New Routes to Enaminones and Dienaminones from Benzotriazole Derivatives

Alan R. Katritzky,* Richard A. Barcock, Qui-He Long, Marudai Balasubramanian, Nageshwar Malhotra, John V. Greenhill

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-2046, USA

Received 11 June 1992

A new method has been developed for the regioselective preparation of enaminones and dienaminones starting from *N*-[1-(4-methylphenylamino)ethyl]benzotriazole employing mild conditions. Thus, 1-substituted 3-(4-methylphenylamino)-2-propen-1-ones, 1-(4-methylphenylamino)-1-hexen-3-one, ethyl 3-(4-methylphenylamino)-2-propenoate, 1-cyclohexyl-5-(phenylamino)-2,4-pentadien-1-one and ethyl 5-(arylamino)-2,4-pentadienoates are prepared in good yields.

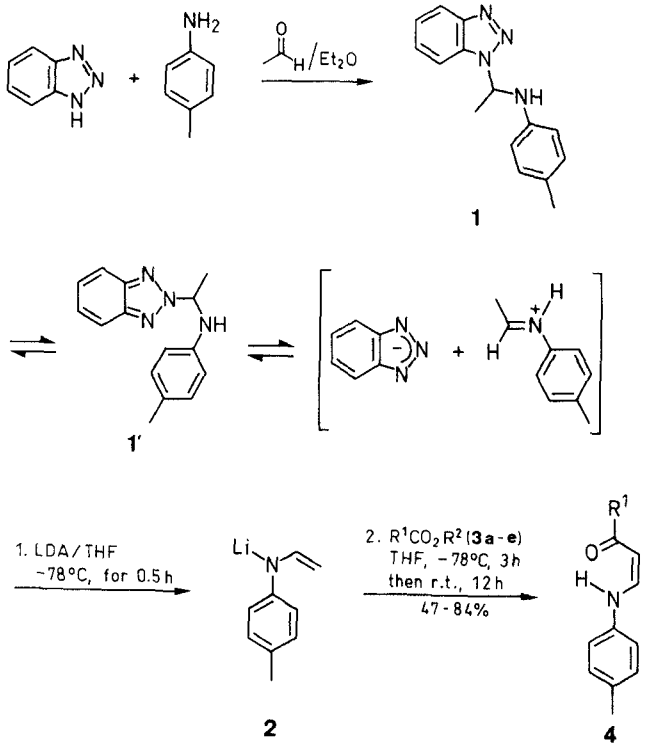
The reactivities of enaminones and dienaminones make them attractive intermediates for the preparation of heterocycles. Oxazoles, pyridinones, quinolines, dibenzodiazepines, tetrahydrobenzoxazines, tetronic acids, tetrahydrophenanthridines and aza steroids have all been made from enaminones.[1-3] New syntheses of pyranones and pyridine derivatives have recently been developed.[4] Enaminones are also valuable in other synthetic procedures. For example, a recently published method allows the carbon chain of a 1,3-dione to be extended by the alkylation of the dianion of a derived enaminone.[5]

Enaminones are commonly prepared from amines and 1,3-diketones, a successful procedure both for symmetrical 1,3-diketones[6] and for compounds containing two carbonyl groups exhibiting substantially different reactivity;[7,8] otherwise, mixtures are obtained which are often difficult to separate. Other methods of preparation include the addition of amines to acetylenic ketones,[9] reactions between formamide dimethylacetals and ketones,[10-12] β-chlorovinyl ketones and amines,[13] β-dialkoxy ketones and amines,[14] and ring-opening of isoxazoles with samarium diiodide.[15] Also, a number of β-amino ketones have been dehydrogenated under the influence of palladium chloride to give enaminones.[16] More recently reported preparations include the reaction of imine anions with esters[17] and the heating of triethyl orthoformate, a ketone and a secondary amine under pressure.[18] However, all these methods have limitations with respect to the availability of the starting materials, the involvement of several steps and, in the last example, the prolonged use of high temperatures.

