Synthesis of Highly Functionalized Pyrrole Derivatives via a Four-Component Reaction of Two Primary Amines and Diketene in the Presence of Nitrostyrene

Abdolali Alizadeh,* Atieh Rezvanian, Hamid R. Bijanzadeh

Department of Chemistry, Tarbiat Modares University, P.O. Box 14115-175, Tehran 18716, Iran
Fax +98(21)88006544; E-mail: abdol_alizad@yahoo.com; E-mail: aalizadeh@modares.ac.ir

Received 7 November 2007; revised 2 December 2007

Abstract: The one-pot synthesis of highly functionalized pyrrole derivatives from the reaction of an enaminone, which can be derived from the reaction between two primary amines and diketene, in the presence of nitrostyrene is described. The reaction occurred under neutral conditions and in excellent yields.

Key words: amine, diketene, enaminones, nitrostyrene, pyrrole, multicomponent reaction

N-Heterocycles receive considerable attention in the literature as a consequence of their exciting biological properties and their role as pharmacophores.[1] Of these heterocycles, the pyrrole ring is one of the most fundamental.[2] Pyrrole and its derivatives are ubiquitous among naturally occurring organic compounds.[3] They can take part in several stereoselective transformations, such as conjugate additions,[4] cycloadditions,[5] acyliminium ion chemistry,[6] and allylic substitutions.[7] The synthesis, reactions and biological activities of pyrroles stand as an area of research in heteroaromatic chemistry and this structural motif appears in a large number of pharmaceutical agents and natural products.[8,9]

Pyrrole and several pyrrole derivatives, especially the methyl homologues, are found in coal-tar and bone oil. The biological importance of pyrrole and its derivatives cannot be overemphasized because several natural pigments, such as heme, chlorophyll and bile pigments, or enzymes like the various cytochromes, include the pyrrole nucleus. Many alkaloids and at least two amino acids, namely, proline and hydroxyproline, also contain the reduced pyrrole ring (pyrrolidine).[10]

An interesting and versatile pyrrole synthesis involves enamines and enaminones.[11–13] Enaminones are versatile, readily obtainable reagents and their chemistry has received considerable attention in recent years.[14–17] The enaminones are thus an important class of organic synthetic intermediates. They have a very high impact as synthons for the synthesis of various heterocyclic and biologically active analogues,[18] including anticonvulsant,[19] anti-inflammatory[20] and antitumor agents,[21] dopamine auto-receptor agonists, acetylcholinesterase inhibitors and oxytocin antagonists.[22]

SYNTHESIS 2008, No. 5, pp 0725–0728
Advanced online publication: 08.02.2008
DOI: 10.1055/s-2008-1032168; Art ID: Z25407SS

In the context of our ongoing studies on heterocyclic construction mediated by the enaminone intermediate,[23,24] the possibility of trapping the intermediate formed between two primary amines and diketene with nitrostyrene, appeared attractive from the viewpoint of devising a novel multicomponent reaction (MCR).

In the present work, we wish to report a novel one-pot, four-component reaction between an enaminone, derived from the addition of various primary amines to diketene, and nitrostyrene, leading to highly functionalized 1*H*-pyrrole-3-carboxamide derivatives **4**.

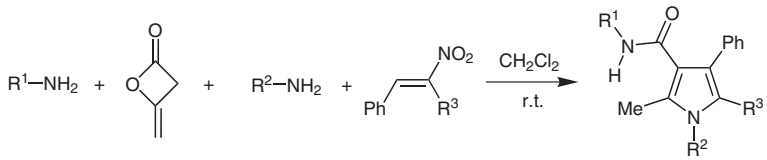
The reaction of *N*-alkyl-3-oxobutanamide **5**, which was derived from the addition of a primary amine **1** to diketene, with primary amine **2** in dichloromethane at ambient temperature, leads to enaminocarbonyl compound **6** (Scheme 1). Subsequently, reaction of these in situ prepared enaminones **6** with nitrostyrene leads to pyrrole derivatives **4** in 80–90% yields. (Table 1).

