JOC*Note*

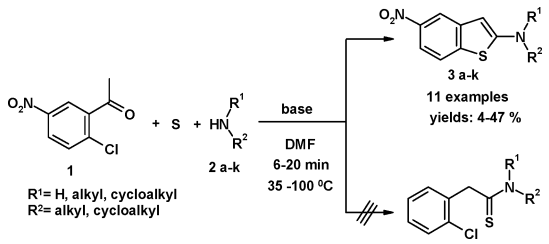
One-Pot Synthesis of Substituted 2-Aminobenzo[*b*]thiophenes†

Andrey Y. Solovyev, Dmitry A. Androsov, and Douglas C. Neckers*

Center for Photochemical Sciences, Bowling Green State University, Bowling Green, Ohio 43403

neckers@photo.bgsu.edu

Received October 16, 2006



Reaction of 1-(2-chloro-5-nitrophenyl)ethanone **1**, via Willgerodt−Kindler routes, using the primary and secondary amines **2a**−**k** resulted in a simple, efficient three-component one-pot synthesis of 2-aminobenzo[*b*]thiophenes **3a**−**k**.

Though derivatives of 2-dimethylamino-6-hydroxybenzo[*b*]-thiophene are important intermediates in the synthesis of the selective estrogen receptor modulators, raloxifene and analogues,[1−4] 2-aminobenzo[*b*]thiophenes in general belong to an elusive group of benzo[*b*]thiophenes. 2-Aminobenzo[*b*]thiophene itself is obtained in five steps (overall yield 48%) from thiosalicylic acid. The key reaction involves thioether cleavage of *ortho*-benzylmercaptophenylacetonitrile. In contrast to 2-hydroxybenzo[*b*]thiophene, which exists mainly as the tautomeric keto form, 2-aminobenzo[*b*]thiophene exists preferably in the amino form.[5] Other 2-aminobenzo[*b*]thiophenes synthesized classically include 2-morpholinobenzo[*b*]thiophene, which was obtained by the addition of morpholine to the C^2-C^3 bond of benzo[*b*]-thiophene in the presence of its alkali metal salt (yield 45%) followed by aromatization with sulfur at 250 °C (yield 60%),[6] 2-piperidinobenzo[*b*]thiophene prepared in 85% yield by heating a mixture of 2-bromobenzo[*b*]thiophene and piperidine in a sealed tube at 220 °C for 28 h and in 20% yield by heating a mixture of 3-bromobenzo[*b*]thiophene and piperidine in a sealed tube at 250−260 °C for 46 h,[7] and hydrogenation of 2-(phenylazo)-3,4,6-trimethylbenzo[*b*]thiophene in the presence of acetic anhydride which afforded 2-acetamido-3,4,6-trimethylbenzo[*b*]-thiophene (yield 18%).[8] 2-Dimethylamino-6-benzyloxybenzo-[*b*]thiophene was prepared in two steps through the treatment of a mixture 4-benzyloxybenzaldehyde and *N*,*N*-dimethylthioformamide with LDA at −78 °C and following cyclization−aromatization with $MeSO_3H$.[4]

Herein we report a simple, efficient three-component *one-pot* synthesis of a variety of 2-aminobenzo[*b*]thiophenes.

The reaction of 1-(2-chloro-5-nitrophenyl)ethanone **1** with primary and secondary amines under Willgerodt−Kindler conditions resulted in 2-aminobenzo[*b*]thiophenes **3a**−**k** (Scheme 1).

In general, it was found that a nitro group *para* to the chlorine atom promotes the reaction. Reaction did not occur in the absence of the nitro group. For example, 1-(2-chlorophenyl)-ethanone yielded a complex mixture of products but no corresponding benzo[*b*]thiophene.

The nature of the base is not important. K_3PO_4, NaOAc, or excess of amine could serve as a base. Primary amines give better yields of aminobenzo[*b*]thiophenes than secondary amines.

The reaction crucially depends on the concentration of the amine. A 1.5−3-fold excess is preferable for secondary amines, and a 1.5−2-fold excess is preferable for primary amines. The nature of the byproducts depends on the amine. In the case of primary amines, the main byproduct is 3-methyl-5-nitrobenzo-[*d*]isothiazole and becomes dominant in the presence of 8−10-fold excess of amine. In contrast, in the case of secondary amines, the main byproduct is the product of nucleophilic substitution in the benzene ring.

We found that the optimal ratio of acetophenone/sulfur is about 1:5. Generally, better yields from primary amines were observed at lower temperature (35−60 °C) while higher temperature (60−100 °C) worked better for the secondary amines. In contrast, primary amines are usually more reactive than secondary amines in the classical Willgerodt−Kindler reaction.[9] DMF was found to be the most favorable solvent.

Steric effects play an important role. The yield of 2-cyclopentylaminobenzo[*b*]thiophene **3f** (40%) is higher than the yield of 2-cyclohexylaminobenzo[*b*]thiophene **3g** (19%). Sterically hindered di-*N*-butylamine, diallylamine, and diisopropylamine failed to react, and aromatic (aniline) and heterocyclic (benzotriazole) amines failed to react. An attempt to obtain N-unsubstituted benzothiophene using NH_4Cl in the presence of NaOAc afforded 3-methyl-5-nitrobenzo[*d*]isothiazole **4** (yield 78%, Scheme 2). The synthesis of **4** under harsh conditions is reported in the literature.[10]

Whereas the classical Willgerodt−Kindler reaction requires high temperature and prolonged heating,[11,12] microwave

† Contribution #604 from the Center for Photochemical Sciences.

