Facile One-Pot Three-Component Synthesis of Functionalized Pyridylfuran-2-amines

by **Mehdi Adib***[a]), **Mohammad Hosein Sayahi**[a]), **Somayeh Aali Koloogani**[a]), and **Peiman Mirzaei**[b])

[a]) School of Chemistry, University College of Science, University of Tehran, P.O. Box 14155-6455, Tehran, Iran (phone/fax: +98-21-66495291; e-mail: madib@khayam.ut.ac.ir)

[b]) Department of Chemistry, Shahid Beheshti University, Tehran, Iran

The reactive 1:1 zwitterionic intermediates generated *in situ* from the reaction between a series of isocyanides and diaroylacetylenes were trapped by pyridine carbaldehydes to yield highly functionalized 5-pyridylfuran-2-amines in good yields (82–93%).

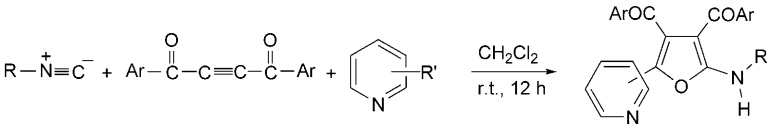
Introduction. – Polysubstituted furans play an important role in organic chemistry, not only due to their presence as key structural units in many natural products [1] and in pharmaceuticals [2], but also because they are often used as building blocks in synthetic chemistry. For this reason, the synthesis of polysubstituted furans continues to attract the interest of many organic chemists.

Until now, only few papers dealing with the synthesis of furylpyridines have been published [3–7]. As part of our current studies on the development of new routes in heterocyclic chemistry [8–11], we now wish to report a facile one-pot three-component synthesis of polyfunctional 5-pyridylfuran-2-amines.

Results and Discussion. – We have synthesized a series of furylpiperidines by the ready 1:1:1 condensation of the isocyanides **1**, the diaroylacetylenes (=1,4-diaryl-but-2-yne-1,4-diones) **2**, and the pyridine carbaldehydes **3** in CH_2Cl_2 at ambient temperature. As can be seen from the *Table*, the resulting furylpyridines **4** were obtained in 82–93% yield. The reactions were carried out by first mixing the pyridine carbaldehyde and the diaroylacetylene, before the isocyanide was added slowly. The reactions proceeded spontaneously in CH_2Cl_2, and were all complete within 12 h.

Compounds **4** were identified on the basis of elemental analyses, IR, ^{1}H- and ^{13}C-NMR, and MS data. The mass spectrum of **4a** displayed the M^+ signal at m/z 450, in accord with a 1:1:1 adduct. Its ^{1}H-NMR spectrum exhibited characteristic signals at δ(H) 1.35–2.25 (series of m) for the five CH_2 groups of the cyclohexyl moiety, and a symmetric *multiplet* at δ(H) 4.04 for the cyclohexyl methine H-atom, along with characteristic aromatic signals at δ(H) 7.04–8.36. The NH H-atom was observed at δ(H) 8.56 (d, ^3J = 8.0 Hz) due to vicinal coupling with the cyclohexyl methine group. The ^{1}H-decoupled ^{13}C-NMR spectrum of **4a** showed 23 distinct resonances, in agreement with the proposed structure. Partial assignment of these resonances are given in the *Exper. Part*. The ^{1}H- and ^{13}C-NMR spectra of compounds **4b**–**h** were similar to those of **4a**, except for the signals of the aryl substituents, the alkylamino moieties, and the