The structures of compounds **4a**–**g** were deduced from their elemental analysis, IR, and high-field ^{1}H and ^{13}C NMR spectra. No products other than **4** could be detected. The mass spectrum of **4a** displayed the molecular ion peak at $m/z = 298$, which is consistent with the 2,5-dimethyl-4-phenyl-*N*^{3},1-dipropyl-1*H*-pyrrole-3-carboxamide structure.

The ^{1}H NMR spectrum of **4a** exhibited nine signals that were readily recognized as arising from four methyl groups (δ = 0.63 ppm, t, $^3J_{H–H}$ = 7.3 Hz; δ = 0.98 ppm, t, $^3J_{H–H}$ = 7.4 Hz; δ = 2.08, s and δ = 2.58 ppm, s), four methylenes (δ = 1.14–1.22, m; δ = 1.66–1.73 ppm, m; δ = 3.08 ppm, q, $^3J_{H–H}$ = 5.8 Hz; δ = 3.76 ppm, t, $^3J_{H–H}$ = 7.7 Hz) and an NH group (δ = 4.96 ppm). The phenyl moiety gave rise to characteristic signals in the aromatic region of the spectrum. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 17 distinct resonances that were in agreement with the 2,5-dimethyl-4-phenyl-*N*^{3},1-dipropyl-1*H*-pyrrole-3-carboxamide structure. The ^{1}H and ^{13}C NMR spectra of compounds **4b**–**e** were similar to those of **4a**, except for the aromatic moiety, which exhibited characteristic signals with appropriate chemical shifts for the specific substitution patterns.

Although the mechanism of the reaction between nitrostyrene **3** and enaminone **6**, has not yet been established in an experimental manner, a possible explanation is proposed in Scheme 2. On the basis of the well-established chemistry of enaminone nucleophiles,[25] it is reasonable to as-

Table 1 Reaction of Amines **1**, **2** and Diketene in the Presence of Nitrostyrene **3**

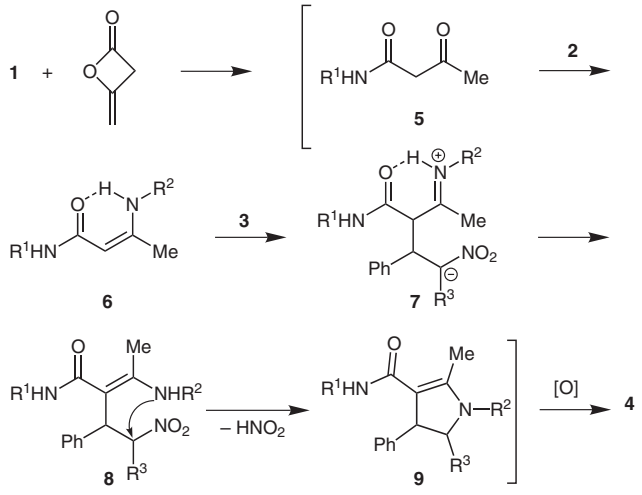


1 2 3 4

4	R^1	R^2	R^3	Yield of **4** (%)
a	Pr	Pr	Me	90
b	*t*-Bu	Pr	Me	90
c	*i*-Bu	Pr	Me	85
d	allyl	Pr	H	90
e	Pr	allyl	H	80
f	*t*-Bu	allyl	H	85
g	*i*-Bu	*i*-Bu	H	90

sume that **4** results from reaction of the primary amine **2** with *N*-alkyl-3-oxobutanamide **5** (which is derived from the addition of primary amine **1** to diketene) and subsequent attack of the resulting reactive enamine **6** on the nitrostyrene, to yield a betaine **7** that rearranges to intermediate **8**. Cyclization of the intermediate **8** and subsequent loss of a nitrite anion leads to intermediate **9**. Finally, intermediate **9** apparently oxidizes[26] under the reaction conditions employed, to produce compound **4** (Scheme 1).

In conclusion, we have demonstrated a simple and novel synthesis of pyrrole derivatives in a one-pot operation from primary amines, diketene and nitrostyrene. The present method carries the advantage that, not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modification. The simplicity of the present procedure makes it an interesting alternative to complex multistep approaches.



