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Superintendencia de Industria y Comercio
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Referencia : Expediente No. 09.011.556
Asunto : Solicitud de Patente para: **PROCESO PARA LA
PREPARACIÓN DE 5-(1- ALQUILTIO)ALQUILPIRIDINAS
2-SUBSTITUIDAS**
Solicitante : **DOW AGROSCIENCES LLC**
Clase : C07D 213/032
Fecha de Solicitud : 06 de febrero de 2009

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, de conformidad con la sustitución de poder otorgada a mí por el doctor Emilio FERRERO me refiero al oficio No. 11778 notificado por fijación en lista del 04 de julio de 2012.

2. Mediante oficio No. 11778 el Examinador a cargo del estudio de patentabilidad de la presente solicitud, en virtud del artículo 46 de la Decisión 486, solicitó la presentación de los siguientes documentos:

2.1.1. MARZINZIK A L et al. "Key intermediates in combinatorial chemistry: Access to various heterocycles from α , β -unsaturated ketones on the solid phase". Journal of Organic Chemistry. 1998; Vol 63, No 3, Pag 723-727

2.1.2. BARTOLI G et al. "Reaction of dianions of acyclic neta-enamino ketones with electrophiles 3 Nitriles: Synthesis of pyridine and pyrimidine derivatives". Journal of Organic Chemistry. 1992; Vol 57, No 22, Pag 6020-6025

3. Respuesta al requerimiento

Con el ánimo de dar respuesta al requerimiento formulado por el Examinador, se presenta junto con el presente memorial, copia de los dos documentos arriba mencionados.

4. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito que se continúe su tramitación.

5. Anexos

- Documento: MARZINZIK A L et al. "Key intermediates in combinatorial chemistry: Access to various heterocycles from α , β -unsaturated ketones on the solid phase". Journal of Organic Chemistry. 1998; Vol 63, No 3, Pag 723-727.
- Documento: BARTOLI G et al. "Reaction of dianions of acyclic neta-enamino ketones with electrophiles 3 Nitriles: Synthesis of pyridine and pyrimidine derivatives". Journal of Organic Chemistry. 1992; Vol 57, No 22, Pag 6020-6025.

Señor Director,


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No. M-2012-226309\CNV

Key Intermediates in Combinatorial Chemistry: Access to Various Heterocycles from α,β -Unsaturated Ketones on the Solid Phase

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The value of α,β -unsaturated ketones as key intermediates for the combinatorial assembly of four different templates on the solid phase, namely pyrimidines, dihydropyrimidinones, pyridines, and pyrazoles, was explored with individual syntheses of variably substituted model compounds. Starting from aldehydes grafted on polystyrene support, the Wittig and the Claisen–Schmidt reaction conditions were adapted to efficiently prepare α,β -unsaturated ketones on the solid phase. Further derivatization of the α,β -unsaturated ketones to form pyrimidines succeeded with a number of amidines. In a feasibility study, the potential to obtain, in a modular fashion, other small heterocycles from the same intermediates was assessed. In this solid-phase approach α,β -unsaturated carbonyl intermediates can act as a three-carbon component and a primary enamine is utilized to complement the system for pyridine ring formation. Instead, with *N*-methylurea a dihydropyrimidinone is obtained. As an alternative, substituted hydrazines are incorporated in one orientation, providing pyrazoles with defined regioisomerism. The study indicates that α,β -unsaturated ketones grafted on the solid phase can take a pivotal role as branching points in a number of synthetic diversity schemes and, therefore, represent versatile intermediates for the efficient preparation of combinatorial *small molecule* libraries.

Introduction

The ability to generate large numbers of compounds rapidly in parallel processes, rather than by sequential reiteration of individual syntheses, is one of several factors that contribute to the appeal of combinatorial chemistry for drug discovery.¹ Another consequence of the developments in this area is the growing choice of modular reaction schemes, which provide high molecular diversity with broadly applicable reaction steps, under standardized conditions.²

The search for new valuable drug candidates not only demands that numerous structural subunits (building blocks) are combined on a particular backbone or template but also that a rich variety of such scaffolds is provided. This takes into account that the core structure of a compound class contributes to the pharmacological profile, in addition to the effects it mediates by directing the spatial arrangement of the pharmacophoric substituents. Occasionally, reports in the literature have indicated that, from certain intermediate structures grafted on the solid phase, it is possible to derive more than one type of heterocyclic compound libraries, e.g., pyrrolidines,³ thiazolidines,⁴ metathiazanones⁴ and β -lactams⁵ from immobilized aldimines, or dioxopiperazines

and dioxomorpholines from α -bromo-substituted dipeptides,⁶ or pyrazoles and isoxazoles from β -diketones.⁷

Here we discuss the value of α,β -unsaturated ketones as key intermediates for the combinatorial assembly of four different templates on the solid phase, namely pyrimidines, dihydropyrimidinones, pyridines, and pyrazoles, indicating that the potential to branch out to an even larger choice of scaffolds is worth exploring.

Results and Discussion

From the various reactions that afford α,β -unsaturated ketones, we chose to concentrate on the Wittig and the Claisen–Schmidt reaction, in view of the expected ease to adapt conditions to the solid-phase format. Aldol condensations, which provide β -ketols on solid support, have been described.⁸ One early example reporting the solid-phase synthesis of formylchalcone⁹ was not reproducible, under the given conditions, on the support and linkage we worked with, leading in fact exclusively to Michael adducts. A particular advantage of the base-catalyzed Claisen–Schmidt reaction is the large choice of commercially available carbonyl building blocks suitable to react with the aldehydes grafted on the solid support. Such immobilized aldehydes (e.g., **2**) are easily obtained by standard amide coupling protocols,¹⁰ utilizing *N,N*-diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) on polystyrene with the Rink linker¹¹

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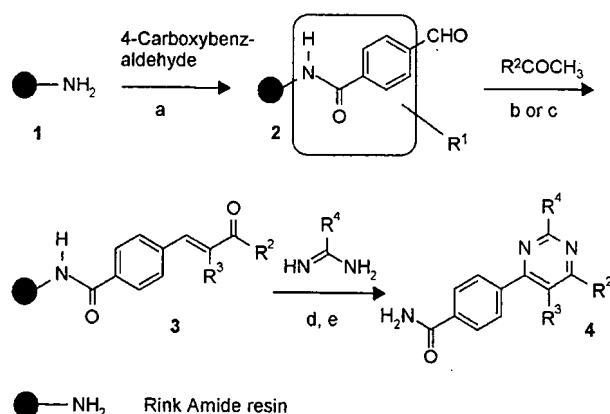


Figure 1. Key: (a) 3 equiv of $HOOCC_6H_4CHO$, 3.3 equiv of DIC, 3.3 equiv of HOBT, DMA, rt, 1 h; (b) 20 equiv of R^2COCH_3 , 20 equiv of LiOH, DME, rt, 16 h; (c) 7.5 equiv of $R^2COC(PPh_3)_3$, DMA, 60 °C, 4 h; (d) 10 equiv of $R^4CNH(NH_2)$, DMA, air, 100 °C, 16 h; (e) 20% TFA/ CH_2Cl_2 , rt, 15 min.

Table 1. α,β -Unsaturated Ketones 3

entry	R^2	R^3	% purity of crudes ^a	% yield ^b
3a	Ph	H	93	98
3b	2,4-(CH_3O) $_2C_6H_3$	H	94	64
3c	2-pyrrolyl	H	>95	83
3d	CH_3	H	>95	67
3e	Ph	CH_3	>95	71

^a Purity determined by C-18 RP HPLC. ^b Isolated yields after preparative HPLC.

1. 4-Carboxybenzaldehyde, but also other aldehydes with furan or thiophene moieties, are coupled to the carrier with quantitative yield (data not shown), representing a first variable site R^1 for diversity generation (see Figure 1). Throughout the experiments reported here, we utilized resin-bound benzaldehyde 2 for all downstream derivatizations; the 4-carboxy substituent represented a convenient handle for the reversible attachment to the solid support.

For the following condensation we examined bases with sufficient solubility and aprotic solvents, which would better suit the requirements of solid-phase reaction conditions, than the reagents commonly used for analogous reactions in solution¹² (sodium hydroxide or sodium ethoxide in ethanol). Best results were obtained with LiOH in DME at room temperature. Under these specific conditions no Michael adduct was formed. Variably substituted acetophenones afforded chalcone derivatives 3a–c of satisfactory purity. Table 1 lists purities of crude products, determined by HPLC analysis after cleavage from the resin with 20% TFA in dichloromethane. Even the presence of a weakly acidic heterocycle seems acceptable, since compound 3c was obtained without detectable side products. On the other hand, the simultaneous introduction of an R^3 residue, namely a methyl substituent by usage of propiophenone instead of acetophenone, was not successful under the same or similar reaction conditions. Rather than attempting to expand the scope of the aldol reaction by applying more stringent conditions, we opted to access R^3 -substituted compounds by the Wittig reaction. An advantage of the Wittig reaction in combinatorial chemistry is its broad applicability, being compatible with various functional

Table 2. Examples of Characterized Products 4–7

entry	R^2	R^3	R^4	% purity of crudes ^a	% yield ^b
4a	Ph	H	4-MeOC $_6$ H $_4$	>95	98
4b	Ph	H	2-thienyl	>95	83
4c	Ph	H	Me	>95	56
4d	Ph	H	4-pyridyl	>95	98
4e	Ph	H	NH $_2$	>95	94
4f	Me	H	Ph	>95	56
4g	Ph	Me	4-MeOC $_6$ H $_4$	>95	38
4h	2,4-(MeO) $_2C_6H_3$	H	Ph	82	52
4i	2-pyrrolyl	H	Ph	78	60
5				93	46
6				94	84
7				83	73

^a Purity determined by C-18 RP HPLC. ^b Isolated yields after preparative HPLC.

groups. Entries 3d and 3e were obtained in excellent purity by Wittig reaction of the appropriate 2 and the corresponding triphenylphosphonium bromide with NaOEt at 60 °C in dimethylacetamide (DMA). The phosphorus ylides are readily available from α -bromo ketones by the Arbuzov reaction and treatment with a strong base, such as NaOEt.

