril-5 hidroxí-1,2,4-triazinas.

Los principales métodos de preparación de las α -triazinonas-5 por heterociclización recurren a la condensación de un derivado α -dicarbonilado con una amidrazona ⁽¹⁻³⁾, o de su hidrazona con un imidato ⁽³⁾. En esta nota, mencionamos un método simple de síntesis de diaril-3,6 hidroxí-5 triazinas-1,2,4 que no requieren la preparación de un derivado α -dicarbonilado.

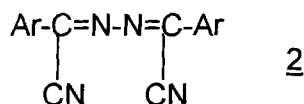
En un trabajo reciente, hemos demostrado que los nitrilos α -tioeteres α -bromados $\text{Ar-CBr}(\text{SEt})-\text{CN}$ 1, fácilmente preparados a partir de ArCHO , mediante la

acción de una amina, conducían fácilmente a los α -iminonitrilos $\text{Ar-C}(\text{CH})=\text{N-Ar}$ ⁽⁴⁾. Generalizando este estudio, hemos podido observar que la acción de la hidrazina (1,35 mol/mol) sobre 1 permitía acceder a las azinas



de los α -cetonitrilos aromáticos 2 (Tabla I) prácticamente desconocidos ⁽⁵⁾.

TABLA I



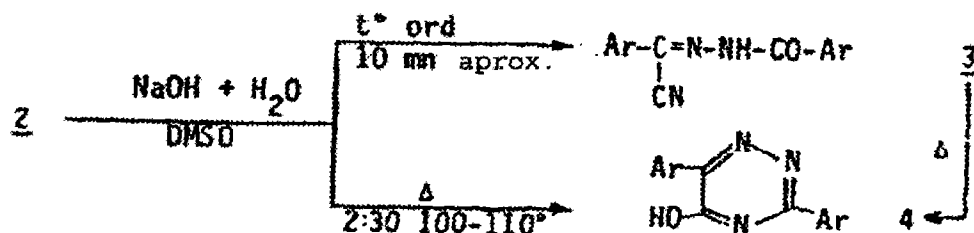
	<u>2a</u>	<u>2b</u>	<u>2c</u>	<u>2d</u>	<u>2e</u>
Ar	Ph	<i>o</i> -C1-Ph	<i>p</i> -C1-Ph	<i>m</i> -MeO-Ph	<i>p</i> -CH ₃ -Ph
Rdt %*	65	44	56	51	67
F°C	208-209**	156-157	261-262	216.5-217	246.5-247

* Rdt en producto puro con respecto al derivado bromado 1

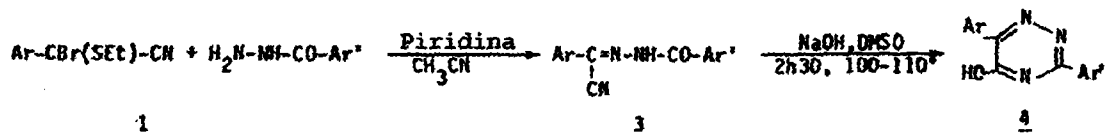
** Lit. ⁽⁵⁾ F = 205-206°

A diferencia de los α -iminonitrilos, los cuales son fácilmente hidrolizados en benzoilánilinas bajo la acción de la sosa ⁽⁶⁾, las azinas 2 no se transforman bajo la acción de esta base en dibenzoilhidrazinas, pero, a la temperatura ambiental, en α -cianobenzilideno hidrazidas 3 (Rdt 88-95%) luego, mediante calentamiento, en hidroxí-5 triazinas-1,2,4 4 sustituidas por dos grupos arilos idénticos.

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Es posible generalizar y mejorar este método haciendo reaccionar sobre 1 una acilhidrazina en presencia de piridina (1,2 mol/mol), lo cual permite obtener derivados sustituidos por dos grupos arilos idénticos o diferentes (Tabla II)



La estructura de estos compuestos ha sido verificada por RMN, espectrografía de masa e IR (de conformidad con las observaciones de la literatura para el derivado difenilado 4a ⁽³⁾, estos compuestos existen básicamente en estado sólido bajo la forma hidroxí-5 triazina).

TABLA III

$\text{Ar}-\text{C}(\text{CN})=\text{N}-\text{NH}-\text{C}(=\text{O})-\text{Ar}' \quad \underline{3}$				$\text{Ar}-\text{C}_6\text{H}_3\text{N}_2-\text{Ar}' \quad \underline{4}$			
Ar	Ph	<i>o</i> -Cl-Ph	<i>p</i> -Cl-Ph	<i>m</i> -MeO-Ph	<i>p</i> -Me-Ph	<i>p</i> -Cl-Ph	<i>p</i> -Cl-Ph
Ar'	Ph	<i>o</i> -Cl-Ph	<i>p</i> -Cl-Ph	<i>m</i> -MeO-Ph	<i>p</i> -Me-Ph	<i>p</i> -MeO-Ph	3-Pyridyl
	<u>3a</u>	<u>3b</u>	<u>3c</u>	<u>3d</u>	<u>3e</u>	<u>3f</u>	<u>3g</u>
Rdt % ¹⁾	89	92	93	95	94	88	83
F ^o C	133-134	130-132	205-206	105-106,5	173-174	164-166	192-193
	<u>4a</u>	<u>4b</u>	<u>4c</u>	<u>4d</u>	<u>4e</u>	<u>4f</u>	<u>4g</u>
Rdt % ²⁾	74	67	62	63	81	70	50
F ^o C	278-279 ³⁾	212,5-214	369-370	194-196	327-328	349-351	328-329,5

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- 1) Rdt en producto puro con respecto a la azina para los derivados 3a a 3e o con respecto al derivado bromado 1 para 3f a 3h.
- 2) Rdt en producto puro con respecto a la azina para 4a a 4e o con respecto al derivado 3 para 4f a 4g.
- 3) lit. $F = 274-276^{\circ}$ ⁽²⁾, $F = 274-275^{\circ}$ ⁽⁷⁾.
- 4) Es importante señalar que, durante la electrolisis básica, el derivado N-acetilado 3h $\text{Ph-C(CN)=N-NH-CO-CH}_3$ sufre una degradación en ácido fenilacético.