Scheme 1

Amines and diketene were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Nitrostyrene was prepared according to the literature procedure.[27,28] Elemental analyses (CHN) were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN MATT 8430 mass spectrometer, operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ with a Bruker DRX-500 Avance spectrometer at 500.1 and 125.8 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 230–240 mesh.

Synthesis of 2,5-Dimethyl-4-phenyl-*N*^{3},1-dipropyl-1*H*-pyrrole-3-carboxamide (4a); Typical Procedure

To a magnetically stirred solution of *n*-propylamine (0.059 g, 1 mmol) and diketene (0.084 g, 1 mmol) in anhyd CH_2Cl_2 (5 mL) was added, after ten minutes, *n*-propylamine (0.059 g, 1 mmol) via a syringe and the mixture was stirred at r.t. for 2 h. A solution of nitrostyrene (0.163 g, 1 mmol) in anhyd CH_2Cl_2 (5 mL) was added at r. t. over 10 min and the reaction mixture was allowed to stir for 3 h. On completion of the reaction, the solvent was removed under reduced pressure and the residue was separated by column chromatography (silica gel; hexane–EtOAc, 5:1) to give the product.

Yield: 0.27 g (90%); yellow oil.

IR (KBr): 3235 (NH), 1620 (CONH), 1530, 1454 (Ar) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.63 (t, ^3J = 7.3 Hz, 3 H, $CH_3CH_2CH_2N$), 0.98 (t, ^3J = 7.4 Hz, 3 H, $CH_3CH_2CH_2NH$), 1.14–1.22 (m, 2 H, $CH_3CH_2CH_2N$), 1.66–1.73 (m, 2 H, CH_2CH_2NH), 2.08 (s, 3 H, CH_3), 2.58 (s, 3 H, CH_3), 3.08 (q, ^3J = 5.8 Hz, 2 H, CH_2NH), 3.76 (t, ^3J = 7.7 Hz, 2 H, CH_2N), 5.11 (s, 1 H, NH), 7.27–7.39 (m, 5 H, Ph).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.30 ($CH_3CH_2CH_2NH$), 11.16 (CH_3CH_2CHN), 11.22 (CH_3), 11.28 (CH_3), 22.50 (CH_2CH_2NH), 23.91 (CH_2CH_2N), 40.74 (CH_2NH), 45.27 (CH_2N), 113.75 (C-3 of pyrrole ring), 119.34 (C-4 of pyrrole ring), 124.76 (C-5 of pyrrole ring), 126.76 (CH of Ph), 128.44 (2 × CH of Ph), 130.81 (2 × CH of

Ph), 132.25 (C_{ipso} of Ph), 136.25 (C-2 of pyrrole ring), 166.18 (CONH).

MS (EI, 70 eV): *m*/*z* (%) = 298 (79) [M$^+$], 283 (15), 269 (4), 256 (21), 240 (100), 212 (19), 197 (19), 128 (16.4), 115 (6), 77 (4), 43 (11).

Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.42; H, 8.73; N, 9.41.

N^3-(*tert*-Butyl)-2,5-dimethyl-4-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide (4b)

Yield: 0.28 g (90%); yellow oil.

IR (KBr): 3410 (NH), 1639 (CONH), 1526, 1442 (Ar) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (t, ^3J = 7.3 Hz, 3 H, CH_3CH$_2$), 1.07 (s, 9 H, *t*-C_4H_9), 1.67–1.72 (m, 2 H, CH$_3$CH_2), 2.09 (s, 3 H, CH$_3$), 2.56 (s, 3 H, CH$_3$), 3.76 (t, ^3J = 7.7 Hz, 2 H, CH_2N), 4.96 (s, 1 H, NH), 7.27–7.40 (m, 5 H, Ph).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.29 (*C*H$_3$CH$_2$), 11.07 (CH$_3$), 11.29 (CH$_3$), 23.93 (CH$_3$*C*H$_2$), 28.57 [C(*C*H$_3$)$_3$], 45.24 [*C*(CH$_3$)$_3$], 50.35 (CH$_2$N), 114.89 (C-3 of pyrrole ring), 119.40 (C-4 of pyrrole ring), 124.46 (C-5 of pyrrole ring), 126.69 (CH of Ph), 128.37 (2 × CH of Ph), 131.03 (2 × CH of Ph), 131.86 (C_{ipso} of Ph), 136.24 (C-2 of pyrrole ring), 165.68 (CONH).