Dienaminones like 5-aminopentadienoic esters are potentially valuable for the synthesis of 2-pyridinones. A number of such esters have been reported, but most are derived from malonic esters, acetoacetic esters or other active methylene compounds via aldol condensations.[19,20] The only unbranched example found resulted from the conjugate addition of diethylamine to ethyl 2-penten-4-ynoate.[21] Also, 5-acetyl-2-pyranone and aniline have been reacted to give 4-acetyl-5-(phenylamino)-2,4-pentadienoic acid.[22]

It has been reported that metalated imines are alkylated at the β-carbon by alkyl halides[23-26] and acylated by esters to yield enaminones.[17] The high reactivity of α-metalated imines[27] and a recent report of their preparation in situ by a base-catalyzed displacement of cyanide from an α-aminonitrile[28] stimulated us to examine the value of benzotriazole intermediates as a route to enaminones via a one-pot procedure. Previous work in our group has shown that *N*-(arylaminoalkyl)benzotriazoles can be generated successfully in high yields from the condensation of benzotriazole, aldehydes and aromatic amines.[29] We have applied this methodology to the synthesis of *N*-[1-(4-methylphenylamino)ethyl]benzotriazole **(1)**, which exists in solution as a mixture of the 1-benzotriazol-yl and 2-benzotriazol-yl isomers as evidenced by its ^1H and ^{13}C NMR spectra.

Treatment of benzotriazole derivative **1** with 2.5 equivalents of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C for 0.5 hours followed by reaction with esters **3a–e** at −78 °C for 3 hours, gave the derived enaminones **4** in high to moderate yield (84–47%). We envisage the reaction proceeding as shown in Scheme 1. Deprotonation of the secondary amine **1**, with concomitant elimination of benzotriazole, followed by further deprotonation gives the *N*-metalated imine **2**. Addition of esters **3** furnishes the mesomerically stabilized enaminones **4**. The enaminone structures of compounds **4** were



3,4	R^1	3	R^2	3,4	R^1	3	R^2
a	Ph	a	Me	d	Pr	d	Me
b	OEt	b	Et	e	1-naphthyl	e	Me
c	*c*-C_6H_{11}	c	Me				

Scheme 1

Table 1. Enaminones **4** Prepared

Product	Yield[a] (%)	mp (°C) bp (°C) Torr	Molecular Formula or Lit. mp (°C)	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)
4a	84	156–158[b]	157–160[33]	2.31 (s, 3 H), 5.98 (d, 1 H, J = 7.8), 6.99 (d, 2 H, J = 8.4), 7.13 (d, 2 H, J = 8.4), 7.13 (d, 2 H, J = 8.4), 7.43–7.51 (m, 4 H), 7.93 (d, 2 H, J = 7.9)
4b	75	110/0.2	$C_{12}H_{15}NO_2$[d] (205.1)	1.30 (t, 3 H, J = 7.0), 2.30 (s, 3 H, 4.20 (q, 2 H, J = 7.0), 4.80 (d, 1 H, J = 8.3), 6.80 (d, 2 H, J = 8.4), 7.10 (d, 2 H, J = 8.4), 7.20 (dd, 1 H, J = 12.8, 8.3), 9.90 (br, 1 H)
4c	65	130–132[b] (243.1)	$C_{16}H_{21}NO$[c] (243.1)	1.26–1.84 (m, 11 H), 2.28 (s, 3 H), 5.28 (d, 1 H, J = 7.8), 6.89 (d, 2 H, J = 8.1), 7.09 (d, 2 H, J = 8.5), 7.25 (d, 1 H, J = 7.8), 11.70 (br, 1 H)
4d	47	98/0.2	$C_{13}H_{17}NO$[d] (203.1)	0.96 (t, 3 H, J = 7.8), 1.66 (m, 2 H), 2.28 (s, 3 H), 2.36 (t, 3 H, J = 7.8), 5.25 (d, 1 H, J = 7.8), 6.89 (d, 2 H, J = 8.1), 7.09 (d, 2 H, J = 8.1), 7.18 (dd, 1 H, J = 12.9, 7.8), 11.65 (br, 1 H)
4e	64	136–138[b]	$C_{20}H_{17}NO$[c] (287.1)	2.33 (s, 3 H), 5.78 (d, 1 H, J = 7.8), 7.03 (d, 2 H, J = 8.1), 7.16 (d, 2 H, J = 8.1), 7.45–7.55 (m, 4 H), 7.72 (d, 1 H, J = 7.1), 7.85–7.91 (t, 2 H, J = 8.1), 8.52 (d, 1 H, J = 9.2), 12.20 (br, 1 H)

