ORGANIC LETTERS

2000
Vol. 2, No. 14
2061−2063

Preparation of 5-Substituted 3-Aminofuran-2-carboxylate Esters

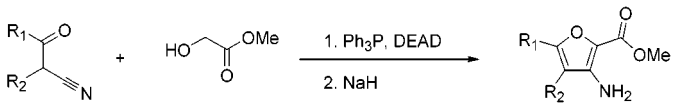
Anikó M. Redman,*,† Jacques Dumas, and William J. Scott*

Department of Chemistry Research, Bayer Research Center, West Haven, Connecticut 06516

william.scott.b@bayer.com

Received April 19, 2000

ABSTRACT

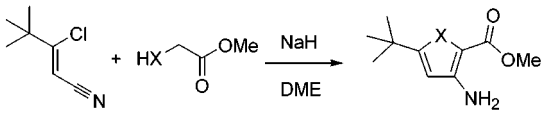


An efficient method for the preparation of 3-aminofuran-2-carboxylate esters has been developed. This method is based on the reaction of an α-cyanoketone with ethyl glyoxylate under Mitsunobu conditions to produce a vinyl ether in good yield. Subsequent treatment of the vinyl ether with sodium hydride afforded the 3-aminofuran. It was also found that a one-pot procedure using the Mitsunobu reaction followed by cyclization afforded the 3-aminofuran in comparable yield. Currently, this method is limited to the synthesis of 5-alkyl-, 5-aryl-, and 4,5-fused bicyclic furans.

During the course of a project directed at the synthesis of antiinflammatory compounds, we had need of a general route for the synthesis of substituted 3-amino-2-thiophenecarboxylate esters and 3-amino-2-furan carboxylate esters. The thiophene esters were readily synthesized via the condensation of *β*-haloacrylonitriles with alkyl thioglycolates under basic conditions.[1] This reaction involves formation of a cis-*β*-(alkylthio) acrylonitrile followed by base catalyzed cyclization to an aminothiophene. Only a small number of the corresponding furan esters have been prepared via *O*-alkylation of α-cyanoketones with halomethyl ketones or by the reaction of hydroxymethyl ketones and esters with *β*-haloacrylonitriles, in each case followed by base-promoted cyclization.[2]

Our initial approach to the furan synthesis was analogous to the above-described thiophene ester synthesis using chloronitrile **1** and replacing methyl thioglycolate with methyl glycolate **2**. After investigating various bases and solvents, the best results were obtained using NaH in DME, which afforded aminofuran **3** in low yields (Scheme 1). No desired product was observed using other bases, including Et_3N, NaOMe, *n*-BuLi, or *tert*-BuLi.

Scheme 1



1 **2** **3**

2a X=S 62%
2b X=O 15-25%

Assuming that the initial alkylation was the limiting step, alternative approaches to formation of the requisite vinyl ether were examined. Synthesis of the vinyl ether via alkylation of 4,4-dimethyl-3-oxopentanenitrile with methyl bromoacetate was unsuccessful. However, it has been reported that 1,3-diketones and 1,3-ketoesters undergo Mitsunobu reactions leading mainly to *O*-alkylated products.[3] Reaction of 4,4-dimethyl-3-oxopentanenitrile (**4**) with ethyl glycolate (**5**) under Mitsunobu conditions produced the

† aniko.redman.b@bayer.com.

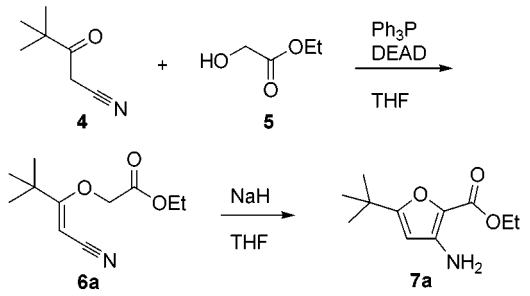
(1) (a) Hartman, H. Liebscher, J. *Synthesis* **1984**, 275−6. (b) Ishizaki, M.; Kato, T. JP 6025221 (1Feb1994); *Chem. Abstr.* **1994**, *121*, 35316.