MS (EI, 70 eV): *m*/*z* (%) = 312 (86) [M$^+$], 297 (8), 284 (3), 270 (3), 256 (30), 240 (100), 212 (20), 197 (19), 168 (9), 128 (15), 115 (7), 77 (6), 57 (20), 42 (35).

Anal. Calcd for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97. Found: C, 76.69; H, 9.10; N, 8.83.

N^3-Isobutyl-2,5-dimethyl-4-phenyl-1*H*-pyrrole-3-carboxamide (4c)

Yield: 0.28 g (90%); yellow oil.

IR (KBr): 3415 (NH), 1636 (CONH), 1530, 1453 (Ar) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.62 (d, ^3J = 6.7 Hz, 6 H, *i*-C_3H_7), 0.99 (t, ^3J = 7.3 Hz, 3 H, CH_3CH$_2$), 1.39–1.44 (m, 1 H, CH), 1.68–1.73 (m, 2 H, CH$_3$CH_2), 2.07 (s, 3 H, CH$_3$), 2.59 (s, 3 H, CH$_3$), 2.96 (t, ^3J = 5.8 Hz, 2 H, CH_2NH), 3.79 (t, ^3J = 4.8 Hz, 2 H, CH$_2$N), 5.20 (s, 1 H, NH), 7.28–7.40 (m, 5 H, Ph).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.28 (*C*H$_3$CH$_2$), 11.16 (*C*H$_3$CH$_2$CHN), 11.22 (CH$_3$), 11.29 (CH$_3$), 19.95 [CH(*C*H$_3$)$_2$], 23.91 (CH$_3$*C*H$_2$), 28.20 [*C*H(CH$_3$)$_2$], 45.28 (CH$_2$NH), 46.53 (CH$_2$N), 113.71 (C-3 of pyrrole ring), 119.32 (C-4 of pyrrole ring), 124.79 (C-5 of pyrrole ring), 126.87 (CH of Ph), 128.55 (2 × CH of Ph), 130.85 (2 × CH of Ph), 132.33 (C_{ipso} of Ph), 136.38 (C-2 of pyrrole ring), 166.25 (CONH).

MS (EI, 70 eV): *m*/*z* (%) = 312 (55) [M$^+$], 298 (76), 283 (14), 256 (47), 240 (100), 212 (28), 197 (28), 128 (24), 77 (9), 43 (34).

Anal. Calcd for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97. Found: C, 76.81; H, 9.06; N, 8.93.

N^3-Allyl-2-methyl-4-phenyl-1-propyl-1*H*-pyrrole-3-carboxamide (4d)

Yield: 0.25 g (85%); yellow oil.

IR (KBr): 3290 (NH), 1652 (CONH), 1540, 1438 (Ar) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (t, ^3J = 7.3 Hz, 3 H, CH_3CH$_2$), 1.73–1.81 (m, 2 H, CH$_3$CH_2), 2.52 (s, 3 H, CH$_3$), 3.79 (t, ^3J = 7.2 Hz, 2 H, CH$_2$N), 3.84 (t, ^3J = 4.3 Hz, 2 H, CH$_2$NH), 4.92 (dd, ^3J = 17.15 Hz, ^2J = 1.46 Hz, 1 H, CH=CH_2), 4.96 (dd, ^3J = 10.35 Hz, ^2J = 1.26 Hz, 1 H, CH=CH_2), 5.40 (s, 1 H, NH), 5.68–5.73 (m, 1 H, C*H*=CH$_2$), 6.53 (s, 1 H, CH-5), 7.33–7.39 (m, 5 H, Ph).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.90 (*C*H$_3$CH$_2$), 11.23 (CH$_3$), 24.15 (CH$_3$*C*H$_2$), 41.73 (CH$_2$NH), 48.25 (CH$_2$N), 113.97 (C-3 of pyrrole ring), 115.67 (C-5 of pyrrole ring), 118.92 (CH=*C*H$_2$), 122.63 (C-4 of pyrrole ring), 126.72 (CH of Ph), 128.49 (2 × CH of Ph), 129.17 (2 × CH of Ph), 133.64 (C_{ipso} of Ph), 134.39 (*C*H=CH$_2$), 135.30 (C-2 of pyrrole ring), 166.20 (CONH).