[a] Yield of isolated product **4** based on **1**.
[b] From MeOH.
[c] Satisfactory microanalyses obtained: C ± 0.17, H ± 0.14, N ± 0.07.
[d] Compounds are oils; characterized by HRMS.

Table 2. Enaminones **4** Prepared, ^{13}C NMR ($CDCl_3$) δ

Product	C=O	C-2	C-3	Others
4a	190.7	93.2	145.3	20.7, 116.3, 127.2, 128.3, 130.2, 131.4, 133.4, 137.7, 139.2
4b	170.4	86.5	143.4	14.4, 20.5, 59.1, 115.3, 129.8, 129.9, 130.0
4c	204.8	95.2	144.0	20.7, 25.7, 25.9, 29.6, 29.7, 50.3, 115.9, 130.1, 132.9, 137.9
4d	201.6	96.4	143.3	13.9, 18.8, 20.6, 44.3, 96.4, 115.9, 130.1, 132.8, 137.9
4e	195.0	97.9	145.0	20.8, 116.4, 124.7, 125.8, 125.9, 126.0, 126.8, 128.2, 130.17, 130.24, 130.5, 133.5, 133.8, 137.7, 139.1

Table 3. Dienaminones **8** Prepared

Product	Yield[a] (%)	Molecular Formula	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)
8a	61	$C_{13}H_{15}NO_2$ (217.1)	1.19 (t, 3 H, J = 7.0), 4.19 (q, 2 H, J = 7.0), 4.83 (m, 2 H, 5.08 (m, 1 H), 6.32 (m, 1 H), 7.17 (m, 2 H), 7.41 (m, 4 H)
8b	67	$C_{14}H_{17}NO_2$ (231.1)	1.20 (t, 3 H, J = 7.0), 4.81 (m, 2 H), 5.10 (m, 1 H), 6.30 (m, 1 H), 7.03 (d, 2 H, J = 8.0), 7.23 (d, 2 H, J = 8.0), 7.42 (d, 1 H, J = 14.0)
8c	58	$C_{15}H_{19}NO_2$ (245.1)	1.18 (t, 3 H, J = 7.0), 2.08 (s, 3 H), 2.35 (s, 3 H), 4.20 (q, 2 H, J = 7.0), 4.80 (m, 2 H), 4.96 (m, 1 H), 6.32 (m, 1 H), 7.10 (m, 3 H), 7.40 (br, 1 H)
8d	63	$C_{14}H_{17}NO_3$ (247.1)	1.20 (t, 3 H, J = 7.0), 3.84 (s, 3 H), 4.20 (q, 2 H, J = 7.0), 4.85 (m, 2 H), 5.08 (m, 1 H), 6.32 (m, 1 H), 6.95 (d, 2 H, J = 9.0), 7.10 (d, 2 H, J = 9.0), 7.40 (d, 1 H, J = 14.0)
8e	62	$C_{15}H_{19}NO_2$ (245.1)	1.26 (t, 3 H, J = 7.0), 1.42 (d, 3 H, J = 1.2), 1.77 (dd, 3 H, J = 6.5, 6.6), 4.22 (q, 2 H, J = 7.0), 5.68 (m, 1 H), 6.14 (d, br, 1 H, J = 14.0), 6.36 (s, 1 H), 7.14–7.26 (m, 6 H)
8f	45	$C_{17}H_{21}NO$[c] (255.2)	0.90–1.68 (m, 11 H), 5.02 (dd, 1 H, J = 14.2, 10.7), 6.35 (m, 1 H), 7.18 (d, 2 H, J = 7.8), 7.51 (m, 3 H), 7.71 (d, 1 H, J = 13.4)