Referencias

- (1) Y. UCHYLITOVA, P. FIEDLER, M. PRYSTAS y P. GUT, *col czech. Chem.Com.*, 36, 1955 (1971)
- (2) M. BRUGGER, H. WAMHOFF y F. KORTE, *An. Chem.*, 755, 101 (1972)
- (3) J. DAUNIS, R. JACQUIER y C. PIGIERE, *Tetrahedron*, 30, 3171 (1974)
- (4) F. POCHAT, *Tetrahedron Letters*, 22, 955 (1981)
- (5) La única azina $\text{Ph-C(CN)=N=N-C(CN)-Ph}$ descrita ha sido preparada en cuatro etapas a partir del dibenzoilacetileno (Rdt 12%), por T. L. GILCHRIST, G.E. GYMER y C. W. REES, *J. chem. Soc, Perkin I*, 1747 (1975)
- (6) H. OHMORI, C. UEDA y M. MASUI, *J. chem. Soc., Perkin II*, 720 (1979)
- (7) H. NEUNHEOFFER y V. BÖNISCH, *An. Chem*, 153 (1976)

Recibido en Francia el 29 de junio de 1981

Nouvelles voies d'accès aux diaryl-3,6 hydroxy-5 triazines-1,2,4
à partir des nitriles α -thioéthers

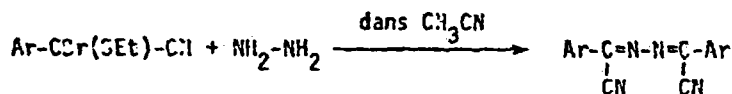
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35042 RENNES, FRANCE

$\text{Ar-C}(\text{CN})=\text{N}=\text{C}(\text{CN})-\text{Ar}$ and $\text{Ar-C}(\text{CN})=\text{N}=\text{N}-\text{CO}-\text{Ar}'$, easily prepared from the bromo-derivatives $\text{Ar-CBr}(\text{SEt})-\text{CN}$, afford in good yields, by heating in a basic medium, 3,6-diaryl-5 hydroxy-1,2,4-triazines.

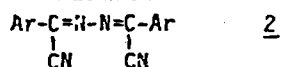
Les principales méthodes de préparation des $\alpha\alpha$ -triazinones-5 par hétérocyclisation font appel à la condensation d'un dérivé α -dicarbonylé avec une amidrazone⁽¹⁻³⁾, ou de son hydrazone avec un imidate⁽³⁾. Nous reportons dans cette note une méthode simple de synthèse de diaryl-3,6 hydroxy-5 triazines-1,2,4 ne nécessitant pas la préparation d'un dérivé α -dicarbonylé.

Dans un travail récent nous avons montré que les nitriles α -thioéthers α -bromés $\text{Ar-CBr}(\text{SEt})-\text{CN}$ 1, aisément préparés à partir de ArCHO , conduisaient facilement par action d'une amine aux α -iminonitriles $\text{Ar-C}(\text{CN})=\text{N}-\text{Ar}$ ⁽⁴⁾. En généralisant cette étude nous avons observé que l'action de l'hydrazine (1,35 mole/mole) sur 1 permettait d'accéder aux azines



des α -cétonitriles aromatiques 2 (Tableau I) pratiquement inconnues⁽⁵⁾.

TABLEAU I



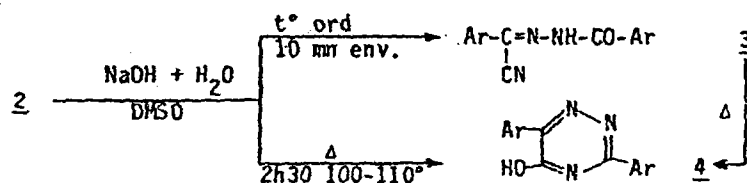
	<u>2a</u>	<u>2b</u>	<u>2c</u>	<u>2d</u>	<u>2e</u>
Ar	Ph	<i>o</i> -Cl-Ph	<i>p</i> -Cl-Ph	<i>m</i> -MeO-Ph	<i>p</i> -CH ₃ -Ph
Rdt %*	65	44	56	51	67
F°C	208-209**	156-157	261-262	216,5-217	246,5-247

* Rdt en produit pur par rapport au dérivé bromé 1

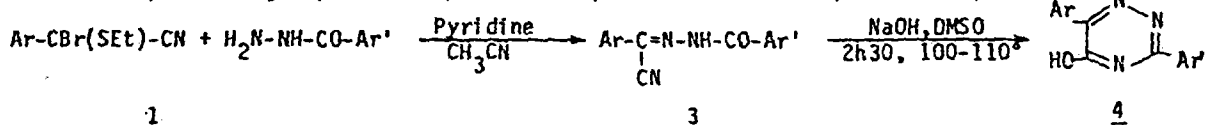
** litt.⁽⁵⁾ F = 205-206°.

A la différence des α -iminonitriles qui sont aisément hydrolysés en benzoylanilines sous l'action de la soude⁽⁶⁾, les azines 2 ne se transforment pas sous l'action de cette base

en dibenzoylhydrazines, mais, à température ordinaire, en α -cyanobenzylidène hydrazides 3 (Rdt 88-95 %) puis, par chauffage, en hydroxy-5 triazines-1,2,4 4 substituées par deux groupements aryles identiques.