Initially, our main focus in further derivatizing the α,β -unsaturated ketones was the conversion to pyrimidines by means of a number of amidines with different steric and electronic properties. Resin-bound 3 was treated with a 0.5 M solution of the appropriate amidine in DMA at 100 °C for 16 h under air atmosphere. Subsequent treatment with 20% TFA in dichloromethane, elution from the support, and evaporation of the cleavage reagents gave 4, which could be analyzed off the resin. At lower temperatures a mixture of a noncyclized, a non-aromatized, and the expected product was obtained. Chalcone 3a can be cyclized with benzamidines bearing electron-releasing substituents, but also with other amidines carrying aromatic or heteroaromatic residues with electron-rich or electron-withdrawing moieties (Table 2, entries 4a, 4b, and 4d). Pyrimidines with an alkyl group or another functional group, like $-NH_2$ in R^4 , can also be synthesized (4c and 4e). Once we had assessed that the substitution pattern of amidines is of minor importance for the cyclization, we were interested in studying the influence of residues other than R^4 . Pyrimidines 4f and 4g were also prepared successfully from the alkyl-substituted intermediate 3d and from enone 3e, with an additional (methyl) substituent in the α -position. In compounds 4h and 4i, the electrophilicity of the COAr moiety is varied again by means of more or less electron-rich substituents, which does not noticeably affect the cyclization.

We also moved on to a simple feasibility study, which assessed the potential to obtain, in a modular fashion, other small heterocycles from the α,β -unsaturated ketones.

The "3+3" pyridine synthesis is one of the numerous synthetic sources of the pyridine ring in solution-phase chemistry.¹³ In our solid-phase approach α,β -unsaturated carbonyl intermediates 3 can act as the three-carbon component and a primary enamine is utilized to comple-

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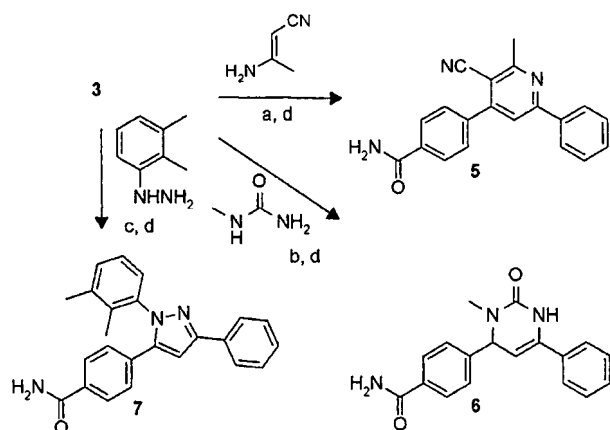


Figure 2. Key: (a) 11 equiv of *t*-BuOK, CH₃CN, rt, 16 h; (b) 10 equiv of CH₃NHCONH₂, 10 equiv of NaOEt, DMA, 16 h, rt; (c) 10 equiv of 2,3-(CH₃)₂C₆H₃NHNH₂, DMSO, 100 °C, 16 h; (d) 20% TFA/CH₂Cl₂, rt, 15 min.

ment the system for ring formation. Such enamines are, for instance, readily available by Thorpe reaction.¹⁴ Ultrasonic irradiation of acetonitrile with potassium *tert*-butoxide in the presence of **3a** provides 3-cyanopyridine **5** at room temperature (Figure 2). The key intermediate, the imino tautomer of 3-aminocrotononitrile, is easily transformed into a reactive carbanion by potassium *tert*-butoxide. Primary enamine synthons other than nitriles, stabilized by conjugation with various electron-withdrawing groups, are under investigation, especially those that afford annelated heterocycles by preliminary Thorpe–Ziegler reaction.

The prospects to discover compounds with pharmacological activity has prompted combinatorial chemists to synthesize dihydropyrimidines in a combinatorial way. One approach has been reported with the Biginelli multicomponent condensation of immobilized ureas, β -keto esters, and aldehydes.¹⁵ Our stepwise reaction scheme allows us to apply the *split-and-mix*¹⁶ methodology and therefore to generate diversity on dihydropyrimidines with high efficiency. Reaction of *N*-methylurea with **3a** in the presence of NaOEt provided dihydropyrimidine **6** in 84% yield as a single regioisomer, identified by magnetic resonance NOE experiments.

We recently published the synthesis of pyrazoles from 1,3-diketones on solid support.⁷ The reaction, although efficient, proceeds without stereoselectivity. The formation of pyrazoles from enones is regiospecific due to the Michael acceptor properties of α,β -unsaturated ketones and due to the difference in reactivity of the two hydrazine nitrogens. Treatment of **3a** with an excess of 2,3-dimethylphenylhydrazine provided only one regioisomer of *N*-phenylpyrazole **7**. The regioisomerism could be elucidated by NMR spectroscopy based on the observed NOE. In a previous experiment, using unsubstituted phenylhydrazine, the assignment was impeded by the overlap of aromatic protons coinciding in two multiplets. Nonaromatized product was also identified as a side product. The purity assessment of crudes (as listed in

Tables 1 and 2) is important in view of the fact that in many instances the components of large libraries cannot be purified individually before testing their activity in screening assays.

In summary, we have indicated that α,β -unsaturated ketones grafted on the solid phase can take a pivotal role as branching points in a number of synthetic diversity schemes and, therefore, represent versatile intermediates for the efficient preparation of combinatorial libraries.

Experimental Section

Reagents were purchased from Aldrich, Fluka, and Novabiochem and used without further purification. ¹H NMR and ¹³C chemical shifts are reported in ppm downfield from TMS. NMR spectra were measured on a Varian 300 MHz instrument. Analytical HPLC was performed using a reversed phase Purospher RP-C18 (5 μ m) column (4 mm $\times$ 125 mm), 215 nm detection, gradient 5–100% B (A = H₂O/0.1% TFA; B = CH₃CN/0.1% TFA) over 20 min, flow = 1 mL/min. Preparative HPLC was performed using a reversed-phase Nucleosil C18 (5 μ m) column (20 mm $\times$ 250 mm), 215 nm detection, 10–90% B over 90 min, flow = 15 mL/min. The mass spectra of the crude products were recorded on a VG Platform II (Micromass, Manchester, U.K.) equipped with an atmospheric pressure ionization (API) source coupled to a Hewlett-Packard 1050 HPLC system. The mass spectrometer was set up as an open access mass spectrometer running under electrospray conditions (ESI-MS). Samples were injected in flow injection analysis mode. The solvent delivery system was methanol/water 90/10 (% v/v) containing 0.1% ammonia.

Coupling Carboxyaldehydes onto the Solid Support (General Procedure). Fluorenylmethoxycarbonyl (Fmoc)-protected 4-[(2',4'-dimethoxyphenyl)aminomethyl]phenoxymethyl resin (Rink amide resin¹¹) (5 g, 2.25 mmol) was subjected to repeated washes with 20% (v/v) piperidine/DMA until the UV absorption at 299 nm in the eluate reached the base-line level. Additional 5 washes (50 mL each) were carried out with pure DMA. Resin **1**, with the deprotected amino group of the linker, was acylated with 22.5 mL of a 0.3 M solution of a carboxyaldehyde (6.75 mmol) at rt (preactivation 40 min with 3.3 equiv of DIC (7.23 mmol) and 3.3 equiv of HOBT (7.23 mmol)) for at least 4 h, until the Kaiser test¹⁷ was negative. The resulting solid-phase grafted aldehydes **2** were utilized for the following derivatizations.

Claisen–Schmidt Reaction on Solid Phase (General Procedure). To a glass vial containing 250.0 mg of aldehyde resin **2** (0.1 mmol) in 5.0 mL anhydrous DME were added 48.0 mg of LiOH·H₂O (2.0 mmol) and 2.0 mmol of the appropriate methyl ketone. The capped vial was shaken for 16 h at rt. The resin was washed with glacial acetic acid, DMA, *i*-PrOH, and CH₂Cl₂ consecutively and dried in vacuo.

In our examples, cleavage from the resin with 20% (v/v) TFA/CH₂Cl₂ for 15 min afforded crude **3a–c** after evaporation. The products were purified by preparative HPLC.

4-(3-Oxo-3-phenylpropenyl)benzamide (3a). From 250.0 mg of the resin was obtained 24.6 mg (98% yield) of product after preparative HPLC: ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.18 (2H, m), 8.08 (1H, bs), 8.04 (1H, d, *J* =

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15.7 Hz), 7.98 (2H, d, $J = 8.8$ Hz), 7.94 (2H, d, $J = 8.7$ Hz), 7.78 (1H, d, $J = 15.7$ Hz), 7.68 (1H, m), 7.58 (1H, m); ^{13}C NMR (75 MHz, DMSO) δ 189.1, 167.5, 167.2, 158.0, 142.8, 137.4, 137.2, 135.6, 133.3, 128.8, 128.7, 128.6, 127.9, 127.9, 127.0, 123.5; HRMS (FAB⁺, m/z) calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_2$ 251.0946, found 251.0945.

4-[3-(2,4-Dimethoxyphenyl)-3-oxopropenyl]benzamide (3b). From 110.0 mg of the resin was obtained 9.0 mg (64% yield) of product after preparative HPLC: ^1H NMR (300 MHz, DMSO- d_6) δ 8.03 (1H, bs), 7.92 (2H, d, $J = 8.4$ Hz), 7.79 (2H, d, $J = 8.5$ Hz), 7.60 (3H, m), 7.42 (1H, bs), 6.66 (2H, m); ^{13}C NMR (75 MHz, DMSO) δ 189.2, 167.2, 164.1, 160.3, 140.0, 137.5, 135.3, 132.1, 128.5, 128.1, 128.0, 121.2, 106.1, 98.6, 56.0, 55.6; HRMS (FAB⁺, m/z) calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_4$ 311.1158, found 311.1158.

4-[3-Oxo-3-(1H-pyrrol-2-yl)propenyl]benzamide (3c). From 300 mg of the resin was obtained 24.0 mg (83% yield) of product after preparative HPLC: ^1H NMR (300 MHz, DMSO- d_6) δ 12.00 (1H, s), 8.05 (1H, s), 7.92 (4H, m), 7.79 (1H, d, $J = 15.7$ Hz), 7.66 (1H, d, $J = 15.7$ Hz), 7.42 (2H, m), 7.18 (1H, m), 6.28 (1H, m); ^{13}C NMR (75 MHz, DMSO) δ 178.4, 168.2, 140.5, 138.4, 136.1, 133.9, 129.2, 128.2, 128.8, 127.6, 125.4, 118.6, 111.1; HRMS (FAB⁺, m/z) calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_4$ 311.1157, found 311.1153.

Preparation of 3d and 3e by Wittig Reaction. A 23.6 mL portion of a 0.25 M solution of the appropriate triphenylphosphorane (5.91 mmol) in DMA was added to 2.0 g (788 μmol) of resin-bound **2**, and the resulting mixture was shaken at 60 °C for 14 h. The resulting mixture was filtered, washed with DMA and *i*-PrOH, and air-dried on the frit. Cleavage of the resin with 20% (v/v) TFA/ CH_2Cl_2 for 15 min provided compounds **3d** and **3e**, respectively.