Table. *Syntheses and Structures a Series of Functionalized Pyridylfurans*



1 **2** **3** **4**

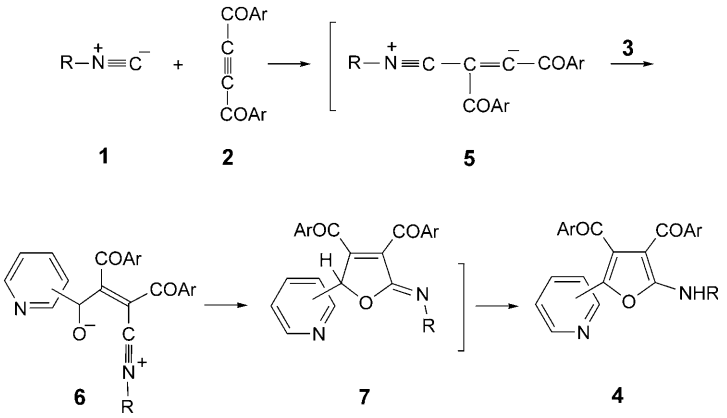
Series	R	Ar	R′	Yield of **4** [%][a])
a	C_6H_{11}	C_6H_5	2-CHO	93
b	C_6H_{11}	C_6H_5	4-CHO	92
c	C_6H_{11}	2,5-Me_2–C_6H_3	2-CHO	86
d	C_6H_{11}	2,5-Me_2–C_6H_3	4-CHO	83
e	*t*-Bu	C_6H_5	2-CHO	87
f	*t*-Bu	C_6H_5	4-CHO	89
g	*t*-Bu	2,5-Me_2–C_6H_3	2-CHO	91
h	*t*-Bu	2,5-Me_2–C_6H_3	4-CHO	82

[a]) Isolated yield.

pyridine rings, which exhibited characteristic signals with appropriate chemical shifts and coupling constants.

On the basis of the well-established chemistry of isocyanides [12–15], it is reasonable to assume that the furylpyridines **4** result from initial addition of the isocyanide to the unsaturated diketone, followed by nucleophilic attack of the 1:1 adduct **5** on the aldehyde under formation of the 1:1:1 adducts **6**. Next, intramolecular cyclization by attack of the alkoxide to the nitrilium moiety yields the intermediate γ-iminolactone **7**, which finally isomerizes to **4** (*Scheme*).

Scheme



1 **2** **5** **6** **7** **4**

In summary, the present method has the advantage that the reaction can be performed under neutral conditions, and that the substances can be mixed without prior activation or modification. The simplicity of our synthetic protocol makes it an interesting alternative to multistep approaches [3–7], and allows the ready preparation of

highly functionalized pyridylfurans of potential synthetic and pharmaceutical interest (see, *e.g.*, [16–19]).

Experimental Part

General. *tert*-Butyl isocyanide, cyclohexyl isocyanide, and pyridine carbaldehydes were obtained from *Merck* (Germany) and *Fluka* (Switzerland), and were used without further purification. Diaroylacetylenes **2** were prepared according to literature procedures [20]. Column chromatography (CC): silica gel *60* (*Merck*). Melting points (M.p.): *Electrothermal 9100* apparatus; uncorrected. IR spectra: *Shimadzu IR-460* spectrometer; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker DRX-500 AVANCE* instrument; at 500.1 and 125.8 MHz, resp., in $CDCl_3$; δ in ppm rel. to Me_4Si (=0 ppm), *J* in Hz. EI-MS (20 eV): *Finnigan MAT-8430* mass spectrometer; in *m*/*z* (rel. %). Elemental analyses: *Heraeus CHN-O-Rapid* analyzer.

General Procedure for the Preparation of Compounds **4**. To a magnetically stirred soln. of **2** (1 mmol) and **3** (107 mg, 1 mmol) in CH_2Cl_2 (6 ml) was added dropwise a soln. of **1** (1 mmol) in CH_2Cl_2 (2 ml) at $-5°$ over 10 min. The mixture was allowed to warm to r.t., and was stirred for 12 h. The solvent was removed, and the residue was purified by CC (SiO_2; hexane/AcOEt 2 : 1) and recrystallization from hexane/AcOEt 1 : 1.