(2) (a) Gewald, K.; Bellmann, P.; Jänsch, H.-J. *Liebigs Ann. Chem.* **1984**, 1702−10. (b) Tronchet, J. M. J.; Martin, O. R. *Helv. Chim. Acta* **1976**, *59*, 945−8. (c) Shiotani, S.; Morita, H.; Ishida, T.; In, Y. *J. Heterocycl. Chem.* **1988**, *25*, 1205−13. (d) Morita, H.; Shiotani, S. *J. Heterocycl. Chem.* **1986**, *23*, 1465−9.

(3) (a) Kurihara, T.; Sugizaki, M.; Kime, I.; Wada, M.; Mitsunobu, O. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 7−12. (b) Bajwa, J. S.; Anderson, R. C. *Tetrahedron. Lett.* **1990**, *31*, 6973−6.

10.1021/ol0059652 CCC: $19.00
Published on Web 06/20/2000

Scheme 2

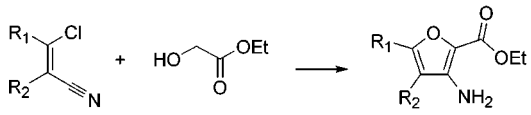


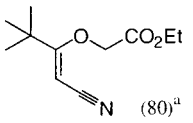
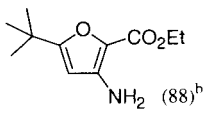
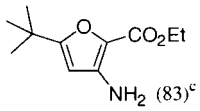
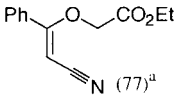
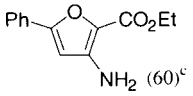
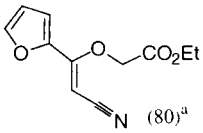
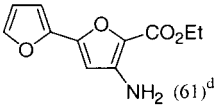
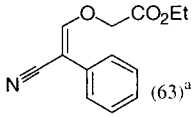
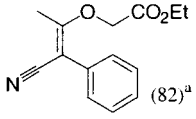
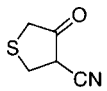
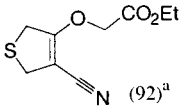
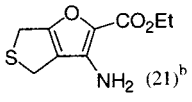
desired vinyl ether **6a** in good yield. Subsequent treatment of vinyl ether **6a** with NaH then afforded 3-aminofuran **7a** (Scheme 2). It was subsequently found that a one-pot procedure using the Mitsunobu reaction followed by cyclization afforded the 3-aminofuran in comparable yield (Table 1, entry 2).

Ethyl glycolate was allowed to react with a number of other cyanoketones (Table 1).[4] When the cyanoketone carried