4-(3-Oxobut-1-enyl)benzamide (3d). From 154.0 mg of the resin prepared with 1-(triphenylphosphoranylidene)-2-propanone was obtained 7.7 mg (67% yield) of product after preparative HPLC: ^1H NMR (300 MHz, DMSO- d_6) δ 8.05 (1H, bs), 7.91 (2H, d, $J = 8.5$ Hz), 7.79 (2H, d, $J = 8.4$ Hz), 7.64 (1H, d, $J = 16.5$ Hz), 6.89 (1H, d, $J = 16.4$ Hz), 2.35 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 198.1, 167.2, 142.0, 137.0, 135.5, 128.5, 128.2, 128.0, 27.4; HRMS (FAB⁺, m/z) calcd for $\text{C}_{11}\text{H}_{11}\text{NO}_2$ 189.0789, found 189.0790.

4-(2-Methyl-3-oxo-3-phenylpropenyl)benzamide (3e). From 300 mg of the resin prepared with 1-phenyl-2-(triphenylphosphoranylidene)-1-propanone¹⁸ was obtained 22.7 mg (71% yield) of product after preparative HPLC: ^1H NMR (300 MHz) δ 8.04 (1H, bs), 7.93 (2H, d, $J = 8.3$ Hz), 7.74 (2H, d, $J = 8.3$ Hz), 7.56 (5H, m), 7.43 (1H, bs), 7.14 (1H, s), 2.19 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 199.2, 168.2, 140.9, 138.9, 138.6, 138.2, 134.9, 132.9, 130.4, 130.1, 129.5, 129.3, 128.5; HRMS (FAB⁺, m/z) calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_2$ 265.1103, found 265.1103.

Cyclization to Pyrimidines 4a–i. To a solution of the corresponding amidine hydrochloride (96 μmol) in 96 μL of DMA was added 96 μL of a 1 M suspension of NaOEt in DMA. Free amidines were used without NaOEt treatment. The suspension was sonicated for 5 min and centrifuged. The resulting solution was added to the resin-bound chalcone derivative **3a** (9.6 μmol) in a vial, and the suspension was vigorously stirred at 100

°C overnight under air atmosphere. The resin was washed with glacial acetic acid, DMA, *i*-PrOH, and CH_2Cl_2 consecutively and dried in vacuo. Cleavage with 20% (v/v) TFA/ CH_2Cl_2 for 15 min afforded pyrimidines **4a–i**.

4-[2-(4-Methoxyphenyl)-6-phenylpyrimidin-4-yl]benzamide (4a). From 250.0 mg of the resin was obtained 37.3 mg (98% yield) of product after preparative HPLC: ^1H NMR (300 MHz, DMSO- d_6) δ 8.55 (7H, m), 8.17 (1H, bs), 8.10 (2H, d, $J = 8.7$ Hz), 7.61 (3H, m), 7.53 (1H, bs), 7.14 (2H, d, $J = 9.0$ Hz), 3.87 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 168.3, 165.1, 164.2, 164.1, 162.5, 140.0, 137.5, 137.2, 132.0, 130.8, 130.6, 129.8, 128.9, 128.3, 128.1, 115.0, 111.0, 56.2; HRMS (FAB⁺, m/z) calcd for $\text{C}_{24}\text{H}_{19}\text{N}_3\text{O}_2$ 381.1477, found 381.1477.

4-(6-Phenyl-2-thien-2-yl-pyrimidin-4-yl)benzamide (4b). From 112.0 mg of the resin was obtained 13.3 mg (83% yield) of product after preparative HPLC: ^1H NMR (300 MHz, DMSO- d_6) δ 8.53 (2H, d, $J = 8.6$ Hz), 8.45 (3H, m), 8.21 (1H, d, $J = 1.3$ Hz), 8.17 (1H, s), 8.09 (2H, d, $J = 8.7$ Hz), 7.83 (1H, d, $J = 5.1$), 7.62 (3H, m), 7.55 (1H, bs), 7.29 (1H, m); ^{13}C NMR (75 MHz, DMSO) δ 168.2, 165.3, 164.2, 161.5, 144.1, 139.5, 137.4, 137.0, 132.3, 131.8, 130.2, 129.9, 129.5, 128.9, 128.3, 128.1, 111.3; HRMS (FAB⁺, m/z) calcd for $\text{C}_{21}\text{H}_{19}\text{N}_3\text{OS}$ 357.0936, found 357.0933.

4-(2-Methyl-6-phenylpyrimidin-4-yl)benzamide (4c). From 92 mg of the resin was obtained 6.0 mg (56% yield) of product after preparative HPLC: ^1H NMR (300 MHz, DMSO- d_6) δ 8.48 (1H, s), 8.42 (2H, d, $J = 9.5$ Hz), 8.35 (2H, m), 8.12 (1H, bs), 8.04 (2H, d, $J = 9.5$ Hz), 7.57 (3H, m), 7.48 (1H, bs), 2.77 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 167.7, 167.3, 164.1, 163.0, 138.9, 136.4, 136.2, 131.0, 128.9, 127.9, 127.3, 127.1, 110.0, 26.1; HRMS (FAB⁺, m/z) calcd for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}$ 289.1215, found 289.1217.

4-(6-Phenyl-2-pyridin-4-ylpyrimidin-4-yl)benzamide (4d). From 109.0 mg of the resin was obtained 15.0 mg (98% yield) of product after preparative HPLC: ^1H NMR (300 MHz, DMSO- d_6) δ 8.99 (2H, m), 8.78 (3H, m), 8.61 (2H, d, $J = 8.6$ Hz), 8.54 (2H, m), 8.20, (1H, bs), 8.10 (2H, d, $J = 8.6$ Hz), 7.63 (3H, m), 7.55 (1H, bs); ^{13}C NMR (75 MHz, DMSO) δ 168.1, 165.7, 164.6, 161.1, 149.6, 147.2, 139.0, 137.6, 136.5, 132.5, 129.8, 128.9, 128.4, 128.3, 124.4, 113.7; HRMS (FAB⁺, m/z) calcd for $\text{C}_{22}\text{H}_{16}\text{ON}_4$ 352.1324, found 352.1324.

4-(2-Amino-6-phenylpyrimidin-4-yl)benzamide (4e). From 125.0 mg of the resin was obtained 13.6 mg (94% yield) of product: ^1H NMR (300 MHz, DMSO- d_6) δ 8.30 (2H, d, $J = 8.7$ Hz), 8.24 (2H, m), 8.10 (1H, bs), 8.01 (2H, d, $J = 8.6$ Hz), 7.80 (1H, s), 7.54 (3H, m), 7.47 (1H, bs); ^{13}C NMR (75 MHz, DMSO) δ 167.3, 164.9, 163.9, 163.2, 139.2, 136.6, 136.0, 130.8, 128.7, 127.8, 127.2, 126.9, 102.4; HRMS (FAB⁺, m/z) calcd for $\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}$ 290.1167, found 290.1167.

4-(6-Methyl-2-phenylpyrimidin-4-yl)benzamide (4f). From 81.8 mg of the resin was obtained 6.0 mg (56% yield) of product after preparative HPLC: ^1H NMR (300 MHz, DMSO- d_6) δ 8.53 (2H, m), 8.41 (2H, d, $J = 8.5$ Hz), 8.15 (1H, s), 8.06 (2H, d, $J = 8.5$ Hz), 8.01 (1H, s), 7.55 (4H, m), 2.63 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 169.4, 168.2, 163.9, 162.8, 139.7, 138.2, 137.2, 131.7, 129.9, 129.5, 128.9, 127.8, 115.7, 25.0; HRMS (FAB⁺, m/z) calcd for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}$ 289.1215, found 289.1219.

4-[2-(4-Methoxyphenyl)-5-methyl-6-phenylpyrimidin-4-yl]benzamide (4g). From 240.0 mg of the resin was obtained 14.3 mg (38% yield) of product after

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preparative HPLC: ^1H NMR (300 MHz, CDCl_3) δ 8.41 (2H, d, $J = 9.1$ Hz), 8.05 (2H, d, $J = 8.6$ Hz), 7.84 (2H, d, $J = 8.6$ Hz), 7.74 (2H, d, $J = 8.0$ Hz), 7.53 (3H, m), 7.00 (2H, d, $J = 9.1$ Hz), 3.86 (3H, s), 2.33 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 168.4, 167.3, 166.5, 162.2, 161.1, 150.4, 142.2, 139.5, 135.7, 130.6, 130.2, 130.1, 130.0, 129.2, 128.3, 123.8, 114.9, 56.2, 18.1; HRMS (FAB^+ , m/z) calcd $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_2$ 395.1634, found 395.1634.

4-[6-(2,4-Dimethoxyphenyl)-2-phenylpyrimidin-4-yl]benzamide (4h). From 94.5 mg of the resin was obtained 9.0 mg (52% yield) of product after preparative HPLC: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.60 (2H, m), 8.43 (1H, s), 8.37 (2H, d, $J = 8.6$ Hz), 8.23 (1H, d, $J = 9.3$ Hz), 8.12 (1H, bs), 8.07 (2H, d, $J = 8.6$ Hz), 7.58 (3H, m), 7.51 (1H, bs), 6.78 (2H, m), 3.98 (3H, s), 3.89 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 168.3, 164.0, 163.7, 163.0, 160.6, 140.3, 138.5, 137.1, 132.8, 131.6, 129.5, 129.1, 128.8, 127.9, 119.1, 115.4, 107.1, 99.7; HRMS (FAB^+ , m/z) calcd for $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_3$ 411.1583, found 411.1581.

4-[2-Phenyl-6-(1H-pyrrol-2-yl)pyrimidin-4-yl]benzamide (4i). From 100 mg of the resin was obtained 10.0 mg (60% yield) of product after preparative HPLC: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.68 (2H, m), 8.41 (2H, d, $J = 8.7$ Hz), 8.06 (2H, d, $J = 8.6$ Hz), 8.03 (1H, s), 7.51 (3H, m), 7.19 (1H, d, $J = 3.7$ Hz), 7.08 (1H, d, $J = 2.5$), 6.33 (1H, dd, $J = 3.7, 2.5$ Hz); ^{13}C NMR (75 MHz, DMSO) δ 168.3, 164.0, 162.7, 158.9, 140.1, 138.4, 137.0, 131.7, 130.3, 129.3, 129.1, 128.9, 127.7, 124.3, 113.2, 111.2, 109.0; HRMS (FAB^+ , m/z) calcd for $\text{C}_{21}\text{H}_{16}\text{N}_4\text{O}$ 340.1324, found 340.1324.