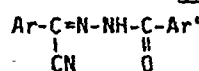


Il est possible de généraliser et d'améliorer cette méthode en faisant agir sur 1 une acylhydrazine en présence de pyridine (1,2 mole/mole), ce qui permet d'obtenir des dérivés substitués par deux groupements aryles identiques ou différents (Tableau II)

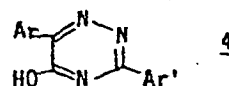


La structure de ces composés a été vérifiée par RMN, spectrographie de masse et IR (conformément aux observations de la littérature pour le dérivé diphenyle 4a⁽³⁾, ces composés existent essentiellement à l'état solide sous la forme hydroxy-5 triazine).

TABLEAU II



et



Ar	Ph	o-Cl-Ph	p-Cl-Ph	m-MeO-Ph	p-Me-Ph	p-Cl-Ph	p-Cl-Ph	Ph
Ar'	Ph	o-Cl-Ph	p-Cl-Ph	m-MeO-Ph	p-Me-Ph	p-MeO-Ph	3-Pyridyl	Me
	<u>3a</u>	<u>3b</u>	<u>3c</u>	<u>3d</u>	<u>3e</u>	<u>3f</u>	<u>3g</u>	<u>3h</u>
Rdt % ¹⁾	89	92	93	95	94	88	83	75
F°C	133-134	130-132	205-206	105-106,5	173-174	164-166	192-193	115-116
	<u>4a</u>	<u>4b</u>	<u>4c</u>	<u>4d</u>	<u>4e</u>	<u>4f</u>	<u>4g</u>	<u>4</u>
Rdt % ²⁾	74	67	62	63	81	70	50	
F°C	278-279 ³⁾	212,5-214	369-370	194-196	327-328	349-351	328-329,5	

1) Rdt en produit pur par rapport à l'azine pour les dérivés 3a à 3e ou par rapport au dérivé bromé 1 pour 3f à 3h.

2) Rdt en produit pur par rapport à l'azine pour 4a à 4e ou par rapport au dérivé 3 pour 4f à 4g.

3) litt. F = 274-276°⁽²⁾, F = 274-275°⁽⁷⁾.

4) Signalons que le dérivé N-acétylé 3h Ph-C(CN)=N-NH-CO-CH₃ subit, lors de l'hydrolyse basique une dégradation en acide phénylacétique.

Références

- (1) Y. UCHYLITOVA, P. FIEDLER, M. PRYSTAS et J. GUT, *Coll. Czech. chem. Comm.*, **36**, 1955 (1971)
- (2) M. BRUGGER, H. WAMHOFF et F. KORTE, *Ann. Chem.*, **755**, 101 (1972)
- (3) J. DAUNIS, R. JACQUIER et C. PIGIERE, *Tetrahedron*, **30**, 3171 (1974)
- (4) F. POCHAT, *Tetrahedron Letters*, **22**, 955 (1981)
- (5) La seule azine Ph-C(CN)=N-N=C(CN)-Ph décrite, a été préparée en quatre étapes à partir du dibenzoylacétylène (Rdt 12%), par T.L. GILCHRIST, G.E. GYMER et C.W. REES, *J. chem. Soc., Perkin I*, 1747 (1975)
- (6) H. OHMORI, C. UEDA et M. MASUI, *J. chem. Soc., Perkin II*, 720 (1979)
- (7) H. NEUNHOEFFER et V. BÖNISCH, *Ann. Chem.*, 153 (1976).

(Received in France 29 June 1981)

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(2) (9) (8)

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A CONVENIENT AND FACILE SYNTHESIS OF 5-TRIFLUOROMETHYL-1,2,4-TRIAZINE DERIVATIVES

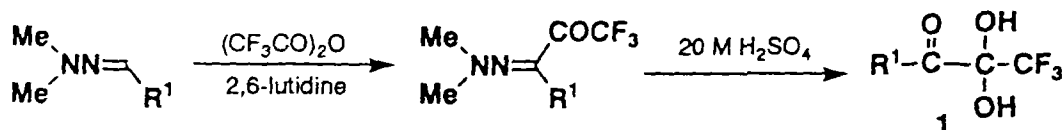
Yasuhiro Kamitori, Masaru Hojo, Ryoichi Masuda,* Masamichi Sukegawa,
Kouji Hayashi, and Ken Kouzeki

Department of Industrial Chemistry, Faculty of Engineering,
Kobe University, Kobe 657, Japan

Abstract - 3-Hydrazono-1,1,1-trifluoroalkan-2-ones (2) and 3-methylhydrazono-1,1,1-trifluoroalkan-2-ones (3) prepared from 1,1,1-trifluoroalkane-2,3-diones (1) reacted with several aldehydes in the presence of aq. NH_4OH to afford 5-trifluoromethyl-2,3-dihydro-1,2,4-triazines (4 and 5) of which oxidation gave 5-trifluoromethyl-1,2,4-triazines (6) and 5-trifluoromethyl-2,5-dihydro-5-hydroxy-1,2,4-triazines (7). Thermal reaction of 5 afforded 1-amino-4-trifluoromethylimidazoles (8).

Triazine derivatives are of special interest owing to their potentially high pharmacological properties applicable to cardiotonics, antihypertensives etc.¹⁻³ In particular, fluorine-containing triazine derivatives may be fascinating target for many organic synthetic chemists.⁴ 1,1,1-Trifluoroalkane-2,3-dione monohydrates (1) which are readily obtainable from a varieties of aldehydes by our three-steps method⁵ may be one of the most useful intermediates accessible to fluorine-containing 1,2,4-triazine derivatives. This prompted us to try synthesis of 5-trifluoromethyl-1,2,4-triazine derivatives from 1. Now we wish to report the results.