MS (EI, 70 eV): *m*/*z* (%) = 284 (23) [M$^+$ + 1], 269 (4), 256 (8), 240 (100), 226 (12), 184 (14), 129 (46), 105 (19), 77 (19), 69 (23), 43 (34).

Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.49; H, 7.81; N, 9.94.

1-Allyl-2-methyl-4-phenyl-N^3-propyl-1*H*-pyrrole-3-carboxamide (4e)

Yield: 0.25 g (90%); yellow oil.

IR (KBr): 3295 (NH), 1651 (CONH), 1539, 1440 (Ar) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.69 (t, ^3J = 7.3 Hz, 3 H, CH_3CH$_2$), 1.21–1.30 (m, 2 H, CH$_3$CH_2), 2.47 (s, 3 H, CH$_3$), 3.11–3.18 (m, 2 H, CH$_2$NH), 4.41–4.42 (d, ^3J = 5.07 Hz, 2 H, CH$_2$N), 5.02 (d, ^3J = 17.0 Hz, 1 H, CH=CH_2), 5.20 (d, ^3J = 10.3 Hz, 1 H, CH=CH_2), 5.29 (br, 1 H, NH), 5.86–5.94 (m, 1 H, C*H*=CH$_2$), 6.50 (s, 1 H, CH-5), 7.18–7.37 (m, 5 H, Ph).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.72 (*C*H$_3$CH$_2$), 11.30 (CH$_3$), 22.55 (CH$_3$*C*H$_2$), 41.11 (CH$_2$NH), 49.00 (CH$_2$N), 114.56 (C-3 of pyrrole ring), 117.39 (C-5 of pyrrole ring), 118.88 (CH=*C*H$_2$), 122.85 (C-4 of pyrrole ring), 126.76 (CH of Ph), 128.46 (2 × CH of Ph), 129.19 (2 × CH of Ph), 133.27 (*C*H=CH$_2$), 133.70 (C_{ipso} of Ph), 135.28 (C-2 of pyrrole ring), 166.22 (CONH).

MS (EI, 70 eV): *m*/*z* (%) = 282 (13) [M$^+$], 257 (20), 224 (100), 183 (30), 129 (43), 105 (34), 56 (83), 43 (96).

Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.52; H, 7.79; N, 9.87.

1-Allyl-N^3-(*tert*-butyl)-2-methyl-4-phenyl-1*H*-pyrrole-3-carboxamide (4f)

Yield: 0.25 g (85%); yellow oil.

IR (KBr): 3315 (NH), 1651 (CONH), 1521, 1439 (Ar) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18 (s, 9 H, *t*-C_4H_9), 2.51 (s, 3 H, CH$_3$), 4.44–4.46 (m, 2 H, CH$_2$N), 5.06 (dd, ^3J = 17.0 Hz, ^2J = 1.0 Hz, 1 H, CH=CH_2), 5.13 (s, 1 H, NH), 5.23 (dd, ^3J = 10.3 Hz, ^2J = 1.1 Hz, 1 H, CH=CH_2), 5.90–5.97 (m, 1 H, C*H*=CH$_2$), 6.52 (s, 1 H, CH-5), 7.25–7.40 (m, 5 H, Ph).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.64 (CH$_3$), 28.64 [C(*C*H$_3$)], 48.96 (CH$_2$N), 50.71 [*C*(CH$_3$)], 115.77 (C-3 of pyrrole ring), 117.35 (C-5 of pyrrole ring), 118.49 (CH=*C*H$_2$), 122.89 (C-4 of pyrrole ring), 126.73 (CH of Ph), 128.33 (2 × CH of Ph), 129.53 (2 × CH of Ph), 133.35 (*C*H=CH$_2$), 135.30 (C_{ipso} of Ph), 141.00 (C-2 of pyrrole ring), 165.53 (CONH).