Synthesis of 3-Cyanopyridine 5. To a vial containing 250 mg of **3a** on Rink amide resin (0.1 mmol) were added 3.7 mL acetonitrile and 125 mg (1.1 mmol) *t*-BuOK. The reaction mixture was sonicated for 50 min at rt under Ar and was allowed to stand for 16 h. The resin was washed with glacial acetic acid, DMA, *i*-PrOH, and CH_2Cl_2 consecutively and air-dried. 4-(3-Cyano-2-methyl-6-phenylpyridin-4-yl)benzamide (**5**) was cleaved from the resin with 20% (v/v) TFA/ CH_2Cl_2 . The crude product was purified by preparative HPLC to obtain 20.5 mg (46% yield) of pure **5**: ^1H NMR (300 MHz DMSO- d_6) δ 8.25 (2H, m), 8.13 (1H, s), 8.06 (3H, m), 7.64 (2H, d, $J = 8.6$ Hz), 7.53 (4H, m), 2.83 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 168.1, 162.9, 159.0, 153.5, 139.6, 137.8, 136.3, 13.4, 129.8, 129.6, 128.8, 128.4, 118.7, 117.9, 110.0, 106.2; HRMS (FAB^+ , m/z) calcd for $\text{C}_{20}\text{H}_{15}\text{N}_3\text{O}$ 313.1215, found 313.1214.

Synthesis of Dihydropyrimidinone 6. To a vial containing 14.2 mg (0.57 mmol) of NaOEt in 1.14 mL of

anhydrous DMA were added 142 mg (57 μmol) of resin loaded with **3a** and 42.0 mg (0.57 mmol) of *N*-methylurea. The reaction mixture was allowed to stand under Ar for 16 h. The resin was washed with glacial acetic acid, DMA, *i*-PrOH, and CH_2Cl_2 consecutively and air-dried. 4-(3-Methyl-2-oxo-6-phenyl-1,2,3,4-tetrahydro-pyrimidin-4-yl)-benzamide (**6**) was cleaved from the resin with 20% (v/v) TFA/ CH_2Cl_2 . The crude product was purified by preparative HPLC to obtain 14.6 mg (84% yield) of pure product: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.79 (1H, d, $J = 1.7$ Hz), 7.94 (1H, bs), 7.88 (2H, d, $J = 8.6$ Hz), 7.50 (2H, m), 7.37 (2H, d, $J = 8.6$), 7.33 (4H, m), 5.19 (1H, dd, $J = 1.7, 5.0$ Hz), 5.15 (1H, d, $J = 5.0$ Hz), 2.70 (3H, s); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 167.6, 153.2, 145.5, 135.3, 133.6, 128.7, 128.4, 128.1, 127.9, 126.2, 125.4, 98.2, 61.7, 32.4; HRMS (FAB^+ , m/z) calcd for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2$ 307.1321, found 307.1321.

Synthesis of Pyrazole 7. To a vial containing 250.0 mg of **3a** on Rink amide resin (0.1 mmol) was added 2 mL of 0.5 M solution of dimethylphenylhydrazine in DMSO. The reaction mixture was shaken for 16 h at rt. The resin was washed with DMA and *i*-PrOH consecutively and air-dried. **7** was cleaved from the resin with 20% (v/v) TFA/ CH_2Cl_2 . The crude product was purified by preparative HPLC to obtain 26.8 mg (73% yield) of 4-[2-(2,3-dimethylphenyl)-5-phenyl-2H-pyrazol-3-yl]benzamide (**7**): ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.84 (2H, d, $J = 8.6$ Hz), 7.77 (2H, d, $J = 8.6$ Hz), 7.43 (2H, m), 7.35 (1H, m), 7.30 (3H, m), 7.19 (2H, m), 7.16 (1H, d, $J = 7.5$ Hz), 2.30 (3H, s), 1.87 (3H, s); ^{13}C NMR (75 MHz, DMSO) δ 168.0, 151.6, 145.3, 140.1, 139.1, 134.9, 134.6, 133.6, 133.1, 131.4, 129.6, 128.8, 128.5, 128.2, 126.9, 126.6, 126.2, 104.7, 20.7, 14.6; HRMS (FAB^+ , m/z) calcd for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}$ 367.1685, found 367.1687.

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Supporting Information Available: ^1H NMR spectra of products of type **3** and **4** and of compounds **5**–**7**, including NOE spectra of **6** and **7**. IR spectrum of **3a**, measured by the *single bead* technique (20 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.

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Reaction of Dianions of Acyclic β -Enamino Ketones with Electrophiles. 3.[†] Nitriles: Synthesis of Pyridine and Pyrimidine Derivatives

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A new method for the construction of pyridine and pyrimidine derivatives is described, based on the electrophilic attack of nitriles to dianions of β -(monoalkylamino)- α,β -unsaturated ketones and the subsequent cyclization of the addition product. The reaction proceeds in good to high yields with both α' - and γ -dianions which are regioselectively generated. The reaction of γ -dianions with nitriles is strongly influenced by temperature. The γ -addition products cyclize to 4-aminopyridines when the reaction is run below -50°C . From reactions performed over 0°C pyrimidines arising from addition of 2 mol of nitriles are isolated. Owing to the polar conditions employed, a side metalation reaction is observed with aliphatic nitriles. On the other hand, the α' -addition products can be isolated in neutral conditions but they cyclize to 4-pyridinones in strong acidic media.

The reaction of anions and dianions with nitriles has been widely employed for the synthesis of pyridine derivatives. The aim of these syntheses is generally the preparation of 1,5-diamino derivatives of 5-imino ketones. For example, the former intermediate is obtained from addition to nitriles of metalated α,β -unsaturated imines¹ or of 2-methyleneallyl dianion.² However, the utility of these reactions is restricted by the low yields in the first method and by the introduction of 12 mol of the nitrile in the second one, which allows only the synthesis of pyridines with two identical substituents in the 2- and 6-positions, respectively. 5-Imino ketones can be prepared by reaction of β -diketone dianions with nitriles in liquid ammonia,³ but the reaction is limited to symmetrical ketones because of regioselectivity problems. Acetoacetonitrile dianion reacts with nitriles as well,⁴ but this reaction works well only with a few nitriles. Another approach to the synthesis of pyridine derivatives involves metal-promoted addition of nitriles to the intercarbonylic methylene of β -dicarbonyls.⁵

We recently used dianions of the β -(monoalkylamino)- α,β -unsaturated ketones as versatile intermediates for the regioselective alkylation of the α' - and γ -positions of unsymmetrical acyclic 1,3-dicarbonyl derivatives.⁶ The γ -dianions 2 and the α' -dianions 3 were generated by treatment with MeLi/TMEDA (γ -conditions) or LTMP (α' -conditions), respectively (Scheme I). Anilino derivatives were found to prevent competitive equilibration of the α' -dianion into the most stable γ -isomer.^{6b}

These findings and the ready availability of the starting materials suggested the reaction of γ - and α' -dianions with nitriles to be a suitable route to the synthesis of 4-pyridinamines or 4-pyridinones, respectively.

In this paper, we report the results of the addition of nitriles at both the γ - and the α' -position of β -(monoalkylamino)- α,β -unsaturated ketones.

When a solution of a nitrile 4 is added to a solution of γ -dianion 2⁶ at -50°C , followed by quenching with saturated ammonium chloride, 4-pyridinamines 7 are obtained in good to high yields (Scheme II, Table I).

It is noteworthy that a large variety of enamines can be employed in this reaction. In fact, under the γ -conditions, detectable amounts of products arising from attack

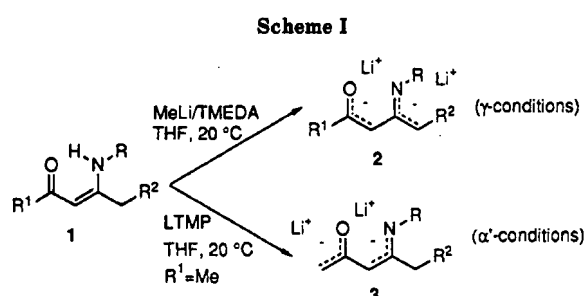


Table I. Reaction between γ -Dianions 2 and Nitriles 4 in THF at -50°C for 15 min Followed by Quenching with Ammonium Chloride

dianion	nitrile	pyridine	yield (%)
2a	4a	7aa	70
2a	4b	7ab	84
2a	4c	7ac	90
2a	4d	7ad	83
2a	4e	7ae	57 ^a
2a	4f	7af	51 ^b
2a	4g	7ag	0 ^c
2b	4a	7ba	84
2c	4a	7ca = 7ab	63
2d	4a	7da	95
2e	4a	7ea	80

^a Based on 58% reacted enammonone. ^b Based on 34% reacted enammonone. ^c After 48 h starting materials were recovered.

at the α' -position have never been found. The isopropylimino derivative of ethyl acetoacetate 1e gives the interesting 4-amino-2-pyridinone system.

α,β -Unsaturated nitriles such as cinnamionitrile give mainly conjugate addition products. Tertiary nitriles such as pivalonitrile failed to yield pyridines, and reactants were

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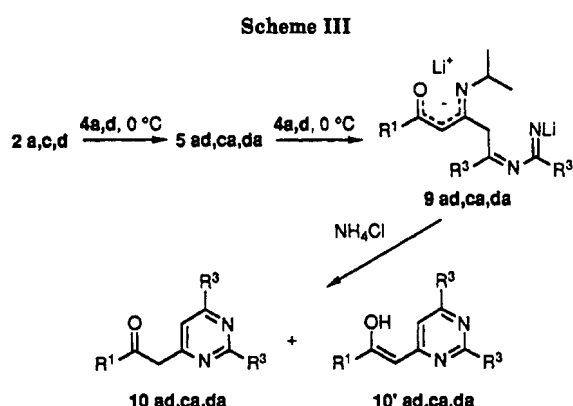
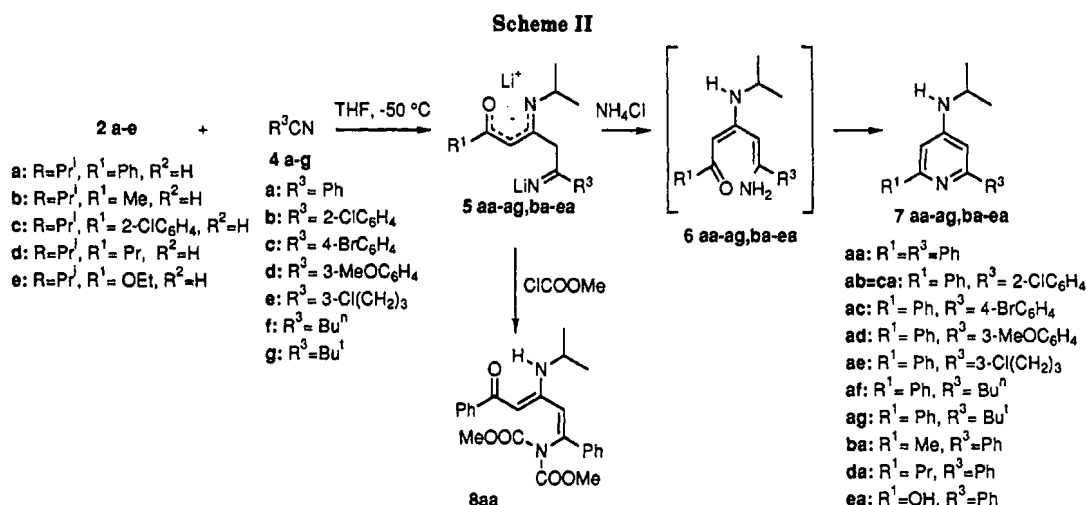
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recovered unaltered after 48 h. Owing to the very polar conditions employed, aliphatic nitriles undergo competitive proton abstraction from the dianion leading to a mixture of starting materials and pyridine. The separation of the products can be easily accomplished, and the yields of recovered pyridine calculated with respect to reacted enaminone are good. Competitive transmetalation^{1,2,4} and steric requirements⁴ are common features of many syntheses of pyridines involving reactions of anions or dianions with nitriles.