By usual method,⁵ trifluoroacetylation of aldehyde dimethylhydrazones with the use of



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trifluoroacetic anhydride gave 3-dimethylhydrazono-1,1,1-trifluoroalkan-2-ones, which were hydrolyzed with hot 10M H_2SO_4 affording **1** as monohydrates. Thus obtained **1** was treated with hydrazine hydrate in MeOH affording 1,1,1-trifluoro-3-hydrazonoalkan-2-ones (**2**) in good yields. Similarly **1** reacted with methylhydrazine in AcOH to give 1,1,1-trifluoro-3-methylhydrazonoalkan-2-ones (**3**) in high yields. A mixture of **2** and various aldehydes dissolved in MeOH reacted for 24 h with 28% aq. NH_4OH . The reaction mixture was treated with 1M HCl to afford 5-trifluoromethyl-2,3-dihydro-1,2,4-triazine (**4**). Similarly, 2-methyl derivatives (**5**) could be obtained. When we omitted above treatment with 1 M HCl, 5-trifluoromethyl-2,3,4,5-tetrahydro-5-hydroxy-1,2,4-triazines (**4'** or **5'**)⁶ could be obtained, in some cases of **5'**, together with small amounts of **5**. Apparently dil. HCl catalyzes dehydration of **4'** and **5'** to the corresponding **4** and **5**, respectively. Purification by silica gel column chromatography also completely converted **4'** and **5'** to **4** and **5**, respectively. Results are summarized in Table 1. Dihydrotriazines (**4**) and (**5**) are fairly stable compounds but **5** was gradually oxidized under atmosphere to 5-trifluoromethyl-2,5-dihydro-5-

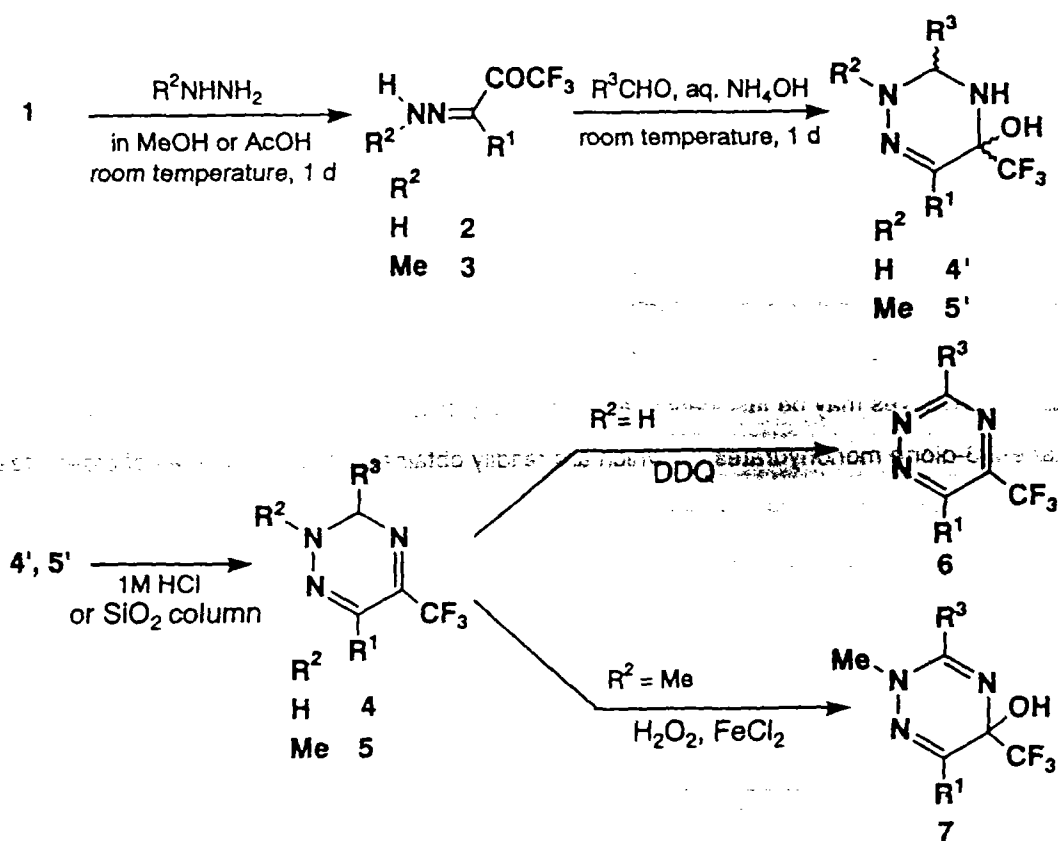


Table 1. Synthesis of 5-Trifluoromethyl-2,3-dihydro-1,2,4-triazines (4 and 5).