[2-(Cyclohexylamino)-5-(pyridin-2-yl)furan-3,4-diyl]bis(phenylmethanone) (**4a**). Yield: 93%. Yellow crystals. M.p. 138–139°. IR (KBr): 3270 (NH), 1676, 1630 (C=O), 1542, 1464, 1404, 1229, 893, 692. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.35–2.25 (*m*, 10 H); 4.04 (*m*, 1 H); 7.04 (*t*, *J*=6.9, 1 H); 7.07 (*t*, *J*=7.6, 2 H); 7.18–7.25 (*m*, 5 H); 7.40 (*t*, *J*=7.4, 1 H); 7.55 (*d*, *J*=7.5, 2 H); 7.58 (*d*, *J*=8.0, 1 H); 7.65 (*t*, *J*=7.4, 1 H); 8.36 (*d*, *J*=3.3, 1 H); 8.56 (*d*, *J*=8.0, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.44; 25.37; 33.28; 51.41; 100.13; 119.20; 121.52; 122.88; 127.15; 127.65; 127.87; 128.89; 130.07; 132.57; 136.24; 137.57; 140.34; 140.69; 147.81; 149.34; 163.10; 190.18; 191.84. EI-MS: 451 (27, $[M+1]^+$), 450 (7, M^+), 383 (23), 368 (23), 325 (40), 264 (39), 236 (25), 205 (23), 105 (100), 77 (33), 27 (32). Anal. calc. for $C_{29}H_{26}N_2O_3$ (450.54): C 77.31, H 5.82, N 6.22; found: C 77.3, H 5.8, N 6.3.

[2-(Cyclohexylamino)-5-(pyridin-4-yl)furan-3,4-diyl]bis(phenylmethanone) (**4b**). Yield: 92%. Yellow crystals. M.p. 114–115°. IR (KBr): 3265 (NH), 1670, 1634 (C=O), 1593, 1554, 1460, 1404, 1336, 1234, 1045, 889, 692. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.29–2.20 (*m*, 10 H); 3.93 (*m*, 1 H); 7.06 (*t*, *J*=7.6, 2 H); 7.13 (*d*, *J*=7.0, 2 H); 7.17 (*t*, *J*=7.5, 2 H); 7.22 (*t*, *J*=7.3, 1 H); 7.37 (*t*, *J*=7.4, 1 H); 7.38–7.43 (*m*, 4 H); 8.39 (*d*, *J*=7.9, 1 H); 8.50 (*d*, *J*=6.0, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.43; 25.30; 33.20; 51.70; 100.40; 118.50; 124.32; 127.12; 127.84; 128.12; 128.79; 130.43; 133.26; 136.22; 137.08; 139.24; 140.27; 149.77; 162.56; 190.06; 192.06. EI-MS: 450 (33, M^+), 406 (22), 105 (100), 77 (20), 55 (41), 40 (25), 29 (30). Anal. calc. for $C_{29}H_{26}N_2O_3$ (450.54): C 77.31, H 5.82, N 6.22; found: C 77.4, H 5.7, N 6.2.

[2-(Cyclohexylamino)-5-(pyridin-2-yl)furan-3,4-diyl]bis[(2,5-dimethylphenyl)methanone] (**4c**). Yield: 86%. Yellow crystals. M.p. 153–154°. IR (KBr): 3288 (NH), 1670, 1632 (C=O), 1547, 1468, 1342, 1282, 1040, 772. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.30–1.90 (*m*, 8 H); 2.04 (*s*, 3 H); 2.05 (*s*, 3 H); 2.18–2.22 (*m*, 2 H); 2.24 (*s*, 3 H); 2.25 (*s*, 3 H); 4.02 (*m*, 1 H); 6.75 (*s*, 1 H); 6.79 (*d*, *J*=7.7, 1 H); 6.86 (*d*, *J*=7.6, 1 H); 6.94 (*d*, *J*=7.7, 1 H); 6.99 (*dd*, *J*=4.5, 6.2, 1 H); 7.08 (*d*, *J*=7.6, 1 H); 7.34 (*s*, 1 H); 7.51 (*d*, *J*=8.0, 1 H); 7.59 (*t*, *J*=7.9, 1 H); 8.35 (*d*, *J*=4.1, 1 H); 8.58 (*d*, *J*=6.8, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 18.51; 20.51; 20.76; 21.44; 24.54; 25.11; 33.32; 51.49; 101.02; 118.97; 121.24; 124.90; 127.60; 129.64; 129.92; 131.64; 131.69; 132.59; 132.95; 134.26; 134.36; 135.36; 136.18; 137.67; 139.77; 140.03; 148.00; 149.36; 162.80; 191.61; 192.45. EI-MS: 507 (30, $[M+1]^+$), 506 (10, M^+), 410 (25), 374 (20), 353 (31), 324 (17), 304 (33), 275 (28), 248 (17), 219 (12), 133 (100), 105 (68), 77 (27), 55 (18), 29 (31). Anal. calc. for $C_{33}H_{34}N_2O_3$ (506.64): C 78.23, H 6.76, N 5.53; found: C 78.3, H 6.8, N 5.3.