The reaction seems to proceed as depicted in Scheme II. The cyclization step occurs only after quenching of the lithium salt 5 with ammonium chloride. In fact, the addition of methylchloroformate to the solution of 5aa leads to the isolation of the linear derivative 8aa.⁷ The cyclization is faster than hydrolysis of the imino and enamino functions even when the mixture is quenched with 10% hydrochloric acid. In fact, pyridinamine 7aa was recovered in 72% yield under these conditions.

Finally, the temperature drastically influences the reaction course. At 0 °C and higher, a completely different reaction pathway was observed. Quenching of the mixture and separation of the main product by chromatography allowed pyrimidines arising from incorporation of 2 mol of nitrile to be isolated in good yields (Scheme III).

The molar ratio between enaminone and nitrile does not influence the reaction course. In fact, over 0 °C a deficit of nitrile causes starting enaminone to be isolated together with pyrimidine, whereas below -50 °C the exclusive for-

Table II. Reaction between γ -Dianions 2a,c,d and Nitriles 4 in THF at 0 °C for 15 min Followed by Quenching with Ammonium Chloride

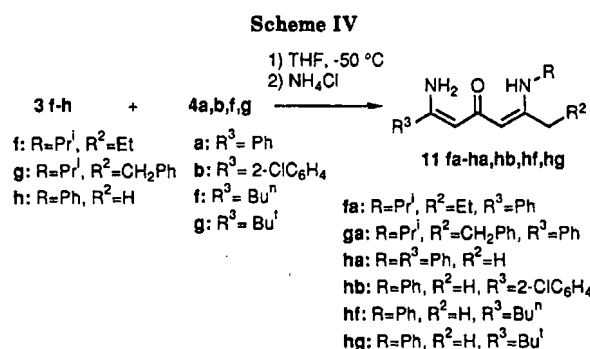
dianion	nitrile	molar ratio 4:2	yield (%)		enol vs keto ratio
			10	7	
2a	4d	2.5:1	84 (ad)		100:1
2a	4d	1.5:1 ^a	51 (ad)		
2a	4d	2.5:1 ^b		82 (ad)	
2c	4a	2.5:1	62 (ca)		100:1
2d	4a	2.5:1	70 (da)		1:2

^a 25% of starting enaminone is recovered. ^b Carried out at -50 °C.

Table III. Yields and Relevant Physical Data of Products from the Reaction between α' -Dianions 3 and Nitriles 4 in THF at -50 °C for 15 min Followed by Quenching with Ammonium Chloride

dianion	nitrile	product	yield (%)	δ_{H_α} and $\delta_{\text{H}_\alpha'}$	δ_{NH}	$\delta_{\text{C=O}}$
3f	4a	11fa	87	4.85, 5.20	10.55	191.15
3g	4a	11ga	84	5.29, 5.29	10.59	190.86
3h	4a	11ha	61	5.12, 5.29	12.40	191.42
3h	4b	11hb	88	5.00, 5.04	12.43	191.46
3h	4f	11hf	83	6.14, 6.15	12.17	180.72
3h	4g	11hg	0 ^a			

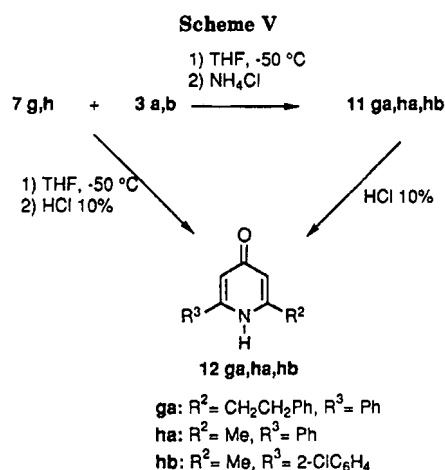
^a After 48 h starting materials were recovered.



mation of pyridine was observed even with an excess of nitrile (Table II).

Very likely under the strongly polar conditions employed, the intermediate 5 is able to add to another mole of nitrile to give 9. Subsequent cyclization and elimination of isopropylamine affords the products 10. Pyrimidines such as 10 were previously prepared by Claisen-like condensation of esters with the anion of 4-methylpyrimidines.⁸

(7) Attempts to trap intermediate 5 with methyl iodide or acetic anhydride were unsuccessful.



Direct cyclization of a suitable intermediate to pyrimidines of structure 10 has not been previously reported, and the present results are a novel approach to these compounds. When a solution of a nitrile is added to a solution of α' -dianion 2⁶ at -50 °C, followed by quenching with saturated ammonium chloride, the expected addition product is isolated in high yields (Scheme IV, Table III).

In contrast to γ -conditions and to the reaction of acetone nitrile dianion,⁴ no side metalation reaction is observed with aliphatic nitriles. Very likely, the absence of a strong complexing agent of the lithium ion makes the α' -dianion a better nucleophile than the γ -isomer. Moreover, the α' -position is less crowded than the γ . In fact, we demonstrated^{8a} that under the γ -conditions the more stable conformation of the dianion 2 constrains both the alkyl group bound to the nitrogen atom and the α' -substituent to shield the γ -position.

On the other hand, under the α' -conditions only the hydrogen atom in the α -position hinders the reactive terminus of dianion 3 in its more stable conformation. Nevertheless, under these experimental conditions, the cyano group of pivalonitrile is too hindered to be attacked and no reaction occurs.

As expected on the basis of the previous findings,^{6b} the *N*-phenyl substituent prevents the formation of pyridines arising from attack at the γ -position. Moreover, it should be noted that an alkyl chain except methyl in the γ -position delays equilibration of the kinetic α' -dianion into the more stable γ -isomer enough to avoid formation of γ -derivatives.

During chromatographic separation of products 11, a partial decomposition on silica gel was observed, which required some care to be taken in the workup (see Experimental Section). After 48 h on silica gel, the almost quantitative conversion of 11 into a 4-pyridinone derivative 12 was observed. Otherwise, the cyclization of 11 to 12 was complete in about 45 min in a 10% methanolic hydrochloric acid solution (Scheme V). Pyridinones can be recovered as well in comparable overall yields in a one-pot procedure by quenching the mixture of enaminone dianion and nitrile with hydrochloric acid (Table IV).

Notwithstanding the presence of two different amino groups, cyclization proceeds always via conjugate addition of the unsubstituted amino function to the α,β -unsaturated ketone, followed by elimination of either aromatic or aliphatic primary amine bound to the β -carbon atom. In

Table IV. Yields of 4-Pyridinones: Comparison between Method A and Method B

pyridinone	method A ^a overall yield ^c (%)	method B ^b yield ^c (%)
12ga	60	62
12ha	55	52
12hb	59	73

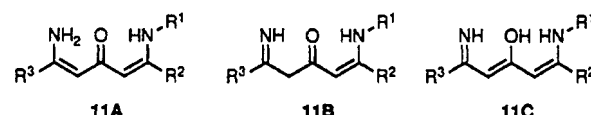
^a Reaction carried out in two stages: preparation of the straight-chain derivative 11, followed by isolation and cyclization in 10% hydrochloric acid in methanol. ^b Reaction carried out in a single stage, quenching the mixture from the reaction of nitrile and α' -dianion with 10% aqueous hydrochloric acid. ^c Calculated on starting enaminone 1.

contrast, it is reported that in the acid-catalyzed cyclization of diketoenamines a different cyclization pathway is followed by aliphatic or aromatic amines,⁹ leading to pyridinones or pyranones, respectively.

Characterization of Compounds. All compounds were identified essentially by their NMR spectra. However, some points should be outlined.

Pyrimidines like 10 are reported⁸ to exist in the keto form. However, both ¹H- and ¹³C-NMR of the prepared pyrimidines show that 4-phenacylpyrimidines are essentially present in solution in the enol form 10'ad,ca rather than in the corresponding keto form 10, very likely owing to a more extended conjugation which stabilizes the former tautomer. On the other hand, when R¹ is an alkyl chain as in 10da, the keto tautomer accounts for 66% of the mixture (Table II).

Compounds 11 can exist as a combination of possible tautomers. It is reported¹⁰ that related macrocycles assume a configuration with two enaminic functions. Moreover, the products arising from reaction of β -dicarbonyls and nitriles at the intercarbonyl methylene were found to exist as β -enaminodiones rather than ketoimines.¹¹ All these structures were supported by X-ray diffraction data.^{10a,11b}



In the ¹H-NMR spectra of compounds 11 (Table III), the presence of a peak near 11 ppm is characteristic of the enaminone system,⁵ and therefore tautomers different from 11A-C can be ruled out. Moreover, the presence of two peaks near 5 ppm each accounting for only one hydrogen atom rules out tautomer 11B. Finally, the ¹³C-NMR signal near 190 ppm assigns the configuration 11A to these products, at least in solution.

To confirm this assignment a single-crystal X-ray analysis of compound 11ha was performed. It is interesting to note that the asymmetric unit is formed by as many as three molecules of 11ha. The C-C, C-N, and C-O bond lengths are similar in all three molecules and comparable with those of similar molecules^{10a} (Table V). The sequence short-long-long-short in the pattern of C1-C5 lengths supported the configuration 11A for the molecules.