R ¹	R ²	R ³	4' : 4 a 5' : 5	product ^b / Yield ^c %	¹ H nmr (CDCl ₃ /TMS) δ
<i>p</i> -MeC ₆ H ₄	H	Et	4 a' : 4 a (1 : 0)	4 a / 65	1.05 (t, <i>J</i> = 5.0 Hz, 3H, CH ₂ Me), 1.78 (m, 2H, CH ₂ Me), 2.30 (s, 3H, Me), 3.24 (s, 3H, NMe), 4.40 (t, <i>J</i> = 6.0 Hz, 1H, CH), 7.01, 7.21 (d, <i>J</i> = 8.0 Hz, 4H, ArH)
<i>p</i> -MeC ₆ H ₄	H	<i>i</i> -Pr	4 b' : 4 b (1 : 0)	4 b / 99	1.08 (d, <i>J</i> = 6.0 Hz, 6H, CHMe), 1.90-2.33 (m, 1H, CHMe), 2.33 (s, 3H, Me), 3.87 (br, d, <i>J</i> = 5.0 Hz, 1H, NCH), 6.70-6.90 (br, 1H, NH), 6.90-7.35 (AA'BB'q, <i>J</i> = 8.0 Hz, 4H, ArH)
<i>p</i> -MeC ₆ H ₄	H <i>o</i> -MeC ₆ H ₄		4 c' : 4 c (1 : 0)	4 c / 73	2.37 (s, 6H, Me), 5.10 (br, 1H, CH), 6.43-6.64 (br, 1H, NH), 6.96-7.73 (m, 8H, ArH)
<i>n</i> -C ₆ H ₁₃	H	<i>i</i> -Pr	4 d' : 4 d (1 : 0)	4 d / 83	0.33-1.83, 1.03 (m and d, <i>J</i> = 6.2 Hz, 17H, <i>n</i> -C ₆ H ₁₁ and CHMe), 1.83-2.83 (m, 3H, =CCH ₂ and CHMe), 6.00-7.00 (br, 1H, NH)
<i>n</i> -C ₆ H ₁₃	H <i>p</i> -MeC ₆ H ₄		4 e' : 4 e (1 : 0)	4 e / 99	0.70-1.93 (m, 11H, <i>n</i> -C ₆ H ₁₁), 2.18-2.90, 2.33 (m and s, 5H, =CCH ₂ and Me), 4.87 (s, 1H, NCH), 6.84-3.34, 6.70-7.70 (AA'BB'q and br, <i>J</i> = 8.0 Hz, 5H, ArH)
<i>p</i> -MeC ₆ H ₄	Me	<i>i</i> -Pr	5 a' : 5 a (1 : 0)	5 a / 83	1.01 (d, <i>J</i> = 6.6 Hz, 6H, CHMe), 2.24 (m, 1H, CHMe), 2.30 (s, 3H, Me), 3.24 (s, 3H, NMe), 4.42 (d, <i>J</i> = 6.4 Hz, 1H, NCH), 7.06, 7.29 (d, <i>J</i> = 9.0 Hz, 4H, ArH)
<i>p</i> -MeOC ₆ H ₄	Me	<i>i</i> -Pr	5 b' : 5 b (1 : 1.5)	5 b / 35	1.05 (d, <i>J</i> = 6.6 Hz, 6H, CHMe), 1.63-2.66 (m, 1H, CHMe), 3.33 (s, 3H, NMe), 3.77 (s, 3H, OMe), 4.48 (d, <i>J</i> = 6.0 Hz, 1H, NCH), 6.81, 7.29 (d, <i>J</i> = 9.0 Hz, 4H, ArH)
<i>p</i> -O ₂ NC ₆ H ₄	Me	<i>i</i> -Pr	5 c' : 5 c (1 : 0)	5 c / 31	1.06 (d, <i>J</i> = 7.0 Hz, 6H, CHMe), 1.98-2.58 (m, 1H, CHMe), 3.45 (s, 3H, NMe), 4.68 (d, <i>J</i> = 7.8 Hz, 1H, NCH), 7.63, 8.24 (d, <i>J</i> = 8.4 Hz, 4H, ArH)
<i>p</i> -MeC ₆ H ₄	Me <i>p</i> -MeC ₆ H ₄		5 d' : 5 d (1 : 0)	5 d / 97	2.37 (s, 6H, Me), 3.11 (s, 3H, NMe), 5.29 (s, 1H, CH), 7.05-7.53 (AA'BB'q x 2, <i>J</i> = 8.0 Hz, 8H, ArH)

a) Products ratio before washing with 1M HCl. b) Product obtained after washing with 1M HCl. c) Yellow syrupy oil was obtained after purification by silica gel column chromatography.

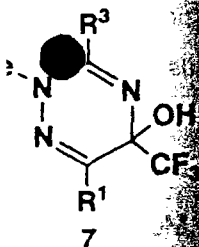
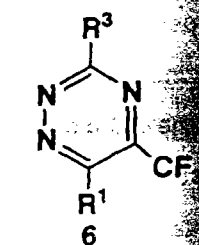
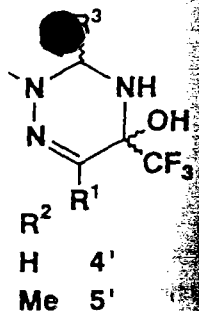


Table 2. Oxidation of 4 and 5 to 6 and 7, respectively.