(4) Procedure A. (*Z*)-3-(Ethoxycarbonylmethoxy)-4,4-dimethyl-pent-2-enenitrile (**6a**): A 0 °C solution of triphenylphosphine (2.72 g, 10.4 mmol, 1.3 equiv) in anhydrous THF (50 mL) was treated with diethyl azodicarboxylate (1.81 g, 10.4 mmol, 1.3 equiv), ethyl glycolate (1.08 g, 10.4 mmol, 1.3 equiv), and 4,4-dimethyl-3-oxopentanenitrile (1.00 g, 8.0 mmol). The resulting solution was allowed to warm to room temperature, stirred for 15 h, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 11 cm × 22 cm, gradient from 5% to 8% EtOAc/hex) to afford vinyl ether **6a** (1.36 g, 80%) as a colorless oil: TLC (5% EtOAc/hex) R_f 0.26; ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 9H), 1.28 (t, J = 7.0 Hz, 3H), 4.24 (q, J = 7.0 Hz, 2H), 4.55 (s, 1H), 5.00 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 27.8, 38.2, 61.5, 67.1, 67.3, 117.0, 167.1, 180.7; CI-LRMS *m*/*z* (rel abundance) 212 ((M + H)$^+$, 100%). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.57; H, 7.90; N, 6.47. (*Z*)-3-(Ethoxycarbonylmethoxy)-3-phenylprop-2-enenitrile (**6b**): mp 37−38 °C; TLC (10% EtOAc/hex) R_f 0.24; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 3H), 4.25 (q, J = 7.0 Hz, 2H), 4.94 (s, 2H), 5.01 (s, 1H), 7.35−7.45 (m, 3H), 7.50−7.58 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 61.5, 67.4, 73.9, 116.3, 126.8, 128.6, 131.2, 132.7, 167.3, 169.9; CI-LRMS *m*/*z* (rel abundance) 232 ((M + H)$^+$, 100%). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.27; H, 5.78; N, 6.01. (*Z*)-3-(Ethoxycarbonylmethoxy)-3-(2-furanyl)prop-2-enenitrile (**6c**): mp 58−59 °C; TLC (10% EtOAc/hex) R_f 0.22; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7.0 Hz, 3H), 4.27 (q, J = 7.0 Hz, 2H), 5.03 (s, 2H), 5.19 (s, 1H), 6.46−6.48 (m, 1H), 6.87 (d, J = 3.7 Hz, 1H), 7.45 (d, J = 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 61.7, 67.6, 70.4, 112.3, 113.0, 116.3, 145.2, 147.4, 159.3, 167.2; CI-LRMS *m*/*z* (rel abundance) 222 ((M + H)$^+$, 100%). Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.87; H, 5.00; N, 6.30. (*E*)-3-(Ethoxycarbonylmethoxy)-2-phenylprop-2-enenitrile (**6d**): TLC (10% EtOAc/hex) R_f 0.15; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.0 Hz, 3H), 4.29 (q, J = 7.0 Hz, 2H), 4.63 (s, 2H), 7.00 (s, 1H), 7.27−7.41 (m, 3H), 7.73−7.77 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 62.0, 70.4, 95.4, 95.4, 118.6, 127.7, 128.5, 130.0, 157.2, 167.3; CI-LRMS *m*/*z* (rel abundance) 232 ((M + H)$^+$, 15%). (*E*)-3-(Ethoxycarbonylmethoxy)-2-phenylbut-2-enenitrile (**6e**): TLC (10% EtOAc/hex) R_f 0.34; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 7.0 Hz, 3H), 2.39 (s, 3H), 4.26 (q, J = 7.0 Hz, 2H), 4.63 (s, 2H), 7.23−7.38 (m, 3H), 7.67−7.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 17.4, 61.8, 65.2, 94.4, 119.9, 127.4, 128.2, 128.3, 129.4, 131.4, 165.1, 167.7; CI-LRMS *m*/*z* (rel abundance) 246 ((M + H)$^+$, 100%). 