MS (EI, 70 eV): *m*/*z* (%) = 296 (59) [M$^+$], 257 (42), 240 (55), 224 (100), 213 (30), 196 (15), 183 (20), 129 (26), 105 (19), 57 (31), 41 (53).

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 7.16; N, 9.45. Found: C, 76.95; H, 7.11; N, 9.38.

N^3,1-Diisobutyl-2-methyl-4-phenyl-1*H*-pyrrole-3-carboxamide (4g)

Yield: 0.28 g (90%); yellow oil.

IR (KBr): 3295 (NH), 1629 (CONH), 1534, 1454 (Ar) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.68 [d, ^3J = 6.6 Hz, 6 H, (CH_3)$_2$CHCH$_2$NH], 0.92 [d, ^3J = 6.6 Hz, 6 H, (CH_3)$_2$CHCH$_2$NH], 1.49–1.54 (m, 1 H, Me$_2$C*H*CH$_2$NH), 1.98–2.03 (m, 1 H, Me$_2$C*H*CH$_2$N), 2.50 (s, 3 H, CH$_3$), 3.01 (t, ^3J = 6.1 Hz, 2 H, CH_2NH), 3.60 (d, ^3J = 7.4 Hz, 2 H, CH_2N), 5.31 (s, 1 H, NH), 6.46 (s, 1 H, CH-5), 7.21–7.37 (m, 5 H, Ph).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.11 (CH_3), 20.06 [2 × (CH_3)$_2$CH], 28.29 [(CH_3)$_2$*C*HCH$_2$NH], 29.87 [(CH_3)$_2$*C*HCH$_2$N], 46.72 (CH_2NH), 54.14 (CH_2N), 114.30 (C-3 of pyrrole ring), 119.52 (CH-5 of pyrrole ring), 122.40 (C-4 of pyrrole ring), 126.74 (CH of Ph), 128.49 (2 × CH of Ph), 129.33 (2 × CH of Ph), 133.60 (C_{ipso} of Ph), 135.58 (C-2 of pyrrole ring), 166.33 (CONH).

MS (EI, 70 eV): *m/z* (%) = 329 (34), 272 (67), 256 (70), 229 (14), 199 (30), 149 (12), 105 (100), 77 (30), 48 (30).

Anal. Calcd for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97. Found: C, 76.83; H, 9.06; N, 8.91.

References

(1) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*, Vol. 2; Katrizky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier: Oxford, **1996**, 207.

(2) (a) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: London, **1977**, 1. (b) Sundberg, R. J. *Comprehensive Heterocyclic Chemistry*, Vol. 4; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, **1984**, 370. (c) Sundberg, R. J. *Comprehensive Heterocyclic Chemistry II*, Vol. 2; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, **1996**, 149. (d) Boger, D. L.; Boyce, C. W.; Labrili, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54.

(3) Boger, D. L.; Boyee, C. W.; Labrili, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54.

(4) (a) Jiménez, M. D.; Ortega, R.; Tito, A.; Fariña, F. *Heterocycles* **1988**, *27*, 173. (b) Koot, W.-J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron: Asymmetry* **1993**, *4*, 1941.

(5) (a) Koot, W.-J.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1992**, *57*, 1059. (b) Cooper, D. M.; Grigg, R.; Hargreaves, S.; Kennewell, P.; Redpath, J. *Tetrahedron* **1995**, *51*, 7791.

(6) Koot, W. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1992**, *33*, 7969.

(7) Cuiper, A. D.; Kellogg, R. M.; Feringa, B. L. *Chem. Commun.* **1998**, 655.

(8) Bean, G. P. In *Pyrroles, Part II, The Synthesis, Reactivity and Physical Properties of Substituted Pyrroles*; Jones, R. A., Ed.; Wiley: New York, **1990**, 105.