[2-(Cyclohexylamino)-5-(pyridin-4-yl)furan-3,4-diyl]bis[(2,5-dimethylphenyl)methanone] (**4d**). Yield: 83%. Yellow crystals. M.p. 97–101°. IR (KBr): 3287 (NH), 1665, 1634 (C=O), 1597, 1549, 1466, 1337, 1172, 1038, 813, 731. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.17–1.77 (*m*, 8 H); 1.80 (*s*, 3 H); 1.94 (*s*, 3 H); 2.01 (*s*, 3 H); 2.02–2.09 (*m*, 2 H); 2.10 (*s*, 3 H); 3.80 (*m*, 1 H); 6.56 (*d*, *J*=1.2, 1 H); 6.60 (*d*, *J*=7.7, 1 H); 6.71 (*dd*, *J*=1.2, 7.6, 1 H); 6.79 (*d*, *J*=7.7, 1 H); 6.97 (*dd*, *J*=1.1, 8.1, 1 H); 7.13 (*d*, *J*=1.1, 1 H); 7.19 (*d*, *J*=5.9, 2 H); 8.33 (*d*, *J*=5.9, 2 H); 8.35 (*d*, *J*=7.5, 1 H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 18.45; 20.55; 20.65; 21.45; 24.48; 25.31; 33.17; 51.71; 101.21; 118.10; 126.04; 127.55; 129.97;

130.13; 131.81; 132.12; 132.89; 133.41; 134.41; 134.63; 134.89; 136.29; 138.04; 138.35; 139.58; 149.82; 162.42; 191.37; 192.82. EI-MS: 506 (82, M^+), 491 (15), 409 (38), 373 (15), 291 (8), 133 (100), 105 (50), 84 (20), 55 (22), 41 (11), 29 (4). Anal. calc. for $C_{33}H_{34}N_2O_3$ (506.64): C 78.23, H 6.76, N 5.53; found: C 78.3, H 6.9, N 5.4.

{2-[(1,1-Dimethylethyl)amino]-5-(pyridin-2-yl)furan-3,4-diyl}bis[phenylmethanone] (**4e**). Yield: 87%. Yellow crystals. M.p. 170–172°. IR (KBr): 3263 (NH), 1678, 1628 (C=O), 1551, 1465, 1373, 1225, 951, 692. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.65 (*s*, 9 H); 6.98 (*dd*, *J* = 4.9, 6.1, 1 H); 7.04 (*t*, *J* = 7.7, 2 H); 7.17–7.23 (*m*, 5 H); 7.37 (*t*, *J* = 7.4, 1 H); 7.55 (*d*, *J* = 7.6, 2 H); 7.57 (*d*, *J* = 7.5, 1 H); 7.62 (*t*, *J* = 7.7, 1 H); 8.25 (*d*, *J* = 4.4, 1 H); 8.88 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 29.72; 53.12; 100.85; 118.73; 121.44; 122.48; 127.15; 127.64; 127.87; 128.91; 130.07; 132.58; 136.32; 137.57; 140.31; 140.98; 147.82; 149.38; 163.32; 190.31; 191.87. EI-MS: 425 (37, M^+), 368 (13), 350 (47), 322 (32), 291 (16), 246 (22), 105 (100), 77 (78), 57 (40), 41 (26), 28 (61). Anal. calc. for $C_{27}H_{24}N_2O_3$ (424.50): C 76.40, H 5.70, N 6.60; found: C 76.3, H 5.8, N 6.5.