3-Cyano-4-(ethoxycarbonylmethoxy)-2,5-dihydrothiophene (**6f**): mp 68 °C; TLC (10% EtOAc/hex) R_f 0.19; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 3.3 Hz, 3H), 3.71−3.79 (m, 4H), 4.24 (q, J = 3.3 Hz, 2H), 4.78 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 33.6, 35.3, 61.8, 67.2, 83.1, 114.5, 167.0, 167.7; CI-LRMS *m*/*z* (rel abundance) 214 ((M + H)$^+$, 100%). Anal. Calcd for $C_9H_{11}NO_3S$: C, 50.69; H, 5.20; N, 6.57. Found: C, 50.81; H, 5.20; N, 6.46. (*Z*)-3-(4-Pyridylmethoxy)-4,4-dimethylpent-2-enenitrile (**6g**): mp 69−70 °C; TLC (30% EtOAc/hex) R_f 0.18; ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 3H), 4.61 (s, 1H), 5.53 (s, 1H), 7.28 (d, J = 5.9 Hz, 2H), 8.61 (dd, J = 4.8, 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.0, 38.3, 67.7, 71.0, 117.6, 121.3, 144.5, 150.0, 180.9; CI-LRMS *m*/*z* (rel abundance) 217 ((M + H)$^+$, 100%). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.11; H, 7.40; N, 12.97. (*Z*)-3-(4-Nitrophenylmethoxy)-4,4-dimethylpent-2-enenitrile (**6h**): mp 89−91 °C; TLC (10% EtOAc/hex) R_f 0.34; ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 9H), 4.65 (s, 1H), 5.63 (s, 2H), 7.56 (d, J = 8.5 Hz, 2H), 8.26 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.0, 38.3, 67.7, 117.7, 123.7, 123.9, 127.7, 142.8, 147.2, 147.7, 180.9; CI -LRMS *m*/*z* (rel abundance) 261 ((M + H)$^+$, 100%). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.66; H, 6.11; N, 10.71. Procedure B. Ethyl 3-amino-5-*tert*-butylfuran-2-carboxylate (**7a**): To a slurry of sodium hydride (62 mg, 2.6 mmol, 1.1 equiv) in anhydrous THF (50 mL) was added vinyl ether **6a** (500 mg, 2.4 mmol). The reaction mixture was stirred for 3 h, treated with a saturated NH_4Cl solution (2 mL), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 50 g, 10% EtOAc/hex) to afford aminofuran **7a** (440 mg, 88%) as a white solid: mp 43−44 °C; TLC (10% EtOAc/hex) R_f 0.19; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 9H), 1.36 (t, J = 7.0 Hz, 3H), 4.32 (q, J = 7.0 Hz, 2H), 4.51 (br s, 2H), 5.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.6, 28.5, 32.9, 59.4, 98.5, 124.5, 144.8, 160.4, 168.1; FAB-LRMS *m*/*z* (rel abundance) 212 ((M + H)$^+$, 100%). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.48; H, 8.06; N, 6.61. Ethyl 3-amino-4,6-dihydrothieno[3,4-*b*]furan-2-carboxylate (**7f**): mp 130−131 °C; TLC (20% EtOAc/hex) R_f 0.31; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, J = 7.0 Hz, 3H), 3.73−3.76 (m, 2H), 3.90−3.93 (m, 2H), 4.33 (q, J = 7.0 Hz, 2H), 4.59 (br s, 2H); CI-LRMS *m*/*z* (rel abundance) 214 ((M + H)$^+$, 100%). Anal. Calcd for $C_9H_{11}NO_3S$: C, 50.69; H, 5.20; N, 6.57. Found: C, 50.53; H, 5.27; N, 6.30. Procedure C. Ethyl 3-amino-5-*tert*-butylfuran-2-carboxylate (**7a**): A 0 °C solution of triphenyl phosphine (14.67 g, 56.0 mmol, 1.4 equiv) in anhydrous THF (200 mL) was treated with diethyl azodicarboxylate (9.74 g, 56.0 mmol, 1.4 equiv), ethyl glycolate (5.82 g, 56.0 mmol, 1.4 equiv), and 4,4-dimethyl-3-oxopentanenitrile (5.00 g, 40.0 mmol). The resulting solution was allowed to warm to room temperature and stirred for 15 h. NaH (2.69 g, 112.0 mmol, 2.8 equiv) was added and the reaction mixture was stirrred for 5 h and then quenched with H_2O (10 mL) and concentrated to approximately 100 mL under reduced pressure. EtOAc (500 mL) was added and the resulting mixture was washed with H_2O (500 mL). The aqueous layer was back-extracted with EtOAc (300 mL). The combined organic layers were washed with a saturated NaCl solution (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 