The three molecules are held together by weak hydrogen bonds. Other hydrogen bonds are found between neighboring molecules, and rows along which the compound

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Table V. Selected Interatomic Distances (Å) and Bond Angles (deg) for One of the Molecules $C_{18}H_{18}N_2O$ with esd's in Parentheses. Complete Data for All Three Molecules Are Available as Supplementary Material

bond lengths		bond angles	
O(1)–C(3)	1.276 (9)	C(5)–N(2)–C(13)	130.9 (6)
N(1)–C(1)	1.345 (9)	N(1)–C(1)–C(7)	116.0 (6)
N(2)–C(5)	1.341 (9)	N(1)–C(1)–C(2)	122.9 (6)
N(2)–C(13)	1.422 (8)	C(7)–C(1)–C(2)	121.1 (6)
C(7)–C(1)	1.501 (9)	C(1)–C(2)–C(3)	124.0 (6)
C(1)–C(2)	1.358 (10)	O(1)–C(3)–C(2)	121.4 (6)
C(2)–C(3)	1.447 (9)	O(1)–C(3)–C(4)	120.3 (6)
C(3)–C(4)	1.435 (10)	C(2)–C(3)–C(4)	118.3 (6)
C(4)–C(5)	1.353 (9)	C(3)–C(4)–C(5)	126.1 (6)
C(5)–C(6)	1.494 (10)	N(2)–C(5)–C(4)	120.3 (6)
		N(2)–C(5)–C(6)	118.6 (6)
		C(4)–C(5)–C(6)	121.1 (6)

grows may be identified. These rows are held together only by weak van der Waals interactions. On the contrary, a related macrocyclic structure^{10a} shows intramolecular and no intermolecular hydrogen bonds. Conversely, from macrocycles in which the N1–C1–C2–C3–O1–C4–C5–N2 atoms lie in a plane, in 11ah two planes can be observed with a dihedral angle of 6–11° depending on the molecule. The phenyl rings, which are all practically planar, form different angles with respect to the central moiety in the three molecules (supplementary material).

In conclusion, the reaction of nitriles with dianions of β -(monoalkylamino)- α,β -unsaturated ketones can be employed to synthesize three different pharmaceutically important¹² six-membered azaheterocycles. The ready availability of the starting materials and the relatively mild reaction conditions employed make this method competitive with known ones.¹³

Experimental Section

¹H- and ¹³C-NMR spectra were recorded in CDCl₃ solutions. *J* values are given in Hz. Melting points are uncorrected. THF was dried by refluxing over sodium wires until the blue color of benzophenone ketyl persisted and then distilled into a dry receiver under nitrogen atmosphere. LTMP was prepared by equimolecular amounts of butyllithium and amine in THF at 0 °C. Commercial methyllithium solutions (Aldrich) were employed under dry atmosphere and were titrated before use. Commercial compounds (Aldrich) were distilled and dried over molecular sieves before use. Isopropylacetoneimine was synthesized according to the literature.¹⁴

1-Phenyl-3-(*N*-isopropylamino)but-2-en-1-one (1a), 4-(*N*-isopropylamino)pent-3-en-2-one (1b), and ethyl 3-(*N*-isopropylamino)but-2-enoate (1e) were synthesized according to Singh and Tandon's procedure.¹⁵ 4-(*N*-Phenylamino)pent-3-en-2-one (1h) was synthesized according to Boatman and Hauser's procedure.¹⁶ 2-(*N*-isopropylamino)hept-2-en-4-one (1d) and 1-(2-chlorophenyl)-3-(*N*-isopropylamino)but-2-en-1-one (1c) were prepared from metalated isopropylacetoneimine and the appropriate esters

according to our procedure.¹⁷ 4-(*N*-Isopropylamino)hept-3-en-2-one (1f) and 6-phenyl-4-(*N*-isopropylamino)hex-3-en-2-one (1g) were prepared from the γ -dianion of 1b and the appropriate bromide according to our procedure.^{6a} γ - and α' -dianions were prepared as described.⁶

Reaction of the γ -Dianion with Nitriles. A. Synthesis of 4-Pyridinamines. A THF solution of the appropriate nitrile 4 (8 mmol) was added to a cooled (–50 °C) solution of the γ -dianion 2 (5 mmol), and the mixture was allowed to stir for 15 min under a nitrogen atmosphere. The solution was poured into saturated aqueous ammonium chloride and extracted with Et₂O. The organic layer was dried and evaporated under reduced pressure and the residue submitted to a chromatographic separation with silica gel (hexane:ether = 1:1 as eluant). The reaction mixture arising from dianion 2a and nitrile 4a was quenched with 10% HCl, neutralized with saturated NaHCO₃, and then treated as above. The pyridinamine 7aa was recovered in 72% yield.

Yields are reported in Table I. Physical data follow.

2,6-Diphenyl-*N*-isopropyl-4-pyridinamine (7aa): mp 85–6 °C; IR (CCl₄) 3428 cm^{–1} (NH); ¹H-NMR (200 MHz) δ 1.30 (d, *J* = 6.24, 6 H, Me), 3.86 (d, hept, 1 H, CH), 4.11 (d, *J* = 10, 1 H, NH), 6.83 (s, 2 H, H₃, H₅), 7.34–7.68 (m, 6 H, ArH) 8.00–8.30 (m, 4 H, ArH); MS *m/z* 288 (M⁺, 63), 273 (100), 246 (8), 231 (4), 219 (4). Anal. Calcd for C₂₀H₂₀N₂: C, 83.3; H, 7.0; N, 9.7. Found: C, 83.1; H, 7.1; N, 9.8.

2-(2-Chlorophenyl)-*N*-isopropyl-6-phenyl-4-pyridinamine (7ab = 7c): oil; IR (CCl₄) 3429 cm^{–1} (NH); ¹H-NMR (200 MHz) δ 1.24 (d, *J* = 6.32, 6 H, Me), 3.75 (d, hept, 1 H, CH), 4.22 (d, *J* = 10, 1 H, NH), 6.69 (d, *J* = 2, 1 H, H₃ or H₅), 6.81 (d, *J* = 2, 1 H, H₅ or H₃), 7.28–7.52 (m, 6 H, ArH), 7.67–7.75 (m, 1 H, ArH), 7.96–8.05 (m, 2 H, ArH); MS *m/z* 324 (M⁺ + 2, 20), 322 (M⁺, 59), 307 (100), 280 (15), 253 (4). Anal. Calcd for C₂₀H₁₉ClN₂: C, 74.4; H, 5.9; N, 8.7. Found: C, 74.2; H, 6.0; N, 8.8.

2-(4-Bromophenyl)-*N*-isopropyl-6-phenyl-4-pyridinamine (7ac): mp 96–97 °C; IR (CCl₄) 3429 cm^{–1} (NH); ¹H-NMR (200 MHz) δ 1.27 (d, *J* = 6.3, 6 H, Me), 3.81 (m, 1 H, CH), 4.15 (bs, 1 H, NH), 6.76 (d, *J* = 1, 1 H, H₃ or H₅), 6.81 (d, *J* = 1, 1 H, H₃ or H₅), 7.33–7.53 (m, 3 H, Ph), 7.57 (d, *J* = 8.6, 2 H, 4-BrPh), 7.94 (d, *J* = 8.6, 2 H, 4-BrPh), 8.00–8.09 (m, 2 H, Ph); MS *m/z* 368 (M⁺ + 2, 67), 366 (M⁺, 67), 353 (100), 351 (99), 324 (11), 272 (4), 245 (3). Anal. Calcd for C₂₀H₁₉BrN₂: C, 65.4; H, 5.2; N, 7.6. Found: C, 65.2; H, 5.3; N, 7.4.

N-Isopropyl-2-(3-methoxyphenyl)-6-phenyl-4-pyridinamine (7ad): mp 85–86 °C; IR (CCl₄) 3429 cm^{–1} (NH); ¹H-NMR (200 MHz) δ 1.27 (d, *J* = 6.4, 6 H, Me), 3.87 (d hept, 1 H, CH), 3.89 (s, 3 H, OMe), 4.17 (d, *J* = 7.6, 1 H, NH), 6.79–6.82 (AB, 2 H, H₃, H₅), 6.98 (dd, *J* = 8, 1.5, 1 H, ArH), 7.34–7.74 (m, 6 H, ArH), 8.05–8.15 (m, 2 H, ArH); MS *m/z* 318 (M⁺, 100), 317 (100), 303 (54), 288 (21). Anal. Calcd for C₂₁H₂₂N₂O: C, 79.2; H, 7.0; N, 8.8. Found: C, 79.0; H, 7.0; N, 8.9.

6-(3-Chlorophenyl)-*N*-isopropyl-2-phenyl-4-pyridinamine (7ae): mp 100–101 °C; IR (CCl₄) 3428 cm^{–1} (NH); ¹H-NMR (200 MHz) δ 0.85–0.96 (m, 2 H, CH₂CH₂CH₂), 1.04–1.14 (m, 2 H, ClCH₂CH₂CH₂), 1.22 (d, *J* = 6.22, 6 H, Me), 1.88–2.04 (m, 2 H, ClCH₂CH₂CH₂), 3.74 (d hept, 1 H, CH), 3.97 (d, *J* = 10, 1 H, NH), 6.22 (d, *J* = 2, 1 H, H₃ or H₅) 6.63 (d, *J* = 2, 1 H, H₅ or H₃), 7.32–7.47 (m, 3 H, ArH) 7.88–7.98 (m, 2 H, ArH); MS *m/z* 252 (M⁺ – HCl, 100), 237 (28), 209 (13), 195 (6). Anal. Calcd for C₁₇H₂₁ClN₂: C, 70.7; H, 7.3; N, 9.7. Found: C, 70.9; H, 7.2; N, 9.7.

2-Butyl-*N*-isopropyl-6-phenyl-4-pyridinamine (7af): oil; IR (CCl₄) 3411 cm^{–1} (NH); ¹H-NMR (200 MHz) δ 0.91 (t, *J* = 6, 3 H, Me(CH₂)₃), 1.05–1.76 (m, 4 H, Me(CH₂)₂CH₂), 1.30 (d, *J* = 6.3, 6 H, Me), 2.72 (t, *J* = 7.2, 2 H, Me(CH₂)₂CH₂), 3.22–3.89 (m, 2 H, CH + NH), 6.25 (bs, 1 H, H₃ or H₅), 6.63 (bs, 1 H, H₅ or H₃), 7.35–7.41 (m, 3 H, ArH), 7.80–7.83 (m, 2 H, ArH); MS *m/z* 268 (M⁺, 4), 253 (8), 239 (12), 226 (100), 211 (6), 184 (5). Anal. Calcd for C₁₉H₂₄N₂: C, 80.6; H, 9.0; N, 10.4. Found: C, 80.8; H, 8.9; N, 10.3.