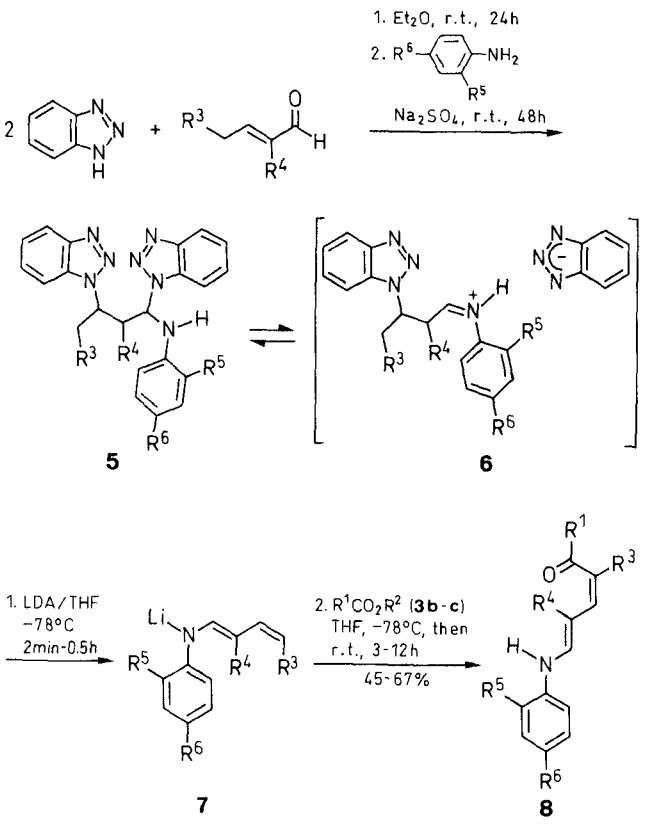
[a] Yield of isolated product **8** based on **5**
[b] Compounds are oils; characterised by HRMS.
[c] Yellow crystals, mp 95–97°C (dec). Some decomposition of product pbserved during chromatography; characterized by HRMS.

Table 4. Dienaminones **8** Prepared, ^{13}C NMR ($CDCl_3$), δ

Product	$\underline{C}H_3CH_2$	$CH_3\underline{C}H_2$	C-.2/C-4	C-3/C-5	C=O	Aryl-C	Others
8a	14.2	62.3	112.8, 113.3	132.7, 134.6	153.4	127.9, 128.4 (2C), 129.2 (2C), 137.9	
8b	14.3	62.3	112.8, 113.2	132.9, 134.6	153.6	128.2 (2C), 130.0 (2C), 135.2, 137.8	21.1
8c	14.4	62.2	112.1, 113.1	133.9, 134.8	153.7	127.7, 128.3, 131,7, 132.0, 135.6, 138.1	17.0. 21.0
8d	14.3	62.4	112.7, 113.2,	133.2, 134.8	153.7	114.5 (2C), 129.5 (2C), 130.6, 159.0	55.3
8e	14.4	62.0	124.3, 125.2	130.0, 132.2	154.6	125.6 (2C), 127.0, 128.5 (2C), 141.9	12.3, 18.2
8f			114.2, 114.9	128.7, 132.1	174.7	128.8 (2C), 128.9 (2C), 135.0, 138.9	25.3, 25.4 (2C), 29.3 (2C), 42.2

confirmed by ^{1}H NMR spectrometry. The size of the coupling constant $J_{CH=CH}$ (7.8–8.3 Hz) suggests the *cis* configuration, as shown.