(9) *The Chemistry of Heterocyclic Compounds*, Parts 1 and 2; Jones, R. A., Ed.; Wiley: Toronto, **1990**.

(10) Baltazzi, E.; Krimen, L. I. *Chem. Rev.* **1963**, *63*, 511.

(11) Kaupp, G.; Schmeyers, J.; Kuse, A.; Atfeh, A. *Angew. Chem. Int. Ed.* **1999**, *19*, 38.

(12) Yavari, I.; Anary-Abbasinejad, M.; Nasiri, F.; Djahaniani, H. *Molecular Diversity* **2005**, *9*, 209.

(13) Nasiri, F.; Pourdavaie, K. *Molecular Diversity* **2007**, *11*, 37.

(14) (a) Reidlinger, C.; Dworczak, R.; Junk, H. *Monatsh. Chem.* **1998**, *129*, 1207. (b) Al-Omran, A.-Z. A.; Elassar, A.; El-Khair, A. *Tetrahedron* **2001**, *57*, 10163.

(15) Cocco, M. T.; Congiu, C.; Onnis, V.; Bernard, A. M.; Piras, P. P. *J. Heterocycl. Chem.* **1997**, *34*, 1347.

(16) Wiberg, K. B.; Snoonian, J. R. *J. Org. Chem.* **1998**, *63*, 1390.

(17) Katritzky, A. R.; Fang, Y.; Donkor, A.; Xu, J. *Synthesis* **2000**, 2029.

(18) (a) Gielen, H.; Li, V. M.; Rosentreter, U.; Schlemmer, K.; Fitzgerald, H.; Nash, K. GB 2383326 A, **2003**; *Chem. Abstr.* **2003**, *139*, 490839. (b) Charushin, V. N.; Mochulskaya, N. N.; Andreiko, A. A.; Filyakova, V. I.; Kodess, M. I.; Chupakhin, O. N. *Tetrahedron Lett.* **2003**, *44*, 2421. (c) Savarin, C. G.; Murry, J. A.; Dormer, P. G. *Org. Lett.* **2002**, *4*, 2071.

(19) Eddington, N. D.; Cox, D. S.; Khurana, M.; Salama, N. N.; Stables, J. P.; Harrison, S. J.; Negussie, A.; Taylor, R. S.; Tran, U. Q.; Moore, J. A.; Barrow, J. C.; Scott, K. R. *Eur. J. Med. Chem.* **2003**, *38*, 49.

(20) Dannhardt, G.; Bauer, A.; Nowe, U. *J. Prakt. Chem.* **1998**, *340*, 256.

(21) Boger, D. L.; Ishizaki, T.; Wysocki, J. R.; Munk, S. A.; Kitos, P. A.; Suntornwat, O. *J. Am. Chem. Soc.* **1989**, *111*, 6461.

(22) (a) Bhosale, R. S.; Suryawanshi, P. A.; Ingle, S. A.; Lokhande, M. N.; More, S. P.; Mane, S. B.; Bhosale, S. V.; Pawar, R. P. *Synlett* **2006**, 933. (b) Zhang, Z.-H.; Yin, L.; Wang, Y.-M. *Adv. Synth. Catal.* **2006**, *348*, 184. (c) Zhang, Z. H.; Hu, J. Y. *Braz. J. Chem. Soc.* **2006**, *17*, 1447.

(23) Alizadeh, A.; Movahedi, F.; Esmaili, A. A. *Tetrahedron Lett.* **2006**, *47*, 4469.

(24) Alizadeh, A.; Movahedi, F.; Masrour, H.; Zhu, L. G. *Synthesis* **2006**, *20*, 3431.

(25) Elassar, A. Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463.

(26) Nomura, M.; Nakata, S.; Hamada, F. *J. Chem. Soc. Jpn.* **2002**, 141.

(27) Gairaud, C. B.; Lappin, G. R. *J. Org. Chem.* **1953**, *18*, 1.

(28) Campbell, N.; Anderson, W.; Gilmore, J. *J. Chem. Soc.* **1940**, 446.