N-Isopropyl-6-methyl-2-phenyl-4-pyridinamine (7ba): mp 90–91 °C; IR (CCl₄) 3450 cm^{–1} (NH); ¹H-NMR (200 MHz) δ 1.25 (d, *J* = 6.28, 6 H, Me), 2.49 (s, 3 H, 6-Me), 3.80 (hept, *J* = 6.28, 1 H, CH), 4.02 (s, 1 H, NH), 6.27 (d, *J* = 1.9, 1 H, H₃ or H₅) 6.64

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(d, $J = 1.9$, 1 H, H5 or H3), 7.5–7.6 (m, 3 H, ArH) 7.85–7.90 (m, 2 H, ArH); MS m/z 226 (M^+ , 46), 211 (100). Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.6; H, 8.0; N, 12.4. Found: C, 79.8; H, 7.9; N, 12.3.

N-Isopropyl-2-phenyl-6-propyl-4-pyridinamine (7da): oil, IR (CCl₄) 3428 cm⁻¹ (NH); ¹H-NMR (200 MHz) δ 0.97 (t, $J = 7.3$, 3 H, Me(CH₂)₂), 1.19 (d, $J = 6.4$, 6 H, Me), 1.50–1.70 (m, 2 H, MeCH₂CH₂), 2.67 (t, $J = 7.7$, 2 H, MeCH₂CH₂), 3.22–3.89 (m, 1 H, CH), 4.28 (bs, 1 H, NH), 6.22 (bs, 1 H, H3 or H5), 6.61 (bs, 1 H, H5 or H3), 7.32–7.40 (m, 3 H, ArH), 7.81–7.91 (m, 2 H, ArH); MS m/z 254 (M^+ , 10), 253 (8), 239 (20), 226 (100), 211 (5). Anal. Calcd for $C_{17}H_{22}N_2$: C, 80.3; H, 8.7; N, 11.0. Found: C, 80.4; H, 8.7; N, 10.9.

4-(N-Isopropylamino)-6-phenylpyrid-2-one (7ea): mp 237–238 °C; IR (CCl₄) 3438 (NH) 1638 (C=O) cm⁻¹; ¹H-NMR (200 MHz) δ 1.20 (d, $J = 6.4$, 6 H, Me), 3.60 (d hept, 1 H, CH), 4.70 (d, $J = 8.1$, 1 H, MeCHNH), 5.44 (d, $J = 1.1$, 1 H, H3 or H5), 5.77 (d, $J = 1.1$, 1 H, H5 or H3), 7.38–7.60 (m, 6 H, ArH + NH); MS m/z 228.1259 (M^+ $C_{14}H_{16}N_2O$ requires 228.1263, 71), 213 (100), 186 (13), 170 (20).

The reaction of cinnamionitrile with dianion 2a was carried out and worked up as described above. 1,5-Diphenyl-3-(N-isopropylamino)-6-cyanohept-2-en-1-one was isolated in 74% yield as an oil: IR (CCl₄) 2251 cm⁻¹ (CN); ¹H-NMR (200 MHz) δ 1.15 (d, $J = 6.2$, 3 H, Me), 1.21 (d, $J = 6.2$, 3 H, Me), 2.70–2.90 (m, 4 H, CH₂CHCH₂), 3.16–3.32 (m, 1 H, CH₂CHCH₂), 3.65 (d hept, 1 H, CH), 5.55 (s, 1 H, CH=), 7.10–7.80 (m, 10 H, ArH), 11.38 (d, $J = 8.8$, 1 H, NH); MS m/z 332 (M^+ , 20), 292 (18), 227 (11), 202 (100), 105 (85), 98 (21), 77 (20). Anal. Calcd for $C_{22}H_{24}N_2O$: C, 79.5; H, 7.3; N, 8.4. Found: C, 79.3; H, 7.4; N, 8.4.

Methyl chloroformate (20 mmol) was added to the cooled reaction mixture arising from enaminone 1a and nitrile 4a. The temperature was allowed to rise, and the mixture was then quenched with ammonium chloride. Workup and chromatographic separation with silica gel (hexane/ethyl acetate (1:1)) afforded 1,5-diphenyl-5-[N,N-bis(dimethoxycarbonyl)amino]-3-(N-isopropylamino)penta-2,4-dien-1-one (8aa) in 46% yield: mp 131–133 °C; IR (CCl₄) 1767, 1578 cm⁻¹ (C=O); ¹H-NMR (200 MHz) δ 1.24 (d, 6 H, $J = 6.2$, Me), 3.71 (s, 6 H, OMe), 3.73 (d hept, 1 H, CH), 5.75 (s, 1 H, CH=), 6.61 (s, 1 H, CH=), 7.26–7.52 and 7.72–7.88 (m, 10 H, ArH), 11.10 (d, 1 H, $J = 8.7$, PrNH); MS m/z 422.1864 (M^+ , $C_{24}H_{28}N_2O_5$ requires 422.1842, 9), 379 (44), 317 (31), 290 (21), 274 (67), 105 (100), 77 (50).

B. Synthesis of Pyrimidines. A THF solution of the appropriate nitrile 4 (12.5 mmol) was added to a solution of the γ -dianion 2 (5 mmol) cooled in an ice bath, and the mixture was allowed to stir for 15 min under a nitrogen atmosphere. The mixture was worked up as described for pyridinamines to isolate pyrimidines 10 (hexane/Et₂O = 7:3 as eluant). When the reaction of dianion 2a (5 mmol) and nitrile 4d (12 mmol) was carried out at –50 °C, after workup, pyridinamine 7ad was recovered in 82% yield and recognized by comparison with a sample synthesized as described above. No formation of the corresponding pyrimidine was detected by GC–MS or TLC analyses. When the reaction of dianion 2a (5 mmol) and nitrile 4d (8 mmol) was carried out at 0 °C, after workup, pyrimidine 10ad was recovered in 51% yield together with 25% of enaminone 1a. No formation of the corresponding pyridinamine was detected by GC–MS or TLC analyses.

Compounds 10ad and 10ca showed NMR spectra in agreement with the enol tautomer 10', while NMR spectra of pyrimidine 10da showed the coexistence of both tautomers.

Yields are reported in Table II. Physical data follow.

2,6-Bis(3-methoxyphenyl)-4-(1-hydroxystyr-2-yl)pyrimidine (10'ad): mp 124–125 °C; ¹H-NMR (200 MHz) δ 3.92 (s, 3 H, MeO), 3.94 (s, 3 H, MeO), 6.18 (s, 1 H, CH=), 7.27 (s, 1 H, H5), 7.34–8.09 (m, 14 H, ArH + OH); relevant ¹³C-NMR (200 MHz) δ 55.70 (q), 93.65 (d), 110.98 (d) 160.53 (s), 163.14 (s), 164.33 (s), 170.10 (s); MS m/z 410.1626 (M^+ $C_{22}H_{22}N_2O_3$ requires 410.1630, 99), 382 (34), 381 (28), 333 (10), 105 (100), 77 (49).

2,6-Diphenyl-4-(1-hydroxy-*o*-chlorostyr-2-yl)pyrimidine (17ca): mp 118–120 °C; ¹H-NMR (200 MHz) δ 5.99 (s, 1 H, CH=), 7.22 (s, 1 H, H5), 7.30–7.73 (m, 11 H, ArH + OH), 8.12–8.25 (m, 2 H, ArH), 8.40–8.55 (m, 2 H, ArH); relevant ¹³C-NMR (200 MHz) δ 98.35 (d), 110.69 (d), 163.23 (s), 163.57 (s), 172.25 (s); MS m/z 386 (M^+ , +2, 22), 384.1023 (M^+ $C_{24}H_{17}ClN_2O$ requires 384.1029,

56), 358 (16), 356 (42), 321 (92), 273 (31), 139 (100), 111 (30), 77 (49).

2,6-Diphenyl-4-(2-oxopent-1-yl)pyrimidine (17da): This compound exists as an equilibrium mixture of keto and enol tautomers in a 2:1 ratio, which gave a single spot by TLC analysis.

Mixture: mp 85–86 °C; MS m/z 316.15668 (M^+ $C_{21}H_{20}N_2O$ requires 316.15756; 39), 301 (11), 273 (18), 246 (100).

Keto tautomer: IR (CCl₄) 1718 cm⁻¹ (CO); ¹H-NMR (200 MHz) δ 0.94 (t, $J = 7.4$, 3 H, Me(CH₂)₂), 1.68 (m, $J = 7.4$, 2 H, MeCH₂CH₂), 2.64 (t, $J = 7.4$, 2 H, MeCH₂CH₂), 3.99 (s, 2 H, CH₂), 7.12 (s, 1 H, H5), 7.45–7.76 (m, 10 H, ArH); relevant ¹³C-NMR (200 MHz) δ 13.69 (q), 17.11 (t), 45.21 (t), 52.20 (t), 114.89 (d), 206.87 (s).

Enol tautomer: IR (CCl₄) 3420 cm⁻¹ (OH); ¹H-NMR (200 MHz) δ 1.02 (t, $J = 7.4$, 3 H, Me(CH₂)₂), 1.69–1.80 (m, 2 H, MeCH₂CH₂), 2.36 (t, $J = 7.2$, 2 H, MeCH₂CH₂), 5.48 (s, 1 H, CH=), 7.26 (s, 1 H, H5), 7.45–7.76 (m, 11 H, ArH + OH); relevant ¹³C-NMR (200 MHz) δ 13.85 (q), 20.17 (t), 39.07 (t), 95.06 (d), 109.75 (d), 178.08 (s).

Reaction of the α' -Dianion with Nitriles. A. Synthesis of Linear Products. A THF solution of the appropriate nitrile 4 (8 mmol) was added to a cooled (–50 °C) solution of the α' -dianion 3 (5 mmol), and the mixture was allowed to stir for 15 min under a nitrogen atmosphere. The solution was treated as described for pyridinamines (hexane/Et₂O (3:2) as eluant) to isolate compounds 11. When the crude product was adsorbed on the silica gel before chromatography a loss of product and the formation of a new product was observed. If the crude product was allowed to stand for 48 h on silica only the new product was then separated. It was recognized as a 4-pyridinone derivative 12. On the other hand, no formation of 12 was observed when the crude of reaction was submitted to the chromatographic purification without previous adsorption.

Yields and physical data for isolated compounds 11 follow.