200 g, 10% EtOAc/hex) to afford aminofuran **7a** (7.03 g, 83%) having identical ^{1}H NMR, ^{13}C NMR, TLC, and LRMS as described in Procedure B. Ethyl 3-amino-5-phenylfuran-2-carboxylate (**7b**): mp 92−104 °C; TLC (20% EtOAc/hex) R_f 0.28; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, J = 7.0 Hz, 3H), 4.38 (q, J = 7.0 Hz, 2H), 4.65 (br s, 2H), 6.37 (s, 1H), 7.32−7.40 (m, 3H), 7.71 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.6, 59.8, 99.9, 124.9, 128.6, 129.0, 129.3, 145.1, 147.1, 156.1, 160.4; EI-LRMS *m*/*z* (rel abundance) 231 (M$^+$, 100%). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.45; H, 5.67; N, 6.19. Procedure D. 3-Amino-2-(4-nitrophenyl)-5-*tert*-butylfuran (**7h**): Neat vinyl ether **6h** (1.004 g, 3.86 mmol) was treated with DBU (40 mL) and the resulting red solution was stirred for 20 min. Water (100 mL) was added and the mixture was extracted with EtOAc (100 mL). The aqueous layer was back-extracted with EtOAc (100 mL). The combined organic layers were washed with a saturated NaCl solution (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 75 g, 20% EtOAc/hex) to afford aminofuran **7h** (802 mg, 80%) as a deep red solid: mp 105−106 °C; TLC (20% EtOAc/hex) R_f 0.30; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 3.66 (br s, 2H), 5.84 (s, 1H), 7.52−7.56 (m, 2H), 8.19 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.7, 32.8, 101.5, 121.3, 124.4, 132.2, 135.0, 138.1, 143.2, 165.3; CI-LRMS *m*/*z* (rel abundance) 261 ((M +,H)$^+$, 100%). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.53; H, 6.18; N, 10.67. Ethyl 3-amino-5-(2-furanyl)furan-2-carboxylate (**7c**): mp 120−121 °C; TLC (20% EtOAc/hex) R_f 0.35; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, J = 7.0 Hz, 3H), 4.35 (q, J = 7.0 Hz, 2H), 4.68 (br s, 2H), 6.26 (s, 1H), 6.45 (dd, J_1 = 1.6 Hz, J_2 = 3.3 Hz, 1H), 6.78 (d, J = 3.3 Hz, 1H), 7.42−7.43 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.3, 60.6, 100.3, 109.2, 112.4, 125.8, 143.8, 145.6, 146.0, 149.0, 161.0; CI-LRMS *m*/*z* (rel abundance) 222 ((M + H)$^+$, 100%). Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.66; H, 4.96; N, 6.34. Procedure E. 3-Amino-2-(4-pyridyl)-5-*tert*-butylfuran hydrochloride (**7g**): To a solution of vinyl ether **6g** (200 mg, 0.92 mmol) in anh. THF (20 mL) was added KO*t*Bu (114 mg, 1.02 mmol, 1.1 equiv) in one portion. The reaction mixture was stirred for 20 min. Water (50 mL) was added and the resulting mixture was extracted with EtOAc (100 mL). The organic layer was washed with a saturated NaCl solution (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in Et_2O (20 mL) and treated with a 1 N HCl solution in Et_2O (20 mL). The resulting precipitate was filtered and washed with Et_2O to afford aminofuran **7g** (155 mg, 72%) as an orange solid: mp 196−198 °C; TLC (free base; 70% EtOAc/hex) R_f 0.20; ^{1}H NMR (DMSO-d_6) δ 1.22 (s, 9H), 6.05 (s, 1H), 7.62 (d, J = 6.6 Hz, 2H), 8.34 (d, J = 6.6 Hz, 2H) 8.2−9.0 (br s, 3H); ^{13}C NMR (DMSO-d_6) δ 28.1, 32.8, 101.4, 101.5, 114.1, 128.1, 139.0, 142.3, 146.2, 170.4; CI-LRMS *m*/*z* (rel abundance) 217 ((M + H)$^+$, 100%). Anal. Calcd for $C_{13}H_{16}N_2O\cdot0.5HCl$: C, 52.36; H, 6.42; N, 9.39. Found: C, 52.46; H, 6.32; N, 9.31.