{2-[(1,1-Dimethylethyl)amino]-5-(pyridin-4-yl)furan-3,4-diyl}bis[phenylmethanone] (**4f**). Yield: 89%. Yellow crystals. M.p. 125–129°. IR (KBr): 3271 (NH), 1660, 1630 (C=O), 1589, 1547, 1456, 1373, 1225, 1069, 950, 820, 696. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.62 (*s*, 9 H); 7.00–7.18 (*m*, 6 H); 7.22 (*t*, *J* = 7.0, 1 H); 7.33–7.42 (*m*, 5 H); 8.49 (*d*, *J* = 6.2, 2 H); 8.67 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 28.71; 52.27; 100.03; 117.48; 122.80; 126.15; 126.90; 127.16; 127.82; 129.51; 132.34; 135.01; 136.06; 138.85; 139.25; 149.17; 161.75; 189.23; 191.28. EI-MS: 424 (60, M^+), 383 (38), 367 (100), 350 (11), 301 (22), 105 (20), 71 (73), 57 (67), 41 (44), 29 (26). Anal. calc. for $C_{27}H_{24}N_2O_3$ (424.50): C 76.40, H 5.70, N 6.60; found: C 76.4, H 5.6, N 6.6.

{2-[(1,1-Dimethylethyl)amino]-5-(pyridin-2-yl)furan-3,4-diyl}bis[(2,5-dimethylphenyl)methanone] (**4g**). Yield: 91%. Yellow crystals. M.p. 111–114°. IR (KBr): 3298 (NH), 1674, 1626 (C=O), 1551, 1463, 1373, 1265, 1207, 1175, 1105, 960, 789. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.64 (*s*, 9 H); 2.01 (*s*, 3 H); 2.02 (*s*, 3 H); 2.21 (*s*, 3 H); 2.23 (*s*, 3 H); 6.71 (*d*, *J* = 1.2, 1 H); 6.75 (*d*, *J* = 7.7, 1 H); 6.83 (*dd*, *J* = 1.6, 7.6, 1 H); 6.91 (*d*, *J* = 7.7, 1 H); 6.96 (*dd*, *J* = 1.1, 7.4, 1 H); 7.05 (*dd*, *J* = 1.4, 7.7, 1 H); 7.32 (*d*, *J* = 1.2, 1 H); 7.50 (*d*, *J* = 8.0, 1 H); 7.59 (*dt*, *J* = 1.7, 7.5, 1 H); 8.28 (*dd*, *J* = 1.1, *J* = 4.9, 1 H); 8.85 (*s*, 1 H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 18.54; 20.53; 20.81; 21.52; 29.72; 53.10; 101.66; 118.52; 121.17; 124.35; 127.67; 129.65; 129.88; 131.63; 131.67; 132.58; 133.01; 134.25; 134.34; 135.31; 136.13; 137.70; 139.66; 140.52; 148.13; 149.56; 163.00; 191.77; 192.57. EI-MS: 480 (50, M^+), 409 (28), 380 (13), 291 (27), 133 (100), 105 (47), 79 (20), 57 (29), 41 (16), 29 (7). Anal. calc. for $C_{31}H_{32}N_2O_3$ (480.61): C 77.47, H 6.71, N 5.83; found: C 77.6, H 6.7, N 5.7.

{2-[(1,1-Dimethylethyl)amino]-5-(pyridin-4-yl)furan-3,4-diyl}bis[(2,5-dimethylphenyl)methanone] (**4h**). Yield: 82%. Yellow crystals. M.p. 90–92°. IR (KBr): 3274 (NH), 1675, 1639 (C=O), 1595, 1550, 1459, 1410, 1339, 1280, 1048, 770. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.65 (*s*, 9 H); 1.91 (*s*, 3 H); 2.08 (*s*, 3 H); 2.13 (*s*, 3 H); 2.25 (*s*, 3 H); 6.68 (*d*, *J* = 1.3, 1 H); 6.73 (*d*, *J* = 7.8, 1 H); 6.85 (*dd*, *J* = 1.3, 7.7, 1 H); 6.93 (*d*, *J* = 7.7, 1 H); 7.12 (*dd*, *J* = 1.1, 7.8, 1 H); 7.25 (*d*, *J* = 1.1, 1 H); 7.32 (*d*, *J* = 6.4, 2 H); 8.48 (*d*, *J* = 6.4, 2 H); 8.78 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.50; 19.60; 19.73; 20.54; 28.66; 52.21; 100.83; 117.09; 124.70; 126.64; 129.05; 129.16; 130.86; 131.17; 131.93; 132.52; 133.43; 133.55; 133.94; 135.22; 137.11; 137.84; 138.49; 148.95; 161.64; 190.49; 192.00. EI-MS: 480 (45, M^+), 423 (7), 409 (57), 328 (8), 301 (10), 133 (100), 105 (40), 79 (15), 57 (23), 41 (12), 29 (7). Anal. calc. for $C_{31}H_{32}N_2O_3$ (480.61): C 77.47, H 6.71, N 5.83; found: C 77.3, H 6.8, N 5.7.