This general method was also applied to the generation of some dienaminone derivatives. Previous work in our group has demonstrated that dienamines can be generated[30] using methodology similar to that applied to enamines.[31] Benzotriazole (2.0 equivalents), an α,β-unsaturated aldehyde (1.0 equivalent) and a primary arylamine (1.0 equivalent) gave the 1,3-bis(benzotriazolyl) substituted arylamines **5** as isomer mixtures of diastereomers and the various 1- and 2-benzotriazolyl derivatives so that the NMR was complex and impossible to assign.[32] The products were too unstable to be recrystallized for elemental analysis and lost the benzotriazole groups too readily in the mass spectrometer to allow accurate mass measurements of the parent ions. However, they could be isolated and kept for a few weeks at 5 °C. Treatment of the bis-substituted benzotriazole derivatives **5** with 3.0 equivalents of LDA in THF at −78 °C followed by reaction with esters **3b,c**, gave the derived dienones **8** in respectable yields (67–45 %). We envisage the reaction pathway proceeding as shown in Scheme 2. Compounds **5** have a tendency towards facile ionization in solution to form intermediates **6** which can be deprotonated sequentially giving access to the lithiated dienamines **7**, which in turn react with the electrophilic esters to provide dienaminones **8**.



5	R^3	R^4	R^5	R^6	8	R^1	R^3	R^4	R^5	R^6
a	H	H	H	H	**a**	OEt	H	H	H	H
b	Me	Me	H	H	**b**	OEt	H	H	H	Me
c	H	H	H	Me	**c**	OEt	H	H	Me	Me
d	H	H	Me	Me	**d**	OEt	H	H	H	OMe
e	H	H	H	OMe	**e**	OEt	Me	Me	H	H
					f	*c*-C_6H_{11}	H	H	H	H

Scheme 2

In summary, we have described a novel method for the preparation of enaminones and dienaminones. In view of the readily accessible starting materials and very easy manipulation of the reaction, this method is a viable alternative to previously reported procedures.

Melting points were determined with a Köfler hot-stage microscope and are uncorrected. ^{1}H NMR (300 MHz) spectra were recorded on a Varian VXR 300 spectrometer in $CDCl_3$ solutions with TMS as internal standard. ^{13}C NMR (75 MHz) spectra were recorded on the same instrument with $CDCl_3$ (δ = 77.0) as reference. Microanalyses were obtained using a Carlo Erba 1106 elemental analyzer at the University of Florida. High resolution mass spectra were recorded on an AEI MS 30 mass spectrometer. Esters **3a–e** were purchased commercially and were distilled prior to use. LDA was purchased from Aldrich as a 1.5 M solution in cyclohexane or as a 2.0 M solution in heptane/THF/ethylbenzene. THF was distilled from sodium benzophenone ketyl under N_2 prior to use. All moisture sensitive reactions were carried out in a dry Ar atmosphere.

1- and 2-[1-(4-Methylphenylamino)ethyl]benzotriazole (1):
This new compound was prepared according to the literature procedure.[29] The product obtained after trituration with Et_2O, was pure by ^{1}H NMR, and used as such in further reactions; yield: 91 %. An analytical sample was obtained after recrystallization from EtOH, white plates; mp 96–97 °C.

$C_{15}H_{16}N_4$ calc. C 71.43 H 6.35 N 22.22
found 71.28 6.29 22.54

MS: *m/z* (%) = 252 (M^+, not seen); 133 (65); 118 (65); 91 (100); 65 (35).

^{1}H NMR ($CDCl_3$/TMS); (a mixture of 1- and 2-benzotriazolyl isomers): δ = 1.92 (d, J = 7.0 Hz); 1.95 (d, J = 7.0 Hz); 2.14 (s); 2.16 (s); 4.70 (d, J = 10.5 Hz); 4.98 (d, J = 7.9 Hz); 6.52 (m); 6.60 (d, J = 8.5 Hz); 6.68 (d, J = 8.5 Hz); 6.92 (m); 7.31–7.44 (m); 7.72 (d, J = 8.3 Hz); 7.83 (m); 8.04 (d, J = 8.3 Hz).