substrate	method ^a	product ^b yield, %	bp or mp ^c °C (solvent)	¹ H nmr (CDCl ₃ /TMS) δ
4 a	A	6 a 77	100/3 torr ^d	1.50 (t, <i>J</i> = 7.8 Hz, 3H, CH ₂ Me), 2.32 (s, 3H, Me), 3.24 (q, <i>J</i> = 7.8 Hz, 2H, CH ₂), 7.14, 7.40 (d, <i>J</i> = 8.0 Hz, 4H, ArH)
4 b	A	6 b 71	90/1 torr ^d	1.49 (d, <i>J</i> = 6.4 Hz, 6H, CHMe), 2.40 (s, 3H, Me), 3.56 (hept, <i>J</i> = 6.4 Hz, 1H, CHMe), 7.17, 7.44 (d, <i>J</i> = 8.0 Hz, 4H, ArH)
4 c	A	6 c 89	150/1 torr ^d	2.44 (s, 3H, <i>p</i> -Me), 2.70 (s, 3H, OMe), 7.14-7.50 (m, 6H, ArH), 7.57 (d, <i>J</i> = 8.0 Hz, 2H, ArH)
4 d	A	6 d 59	70/3 torr ^d	0.63-2.53, 1.42 (m and d, <i>J</i> = 6.2 Hz, 17H, <i>n</i> -C ₅ H ₁₁ and CHMe), 2.90-3.37 (m, 3H, (CH ₂)C ₅ H _{11-n} and CHMe)
4 e	A	6 e 71	48 (<i>c</i> -hexane)	0.67-2.23 (m, 11H, <i>n</i> -C ₅ H ₁₁), 2.40 (s, 3H, Me), 2.87- 3.33 (m, 2H, (CH ₂)C ₅ H _{11-n}), 7.16, 8.40 (d, <i>J</i> = 8.0 Hz, 4H, ArH)
5 a	B	7 a 56	143 (<i>n</i> -hexane)	1.20 (d, <i>J</i> = 6.6 Hz, 6H, CHMe), 2.32 (s, 3H, Me), 2.76 (hept, <i>J</i> = 6.6 Hz, 1H, CHMe), 3.51 (s, 3H, NMe), 3.77-4.06 (br, 1H, OH), 7.04, 7.73 (d, <i>J</i> = 8.4 Hz, 4H, ArH)
5 b	B	7 b 46	154 (<i>n</i> -hexane)	1.20 (d, <i>J</i> = 6.4 Hz, 6H, CHMe), 2.82-3.15 (br, 1H, CH), 3.52 (s, 3H, NMe), 3.75 (s, 3H, OMe), 5.80- 6.00 (br, 1H, OH), 6.76, 7.81 (d, <i>J</i> = 9.0 Hz, 4H, ArH)
5 d	B	7 d 31	180 (benzene)	2.33 (s, 3H, Me), 2.37 (s, 3H, Me), 3.37 (s, 3H, NMe), 4.23 (s, 1H, OH), 7.21 (s, 4H, ArH), 7.28, 7.73 (d, <i>J</i> = 7.6 Hz, 4H, ArH)

a) Method A: Substrate (1 mmol), DDQ (1.1 mmol) and MeCN (5 ml) were used, and the reaction was carried out at ambient temperature for 1 h. Method B: Substrate (1 mmol), H₂O₂ (2 mmol) in the cases of 5 a and 5 b, H₂O₂ (5 mmol) in the case of 5 d, FeCl₂ (0.5 mmol) in the cases of 5 a and 5 d, and FeCl₂ (0.2 mmol) in the case of 5 b were used. MeCN (5 ml) was used in all cases. Reaction was carried out at ambient temperature for 2 d. b) Yields refer to pure isolated compounds. c) Uncorrected. d) Oven temperature.

hydroxy-1,2,4-triazine (7), and after a week about half of 5 were oxidized to 7. However 5-trifluoromethyl-2,3-dihydro-3-hydroxy-1,2,4-triazine, a isomer of 7, was not detected in the mixture at all. Aromatization of 4 to 5-trifluoromethyl-1,2,4-triazines (6) proceeded very easily and cleanly by a

treatment with DDQ. On the other hand, oxidation of **5** with H_2O_2 in the presence of FeCl_2 in MeCN afforded **7**, and in this case too, none of 5-trifluoromethyl-2,3-dihydro-3-hydroxy-1,2,4-triazine was obtained. These results are listed in Table 2.⁷

Interestingly, thermal reaction of **5** afforded *N*-aminoimidazoles (**8**)⁸ in excellent yields (Table 3). For instance, **5 a** was maintained at 100°C for a day to give **8 a** in 99% yield. As is illustrated in Scheme 1, electrocyclic ring opening of **5** and subsequent recyclization by nucleophilic attack of azo nitrogen atom to azomethine carbon atom followed by prototropy are one of the most

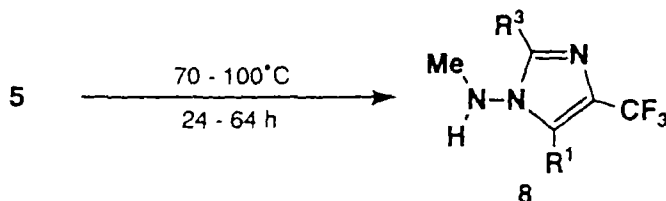


Table 3. Thermal Conversion of **5** to **8**.