This research was supported by the *Research Council of the University of Tehran* (project No. 6102036/1/02).

REFERENCES

[1] B. H. Lipshutz, *Chem. Rev.* **1986**, *86*, 795.
[2] K. Nakanishi, 'Natural Products Chemistry', Kodansha, Tokyo, 1974.
[3] J. L. Duffy, T. A. Rano, N. J. Kevin, K. T. Chapman, W. A. Schleif, D. B. Olsen, M. Stahlhut, C. A. Rutkowski, L. C. Kuo, L. Jin, J. H. Lin, E. A. Emini, J. R. Tata, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2569.

[4] P. Ribereau, G. Queguiner, *Can. J. Chem.* **1983**, *61*, 334; P. Ribereau, G. Queguiner, *Tetrahedron* **1983**, *39*, 3593.
[5] C. Jutz, R. M. Wagner, A. Kroatz, H. G. Lobering, *Justus Liebigs Ann. Chem.* **1975**, *5*, 874.
[6] T. Umemoto, G. Tomizawa, *Tetrahedron Lett.* **1987**, *28*, 2705.
[7] L.-X. Zhao, Y.-S. Moon, A. Basnet, E.-K. Kim, Y. Jahng, J. G. Park, T. C. Jeong, W.-J. Cho, S.-U. Choi, C. O. Lee, S.-Y. Lee, C.-S. Lee, E.-S. Lee, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1333.
[8] M. Adib, M. Mollahosseini, H. Yavari, M. H. Sayahi, H. R. Bijanzadeh, *Synlett* **2004**, 1086.
[9] M. Adib, M. H. Sayahi, B. Aghaaliakbari, H. R. Bijanzadeh, *Tetrahedron* **2005**, *61*, 3963.
[10] M. Adib, K. Ghanbary, M. Mostofi, H. R. Bijanzadeh, *Tetrahedron* **2005**, *61*, 2645.
[11] I. Yavari, M. Adib, F. Jahani-Moghaddam, H. R. Bijanzadeh, *Tetrahedron* **2002**, *58*, 6901.
[12] I. Ugi, 'Isonitrile Chemistry', Academic Press, London, 1971.
[13] I. Ugi, *Angew. Chem., Int. Ed*. **1982**, *21*, 810.
[14] A. Dömling, I. Ugi, *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.
[15] H. M. Walborsky, M. P. Periasamy, in 'The Chemistry of Functional Groups: Supplement C', Eds. S. Patai, Z. Rappaport, Wiley, New York, 1983, Chapt. 20, p. 835–837.
[16] J. Szychowski, J. T. Wrobel, A. Leniewski, *Can. J. Chem.* **1977**, *55*, 3105.
[17] J. T. Wrobel, in 'The Alkaloids', Ed. R. H. F. Manske, Academic Press, New York, 1967, Vol. 9, p. 441; B. Maurer, G. Ohloff, *Helv. Chim Acta* **1976**, *59*, 1169.
[18] R. T. Lalonde, A. I. M. Tsai, C. J. Wang, C. F. Wong, Ger. Pat. 2603176, 1976 (*Chem. Abstr*. **1976**, *85*, 177750a).
[19] E. Wiegand, V. J. Bauer, S. R. Safir, *J. Med. Chem.* **1971**, *14*, 214.
[20] L. Skattebol, E. R. H. Jones, M. C. Whiting, *Org. Synth., Coll. Vol. 4* **1963**, 792; K. Bowden, I. M. Heilborn, E. R. H. Jones, B. C. Weedon, *J. Chem. Soc.* **1946**, 39.

Received November 8, 2005