^{13}C NMR ($CDCl_3$): δ = 20.3, 20.4, 22.3, 22.9, 67.5, 72.5, 110.3, 113.9, 114.2, 118.2, 120.1, 123.9, 126.2, 127.2, 129.0, 129.8, 131.3, 141.8, 142.0, 143.9, 146.5

1-Substituted 3-(4-Methylphenylamino)-2-propen-1-ones (4a,c,e), 1-(4-methylphenylamino)-1-hexen-3-one (4d) and Ethyl 3-(4-Methylphenylamino)-2-propenoate (4b); General Procedure:
LDA (2.5 mL, 5 mmol) was added dropwise to a solution of *N*-[1-(4-methylphenylamino)ethyl]benzotriazole (**1**; 0.50 g, 2 mmol) in THF (30 mL) at −78 °C and stirred at this temperature for 0.5 h. A solution of the ester **3** (2 mmol) in THF (2 mL) was added and stirring continued at −78 °C for 3 h and the reaction allowed to warm to r.t. and stand overnight (12 h). The solvent was removed in vacuo, the residue taken up in EtOAc (30 mL) and washed with NaOH (10 % w/w, 3 × 15 mL), H_2O (2 × 15 mL), brine (15 mL), and dried ($MgSO_4$). The solvent was removed to yield the crude products which were purified by vacuum distillation for **4b–d**, or by trituration with hexane for **4a,e** (Tables 1 and 2).

***N*-[1,3-bis(benzotriazolyl)alkyl]arylamines 5: General Procedure:**[32]
A mixture of the α,β-unsaturated aldehyde (20 mmol) and benzotriazole (4.76 g, 40 mmol) in Et_2O (40 mL) was stirred at r.t for 24 h. The arylamine (20 mmol) followed by anhydr. Na_2SO_4 (6.0 g) was added and stirring continued for 48 h. The mixture was filtered and the solvent evaporated in vacuo to give the product **5** as a solid, which was washed with Et_2O (40 mL), and used without further purification.

Ethyl 5-(Arylamino)-2,4-pentadienoates 8a–e: General Procedure:
LDA (7.8 mmol) was added dropwise to a stirred solution of the *N*-[1,3-bis(benzotriazolyl)alkyl]arylamine **5** (2.6 mmol) in THF (30 mL) at −78 °C. After 2 min, diethyl carbonate (2.6 mmol) was added and the solution allowed to warm to r.t. and stirred for a further 6 h. The solvent was removed in vauco and the residue partitioned between H_2O (20 mL) and CH_2Cl_2 (20 mL). The organic layer was washed with Na_2CO_3 (10% w/w, 20 mL) and H_2O (20 mL) and dried (K_2CO_3). The solvent was removed in vacuo to give the crude product which was purified on a silica gel column (20 cm × 2 cm; 230–400 mesh) using CH_2Cl_2 as eluant (Tables 3 and 4).

1-Cyclohexyl-5-(phenylamino)-2,4-pentadien-1-one (8f):
LDA (4.6 mmol) was added dropwise to a stirred solution of *N*-[1,3-bis(benzotriazolyl)butyl]phenylamine (0.50 g, 1.3 mmol) in THF (15 mL) at −78 °C. The mixture was stirred at −78 °C for 0.5 h and methyl cyclohexanecarboxylate (0.18 g, 1.30 mmol) was added dropwise. Stirring was continued at −78 °C for 3 h and at r.t. for a further 12 h. The solvent was removed in vacuo and the residue taken up into EtOAc (40 mL), washed with NaOH (8% w/w, 3 × 15 mL), H_2O (2 × 15 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the crude product purified by flash column chromatography using alumina (neutral, activity 1, 80–200 mesh) and hexane/EtOAc (4:1) as eluant, to give yellow crystals (Tables 3 and 4).