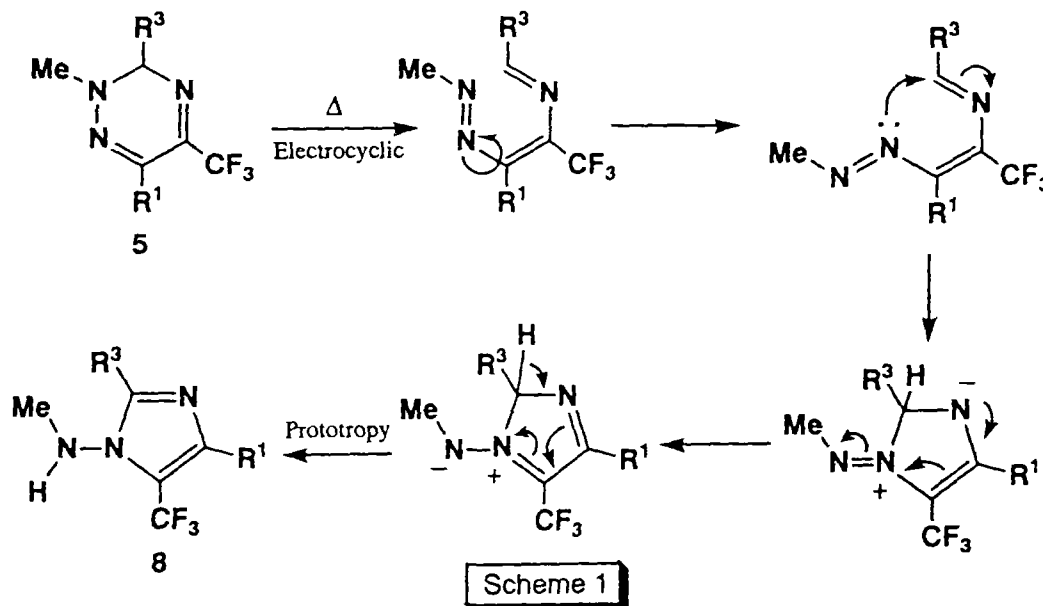
substrate	product	yield ^a / bp ^b % °C/torr	¹ H nmr (CDCl ₃ /TMS)
5 a	8 a	99 / 150/2	1.34 (d, <i>J</i> = 6.4 Hz, CHMe), 2.37 (s, 3H, Me), 2.40 (d, <i>J</i> = 5.8 Hz, 3H, NMe), 3.24 (hept, <i>J</i> = 5.4 Hz, 1H, CHMe), 3.51 (q, <i>J</i> = 5.8 Hz, 1H, NH), 3.77-4.06 (br, 1H, OH), 7.16 (s, 4H, ArH)
5 b	8 b	52 / 150/3	1.35 (d, <i>J</i> = 6.4 Hz, 6H, CHMe), 2.46 (d, <i>J</i> = 4 Hz, 3H, NMe), 3.19 (hept, <i>J</i> = 6.4 Hz, 1H, CHMe), 3.80 (s, 3H, OMe), 4.40-4.90 (br, 1H, NH), 7.25, 6.90 (d, <i>J</i> = 8.0 Hz, 4H, ArH)
5 c	8 c	53 / 190/3	1.60 (d, <i>J</i> = 6.4 Hz, 6H, CHMe), 3.40, 3.43 (hept and s, <i>J</i> = 6.4 Hz, 4H, CHMe and NMe), 6.70-7.25 (br, 1H, NH), 7.48, 8.08 (d, <i>J</i> = 8.0 Hz, 4H, ArH)
5 d	8 d	72 / 121 ^c (c-hexane)	2.37 (s, 3H, Me), 2.40 (s, 3H, Me), 4.70-5.15 (br, 1H, NH), 7.13, 7.20 (d and s, <i>J</i> = 8.0 Hz, 3H, ArH), 7.89 (d, <i>J</i> = 8.0 Hz, 2H, ArH)

a) Yields refer to pure isolated compounds. b) Oven temperature of Kugelrohr distillation. c) Mp uncorrected.

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reasonable reaction path from 5 to 8.

We could present new convenient synthetic method accessible to fluorine-containing 1,2,4-triazine derivatives (4, 5, 6, and 7) and *N*-aminoimidazoles (8) bearing CF₃ group.



EXPERIMENTAL

¹H Nmr and ¹³C nmr spectra were recorded at 60 MHz on a JEOL PMX 60SI and at 22.5 MHz on a JOEL FX90Q, respectively. Ir spectra were taken with a Hitachi model G3. Distillation was performed by Kugelrohr. Mp was measured with Mitamura Riken model 7-12 apparatus.

5-Trifluoromethyl-2,3-dihydro-1,2,4-triazine (4 and 5). General Procedure:

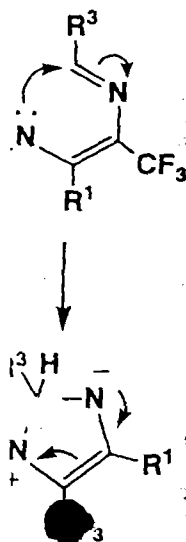
To a mixture of **2** (or **3**, 1 mmol) and aldehyde (1.2 mmol) dissolved in MeOH (5 ml) was added 28% aq. NH₄OH (2 ml), and the mixture was stirred for 24 h at ambient temperature. To the mixture was added CH₂Cl₂ (50 ml) and the whole was washed with 1M HCl and with water. The organic layer was dried over Na₂SO₄ and the solvent was removed to afford 5-trifluoromethyl-2,3-dihydro-1,2,4-triazine (**4** and **5**).

5-Trifluoromethyl-1,2,4-triazines (6) and 5-Trifluoromethyl-2,5-dihydro-5-hydroxy-2-methyl-1,2,4-triazine (7). General Procedure:

Method A: A mixture of **4** (1 mmol) and DDQ (249.7 mg, 1.1 mmol) in MeCN (5 ml) was stirred for 1 h at ambient temperature. The solvent was removed and CH₂Cl₂ (50 ml) was added. Insoluble

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taining 1,2,4-triazine



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nl) was added 2
to the mixture wa
The organic layer
2,3-dihydro-1,2,4-
-2-methyl-1,2,4-

ml) was stirred for
ided. Insoluble

materials were filtered off and filtrate was washed with 1M aq. NaOH. The organic layer was dried over Na₂SO₄ and the solvent was removed to afford 5-trifluoromethyl-1,2,4-triazines (6).

Method B: To a mixture of **5** (1 mmol) and H₂O₂ (2 - 5 mmol) in MeCN (5 ml) was added FeCl₂ (0.2 - 0.5 mmol) and the mixture was stirred for 2 d at ambient temperature. The reaction mixture was poured onto saturated aq. NaHSO₃ and extracted with CH₂Cl₂ (50 ml x 3). The combined extracts were dried over Na₂SO₄ and the solvent was removed to afford 5-hydroxy-2-methyl-5-trifluoromethyl-2,5-dihydro-1,2,4-triazine (7).

4-Trifluoromethyl-1-methylaminolimidazole (8). General Procedure:

Dihydrotriazine (**5**) was heated for 24 h at 100° C and the crude product was purified by Kugelrohr distillation or recrystallization to afford pure 4-trifluoromethyl-1-methylaminoimidazole (**8**).