Table 1. Synthesis of 3-Amino-2-furancarboxylate Esters



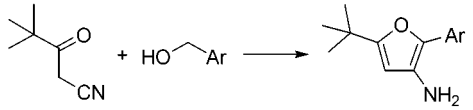
	R_1	R_2	Mitsunobu product (% isolated yield)	3-Aminofuran (% isolated yield)
1	*t*-Bu	H	 (80)[a] **6a**	 (88)[b] **7a**
2	*t*-Bu	H		 (83)[c] **7a**
3	Ph	H	 (77)[a] **6b**	 (60)[c] **7b**
4	furyl	H	 (80)[a] **6c**	 (61)[d] **7c**
5	H	Ph	 (63)[a] **6d**	
6	Me	Ph	 (82)[a] **6e**	
7			 (92)[a] **6f**	 (21)[b] **7f**

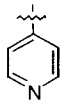
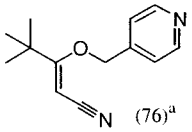
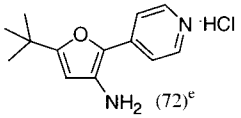
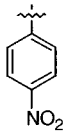
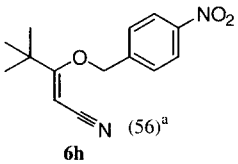
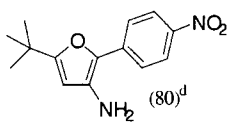
[a] Procedure A. [b] Procedure B. [c] Procedure C. [d] Procedure D.[4]

a phenyl substituent α to the nitrile, the Mitsunobu reaction produced the sterically less congested trans-substituted vinyl ethers as confirmed by NOE experiments[5] (Table 1, entries 5 and 6). These vinyl ethers did not cyclize under basic conditions. Vinyl ethers with no substituents α to the nitrile were found to have cis-configurations and were cyclized under basic conditions to produce the desired 3-aminofurans (Table 1, entries 3 and 4).

Electron-withdrawing substituents other than carboxylic esters are also capable of stabilizing the carbanion necessary for cyclization to the furan. The Mitsunobu products of 4-pyridylcarbinol and 4-nitrobenzyl alcohol proved to be sufficiently acidic to effect cyclization leading to 2-arylfurans **7g** and **7h** (Table 2, entries 8 and 9).

Table 2. Synthesis of 3-Amino-2-arylfurans



	Ar	Mitsunobu product (% isolated yield)	3-Aminofuran (% isolated yield)
8		 (76)[a] **6g**	 (72)[e] **7g**
9		 (56)[a] **6h**	 (80)[d] **7h**

[a] Procedure A. [d] Procedure D. [e] Procedure E, compound isolated as HCl salt.[4]

In summary, an efficient method for the preparation of 3-aminofurans has been developed. Currently, the method is limited to the synthesis of 5-alkyl-, 5-aryl-, and 4,5-fused furans.

Acknowledgment. We thank Peter Demou, László Musza, and Anthony Paiva for NMR spectroscopic and mass spectrometric assistance.

OL0059652

(5) Transverse NOE correlations were obtained on a Bruker DMX-500 spectrometer in phase sensitive mode according to the method of Huang and Shaka (Hwang, T. L.; Shaka, A. J. *J. Am. Chem. Soc.* **1992**, *114*, 3157−9. Cross Relaxation without TOCSY: Transverse Rotating-Frame Overhauser Effect Spectroscopy). NOE cross-peaks were observed between the aromatic ortho protons and the alpha-methylene protons, suggesting that they were on the same side of the double bond.