(1) Greenhill, J.V. *Chem. Soc. Rev.* **1977**, *6*, 277.
(2) Chaaban, I.; Greenhill, J.V.; Akhtar, P. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1593.
(3) Greenhill, J.V.; Moten, M.A.; Hanke, R.; Breitmeier, E.J. *Chem. Res. (S)* **1981**, 66.
(4) Takeuchi, N.; Handa, S.; Koyama, K.; Kamata, K.; Goto, K.; Tobinaga, S. *Chem. Pharm. Bull.* **1991**, *39*, 1655.
(5) Bartoli, G.; Bosco, M.; Cimarelli, C.; Dalpozzo, R.; Palmieri, G. *Synlett* **1991**, 229.
(6) Azzaro, M.; Geribaldi, S.; Videau, B. *Synthesis* **1981**, 880, and references cited therein.
(7) Brown, N.M.D.; Nonhebel, D.C. *Tetrahedron* **1968**, *24*, 5655.
(8) Singh, R.V.; Tandon, J.P. *J. Prakt. Chem.* **1979**, 151; *Chem. Abstr.* **1979**, *90*, 214461.
(9) Tripathi, V.K.; Venkataramani, P.S.; Mehta, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 36.
(10) Abdulla, R.F.; Brinkmeyer, R.S. *Tetrahedron* **1979**, *35*, 1675, and references cited therein.
(11) Schuda, P.F.; Ebner, C.B.; Morgan, T.M. *Tetrahedron Lett.* **1986**, *27*, 2567.
(12) Tseng, S.-S.; Epstein, J.W.; Brabander, H.J.; Frncisco, G. *J. Heterocycl. Chem.* **1987**, *24*, 837.
(13) Pohland, A.E.; Benson, W.R. *Chem. Rev.* **1966**, *66*, 161.
(14) Maggiulli, C.A.; Tang, P.-W. *Org. Prep. Proced. Int.* **1984**, *16*, 31.
(15) Natale, N.R. *Tetrahedron Lett.* **1982**, *23*, 5009.
(16) Murahashi, S.-I.; Tsumiyama, T.; Mitsue, Y. *Chem. Lett.* **1984**, 1419.
(17) Bartoli, G.; Cimarelli, C.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Synthesis* **1990**, 895.
(18) El Cherif, S.; René, L. *Synthesis* **1988**, 138.
(19) DeGraw, J.I.; Tagawa, H. *J. Heterocycl. Chem.* **1982**, *19*, 1461.
(20) Nair, V.; Cooper, C.S. *J. Org. Chem.* **1981**, *46*, 4759.
(21) Krasnava, Zh.A.; Stytsenko, T.S.; Prokof'ev, E.P.; Kucherov, V.A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1973**, *9*, 2008; *Chem. Abstr.* **1974**, *80*, 59397.
(22) Shusherina, N.P.; Lapteva, V.L.; Khrushcheva, O.V. *Zh. Org. Khim.* **1977**, *13*, 1930; *Chem. Abstr.* **1978**, *88*, 22095.
(23) De Kimpe, N.; Stevens, C. *Bull. Soc. Chim. Belg.* **1990**, *99*, 41.
(24) Mistryukov, E.A.; Korshevetz, I.K. *Synthesis* **1984**, 947.
(25) Fraser, R.R.; Banville, J.; Dhawan, K.L. *J. Am. Chem. Soc.* **1978**, *100*, 7999.
(26) Fraser, R.R.; Akiyama, F.; Banville, J. *Tetrahedron Lett.* **1979**, 3929.
(27) Stork, G.; Dowd, S.R. *J. Am. Chem. Soc.* **1963**, *85*, 2178.
(28) Kudzma, L.V.; Spencer, H.K.; Severnak, S.A. *Tetrahedron Lett.* **1988**, *29*, 6827.
(29) Katritzky, A.R.; Rachwal, S.; Rachwal, B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 799.
(30) Katritzky, A.R.; Long, Q.-H.; Lue, P. *Tetrahedron Lett.* **1991**, *32*, 3597.
(31) Katritzky, A.R.; Long, Q.-H.; Lue, P.; Jozwiak, A. *Tetrahedron* **1990**, *46*, 8153.
(32) Katritzky, A.R.; Rachwal, S.; Hughes, C.V.; Wang, Z. unpublished results.
(33) Clesse, F.; Quiniou, H. *Bull. Soc. Chim. Fr.* **1969**, 1940.