REFERENCES AND NOTES

1. Japanese Patent 58 131 937 (1983), Imperial Chemical Industries plc (*Chem. Abstr.*, **1984**, 100, 6567).
2. R. E. Hargreaves, B. J. McLoughlin, and S. D. Mills, *European Patent* 85227 (1983) (*Chem. Abstr.*, **1984**, 100, 6561). I. Sircar, M. H. Cain, and J. G. Topliss, *US Patent* 4 508 718 (1984) (*Chem. Abstr.*, **1985**, 103, 6373).
3. K. Suhasin, T. V. P. Rao, and V. Thirupathaiah, *Curr. Sci.* **1983**, 52, 1133 (*Chem. Abstr.*, **1984**, 100, 156574).
4. Review: R. Filler, "Organofluorine Chemicals and Their Industrial Application", ed. by R. E. Banks, Ellis Horwood, London, 1979, p.123.
5. Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, S. Ohara, and T. Yokoyama, *J. Org. Chem.*, **1988**, 53, 129.
6. For instance, **4 a'**: pale yellow syrupy oil; ¹H nmr (CDCl₃/TMS) δ 0.97 (t, J = 6.2 Hz, 3H, CH₂Me), 1.30-1.86 (m, 2H, CH₂), 2.29 (s, 3H, Me), 3.55-4.02 (m, 1H, CH), 6.00-6.50 (br, 3H, NH and OH), 7.02, 7.47 (d, J = 8.0 Hz, 4H, ArH); ir (KBr) 3280 (s), 2500-3200 (br), 1507 (m), 1456 (m), 1295 (s), 1278 (s), 1252 (m), 1205 (s), 1160 (s), 1123 (s), 1060 (s), 822 (s). **5 a'**: yellow syrupy oil; ¹H nmr (CDCl₃/TMS) δ 1.04, 0.95 (d, J = 6.9 Hz, 6H, CHMe), 2.27 (m, 1H, CHMe), 2.32 (s, 3H, Me), 2.37 (br, 2H, NH and OH), 2.96 (s, 3H, NMe), 3.46 (d of d, J = 7.4 Hz and 2.3 Hz, 1H, NCH), 7.12, 7.59 (d, J = 8.3 Hz, 4H, ArH); ¹³C nmr (CDCl₃/TMS) δ 13.9, 18.4

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(CHMe), 21.2 (Me), 27.6 (CHMe), 40.4 (NMe), 70.9 (NCH), 79.5 (q, $^2J_{CF} = 30.4$ Hz, QCF_3), 123.6 (q, $^1J_{CF} = 288.6$ Hz, CF_3), 128.0, 128.5, 133.9, 137.7 (Ar), 139.6 (N=C); ir (KBr) 2090-3680 (br), 1621 (s), 1586 (m), 1467 (m), 1308 (m), 1290 (m), 1257 (s), 1185 (s), 1174 (s), 1132 (s), 1000 (m), 926 (m), 827 (m), 630 (m) cm^{-1} .

7. For instances, **4 d**: yellow syrupy oil; ir (KBr) 3200 (br), 2895 (s), 1530 (m), 1450 (m), 1357 (m), 1180 (s), 1131 (s), 1030 (s), 715 (w) cm^{-1} . **5 a**: yellow syrupy oil; ^{13}C nmr ($CDCl_3/TMS$) δ 16.8, 19.0 (CHMe), 21.2 (Me), 27.4 (CHMe), 43.6 (NMe), 78.7 (NCH), 123.0 ($^1J_{CF} = 277.6$ Hz, CF_3), 127.3, 129.0, 131.5, 138.1 (Ar), 137.7 (N=C), 147.0 ($^2J_{CF} = 34.0$ Hz, QCF_3); ir (KBr) 2980 (m), 1465 (m), 1372 (m), 1201 (s), 1145 (s), 1030 (s), 826 (s), 767 (m), 724 (m) cm^{-1} . **6 b**: pale yellow oil; ir (KBr) 2950 (m), 1606 (m), 1460 (m), 1398 (s), 1370 (s), 1305 (s), 1261 (s), 1189 (s), 1140 (s), 1104 (s), 1060 (m), 1027 (m), 1008 (m), 903 (m), 825 (m), 804 (s), 731 (m) cm^{-1} . Anal. Calcd for $C_{14}H_{14}N_3F_3$: C, 59.78; H, 5.02. Found C, 59.64; H, 4.89. **7 a**: pale yellow crystal; ^{13}C nmr ($CDCl_3/TMS$) δ 19.2, 20.3 (CHMe), 21.3 (Me), 30.0 (CHMe), 40.4 (NMe), 79.3 ($^2J_{CF} = 32.9$ Hz, QCF_3), 123.7 ($^1J_{CF} = 291.2$ Hz, CF_3), 128.7, 129.5, 130.5, 139.8 (Ar), 138.9 (N=C); ir (KBr) 3600-2100 (br), 1611 (s), 1578 (s), 1459 (s), 1421 (m), 1388 (m), 1368 (m), 1318 (m), 1300 (s), 1284 (s), 1268 (s), 1169 (s), 1126 (s), 1015 (s), 984 (s), 921 (m), 873 (m), 820 (m), 718 (m) cm^{-1} . Anal. Calcd for $C_{15}H_{18}N_3OF_3$: C, 57.50; H, 5.79; N, 13.41. Found C, 57.65; H, 5.77; N, 13.24.
8. For instance, **8 a**: pale yellow oil; ir (KBr) 3330 (w), 2970 (m), 2925 (m), 1508 (m), 1490 (m), 1392 (m), 1299 (m), 1183 (s), 1146 (s), 1095 (s), 963 (m), 807 (m) cm^{-1} . Anal. Calcd for $C_{15}H_{18}N_3F_3$: C, 60.60; H, 6.10; N, 14.13. Found C, 60.50; H, 6.16; N, 13.89.

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