1-Amino-5-(N-isopropylamino)-1-phenylocta-1,4-dien-3-one (11fa): 87%; mp 82.5–83.5 °C; IR (CCl₄) 3486, 3233 (NH₂) 1593 (C=O) cm⁻¹; ¹H-NMR (200 MHz) δ 1.00 (t, $J = 7.3$ H, Me(CH₂)₂), 1.25 (d, $J = 6.5$, 6 H, Me), 1.60 (m, 2 H, MeCH₂CH₂), 2.19 (t, $J = 7.3$, 2 H, MeCH₂CH₂), 3.74 (d hept, 1 H, CH), 4.85 (s, 1 H, CH=), 5.20 (s, 1 H, CH=), 7.32–7.63 (m, 7 H, ArH + NH₂), 10.55 (d, $J = 8.8$, 1 H, PrNH); ¹³C-NMR (200 MHz) δ 14.21 (q), 22.33 (t), 24.59 (q), 34.42 (t), 44.38 (d), 95.86 (d), 97.98 (d), 126.59 (d), 129.12 (d), 129.87 (d), 139.52 (s), 156.79 (s), 164.00 (s), 191.15 (s); MS m/z 272 (M^+ , 60), 229 (26), 214 (67), 185 (100), 146 (34), 126 (29). Anal. Calcd for $C_{17}H_{24}N_2O$: C, 75.0; H, 8.9; N, 10.3. Found: C, 75.2; H, 8.8; N, 10.3.

1-Amino-1,7-diphenyl-5-(N-isopropylamino)hepta-1,4-dien-3-one (11ga): 84%; oil; IR (CCl₄) 3486, 3234 (NH₂) 1584 (C=O) cm⁻¹; ¹H-NMR (200 MHz) δ 1.25 (d, $J = 6.2$, 6 H, Me), 2.4–3.0 (m, 4 H, CH₂CH₂), 3.74 (d hept, 1 H, CH), 5.29 (s, 2 H, CH=), 7.2–7.7 (m, 12 H, ArH + NH₂), 10.59 (d, $J = 9$, 1 H, PrNH); ¹³C-NMR (200 MHz) δ 24.57 (q), 34.19 (t), 35.50 (t), 44.49 (d), 95.88 (d), 97.82 (d), 126.63 (d), 126.76 (d), 128.31 (d), 128.66 (d), 128.98 (d), 129.22 (d), 129.99 (s), 130.19 (s), 157.10 (s), 163.11 (s), 190.86 (s); MS m/z 334 (M^+ , 46), 275 (66), 258 (24), 229 (28), 198 (87), 146 (55), 91 (39), 44 (100). Anal. Calcd for $C_{22}H_{26}N_2O$: C, 79.0; H, 7.8; N, 8.4. Found: C, 79.2; H, 7.9; N, 8.3.

1-Amino-5-(N-phenylamino)-1-phenylhexa-1,4-dien-3-one (11ha): 61%; mp 121–122 °C; IR (CCl₄) 3488, 3243 (NH₂) 1582 (CO) cm⁻¹; ¹H-NMR (200 MHz) δ 2.07 (s, 3 H, Me), 5.12 (s, 1 H, CH=), 5.29 (s, 1 H, CH=), 7.10–7.70 (m, 12 H, ArH + NH₂), 12.40 (s, 1 H, NHPH); ¹³C-NMR (200 MHz) δ 20.47 (q), 97.38 (d), 100.10 (d), 124.46 (d), 124.82 (d), 126.69 (d), 129.26 (d), 129.47 (d), 130.30 (d), 139.04 (s), 140.36 (s), 157.39 (s), 158.48 (s), 191.42 (s); MS m/z 278 (M^+ , 21), 185 (100), 93 (74). Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.7; H, 6.5; N, 10.1. Found: C, 77.5; H, 6.5; N, 10.3.

1-Amino-1-(2-chlorophenyl)-5-(N-phenylamino)hexa-1,4-dien-3-one (11hb): 88%; mp 63.6–64.3 °C; IR (CCl₄) 3497, 3244 (NH₂) 1572 (CO) cm⁻¹; ¹H-NMR (200 MHz) δ 2.03 (s, 3 H, Me), 5.00 (s, 1 H, CH=), 5.04 (s, 1 H, CH=), 7.02–7.57 (m, 11 H, ArH + NH₂), 12.43 (s, 1 H, NH); ¹³C-NMR (200 MHz) δ 20.41 (q), 99.59 (d), 99.81 (d), 124.54 (d), 124.93 (d), 127.40 (d), 129.51 (d), 130.53 (d), 130.64 (d), 132.20 (s), 138.10 (s), 140.28 (s), 156.58 (s), 157.76 (s), 191.46 (s); MS m/z 314 (M^+ , +2, 11), 312 (M^+ , 31), 220 (100), 184 (54), 118 (25), 93 (57), 77 (24). Anal. Calcd for $C_{18}H_{17}ClN_2O$: C, 69.1; H, 5.5; N, 9.0. Found: C, 69.0; H, 5.5; N, 9.1.

6-Amino-2-(*N*-phenylamino)deca-2,5-dien-4-one (11hf): 83%; oil; IR (CCl₄) 3496, 3239 (NH₂) 1572 (CO) cm⁻¹; ¹H-NMR (200 MHz) δ 0.87 (t, *J* = 7.3, 3 H, Me(CH₂)₃), 1.2-1.7 (m, 4 H, Me(CH₂)₂CH₂), 2.31 (s, 3 H, Me), 2.55 (t, *J* = 7.6, 2 H, Me(CH₂)₂CH₂), 6.14 (s, 1 H, CH=), 6.15 (s, 1 H, CH=), 6.6-6.8 and 7.0-7.2 (m, 7 H, ArH + NH₂), 12.17 (br s, 1 H, NH); ¹³C-NMR (200 MHz) δ 13.87 (q), 19.16 (q), 22.35 (t), 31.24 (t), 33.02 (t), 114.07 (d), 115.04 (d), 115.53 (d), 118.74 (d), 129.46 (s), 129.69 (d), 149.69 (s), 154.04 (s), 180.72 (s); MS *m/z* 258 (M⁺, 48), 201 (19), 166 (100), 160 (86), 126 (61). Anal. Calcd for C₁₈H₂₂N₂O: C, 74.4; H, 8.6; N, 10.8. Found: C, 74.5; H, 8.7; N, 10.7.

B. Synthesis of 4-Pyridinones. Method A. Products 11ga, ha, hb (2 mmol) were dissolved in 10 mL of 10% hydrochloric acid in methanol. The solution was stirred at room temperature for 45 min, evaporated, neutralized with aqueous NaHCO₃, extracted with ether, washed with water, dried, and evaporated under reduced pressure, and the residue submitted to a chromatographic separation with silica gel (hexane:ether:methanol = 2:2:1 as eluant).

Method B. A THF solution of the appropriate nitrile 4 (8 mmol) was added to a cooled (-50 °C) solution of the α-dianion (5 mmol), and the mixture was allowed to stir for 15 min under a nitrogen atmosphere. The solution was poured into 10% aqueous HCl and then treated as described above.

Yields of compounds 12 are reported in Table IV. Physical data for isolated compounds 12 follow.

2-Methyl-6-phenyl-4(1*H*)-pyridinone (12ha) and 2-phenyl-6-(2-phenylethyl)-4(1*H*)-pyridinone (12ga) were recognized by comparison with data of literature.³

2-Methyl-6-(2-chlorophenyl)-4(1*H*)-pyridinone (12hb): mp 83-86 °C; IR (CCl₄) 3420 (NH) 1623 (C=O) cm⁻¹; ¹H-NMR (200 MHz) δ 2.33 (s, 3 H, Me), 5.98 (d, *J* = 1.9, 1 H, H3 or H5), 6.05 (d, *J* = 1.9, 1 H, H5 or H3), 7.20-7.42 (m, 5 H, ArH + NH); MS *m/z* 221 (16), 219 (M⁺, 47), 184 (100). Anal. Calcd for C₁₂H₁₀NOCl: C, 65.6; H, 4.6; N, 6.4. Found: C, 65.5; H, 4.7; N, 6.4.

X-ray Data Collection and Structure Refinement. Diffraction data were collected on a Siemens R3m/V automatic

four-circle diffractometer, using a graphite-monochromated MoKα radiation. A 0.12 × 0.36 × 0.51 mm crystal was used for intensity data collection. Lattice parameters were obtained from least-squares refinement of the setting angles of 25 reflections in the 15 ≤ 2θ ≤ 30° range. Lorentz-polarization corrections were applied to the intensity data.

The structures were solved by standard direct methods and subsequently completed by Fourier recycling. The full-matrix least-squares refinement was based on |F_o|. The non-hydrogen atoms, except C atoms of the phenyl groups, were refined anisotropically. All hydrogen atoms were set in calculated positions and refined as riding atoms, with a common thermal parameter. The final *R* values were 0.069, *R'* = 0.079. The weighting scheme used in the last refinement cycles was *w* = 1.0000/*s*²(F_o) + 0.006000(F_o)².

Solutions and refinements were performed with the SHELXL-PLUS system (1989).¹⁸ The final geometrical calculations were performed with the PARST¹⁹ program. Additional material is available from the Cambridge Crystallographic Data Centre.

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Supplementary Material Available: Conditions of crystallographic data collection and structure refinement, tables of atom coordinates, thermal parameters, relevant least-squares planes, possible H-bonds, and bond lengths and angles, and an ORTEP drawing and view of the cell (13 pages). This material is contained in many 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.

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Epoxidation of 5-(Tosylamido)-3-hexen-2-ol Derivatives. Stereochemical Assignment of Product Configuration by NMR and Molecular Mechanics Studies

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Epoxidation of *syn*- and *anti*-5-(tosylamido)-3-hexen-2-ol derivatives was studied using three different epoxidation reagents: (i) *m*-CPBA, (ii) *t*-BuOOH/VO(acac)₃, and (iii) *t*-BuOOH/Ti(O-*i*-Pr)₄. A method for the stereochemical assignment of the 3,4-epoxy-5-(tosylamido)-3-hexen-2-ol derivatives obtained was developed by the use of NMR spectroscopy.

Palladium-catalyzed 1,4-oxidations of conjugated dienes offer unique opportunities to obtain 1,4-stereocontrol in both cyclic and acyclic systems.¹⁻³ In particular, 1,4-chloroacetates and 1,4-diacetates obtained from such oxidations have proved useful in this respect, and recently their use for obtaining a *dual* 1,4-stereocontrol in acyclic

systems was demonstrated.^{4,5} In one application *syn*- and *anti*-amido alcohols 1 were transformed into *cis* 2,5- and *trans* 2,5-disubstituted pyrrolidines 2, respectively, via hydrogenation and ring closure (Scheme I). The synthetic utility of this methodology would be further enhanced by stereoselective mono or dihydroxylation of the double bond prior to cyclization.⁶ In this way stereodefined pyrrolidine

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