(1) Grese, T. A.; Pennington, L. D.; Sluka, J. P.; Adrian, M. D.; Cole, H. W.; Fuson, T. R.; Magee, D. E.; Phillips, D. L.; Rowley, E. R.; Shetler, P. K.; Short, L. L.; Venugopalan, M.; Yang, N. N.; Sato, M.; Glasebrook, A. L.; Bryant, H. U. *J. Med. Chem.* **1998**, *41*, 1272−1283.

(2) Grese, T. A.; Cho, S.; Finley, D. R.; Godfrey, A. G.; Jones, C. D.; Lugar, C. W.; Martin, M. J.; Matsumoto, K.; Pennington, L. D.; Winter, M. A.; Adrian, M. D.; Cole, H. W.; Magee, D. E.; Phillips, D. L.; Rowley, E. R.; Short, L. L.; Glasebrook, A. L.; Bryant, H. U. *J. Med. Chem.* **1997**, *40*, 146−167.

(3) Lee, K. C.; Moon, B. C.; Lee, J. H.; Chung, K.-H.; Katzenellenbogen, J. A.; Chi, D. Y. *Bioorg. Med. Chem.* **2003**, *11*, 3649−3658.

(4) Takeuchi, K.; Kohn, T. J.; Sall, D. J.; Denney, M. L.; McCowan, J. R.; Smith, G. F.; Gifford-Moore, D. S. *Bioorg. Med. Chem.* **1999**, *9*, 759−764.

(5) Stacy, G. W.; Villaescusa, F. W.; Wollner, T. E. *J. Org. Chem.* **1965**, *30*, 4074−4078.

(6) Grandclaudon, P.; Lablache-Combier, A. *J. Org. Chem.* **1978**, *43*, 4379−4381.

(7) Brower, K. R.; Amstutz, E. D. *J. Org. Chem.* **1954**, *19*, 411−414.

(8) Benincori, T.; Sannicolo, F. *J. Org. Chem.* **1988**, *53*, 1309−1312.

(9) Zbruev, O. I.; Stiasni, N.; Kappe, C. O. *J. Comb. Chem.* **2003**, *5*, 145−148.

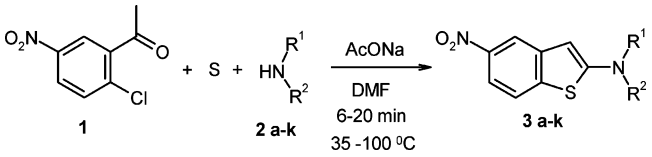
(10) U.S. Patent 6,355,796 B1.

(11) Schwenk, E.; Bloch, E. *J. Am. Chem. Soc.* **1942**, *64*, 3051−3052.

(12) Klingele, M. H.; Brooker, S. *Eur. J. Org. Chem.* **2004**, 3422−3434.

10.1021/jo062141a CCC: $37.00
Published on Web 03/22/2007

SCHEME 1



SCHEME 2

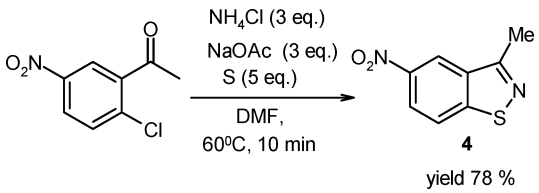


TABLE 1. Reaction Conditions and Yields of 2-Aminobenzo[*b*]thiophenes

entry	R^1	R^2	ratio of amine/S/base	temp (°C)	time (min)	yield of **3** (%)
3a	Me[a]	H	3/5/3	60	10	46
3b	allyl	H	2.17/5/0	45	10	47
3c	*n*-butyl	H	3.2/3/2	60	8	36
3d	benzyl	H	3.8/5/0	60	10	30
3e	*iso*-propyl	H	2.3/5/0	60	10	14
3f	cyclopentyl	H	2.15/5/0	60	10	40
3g	cyclohexyl	H	1.95/5/0	35	6	19
3h	Me[a]	Me	1.5/1.5/1.5	100	180	4
3i	$-(CH_2)_5-$		3.7/3/2	60	15	31
3j	$-(CH_2)_6-$		1.2/1.5/1.5	100	20	10
3k	$-(CH_2CH_2OCH_2CH_2)-$		1.4/5/1.5	100	12	12

[a] As the hydrochloride.

assistance[9,13−15] or special reagents,[16] surprisingly, our reaction proceeded under mild conditions.

In conclusion, we have found and developed a simple, convenient one-pot synthesis of 2-aminobenzo[*b*]thiophenes in which the benzene ring is functionalized. The method allowed us to synthesize a number of earlier unknown heterocycles.

Experimental Section

General Procedure for the Synthesis of 2-Aminobenzo[*b*]-thiophenes (3a−k). 1-(2-Chloro-5-nitrophenyl)ethanone **1** (200 mg, 1.0 mmol), the corresponding amine **2a−k** (1.2−3.8 equiv), DMF (10 mL), elemental sulfur (1.5−5 equiv), and NaOAc (0−3 equiv) (in that order; for molar ratios, see Table 1) were charged into a 50 mL round-bottom flask. The mixture was heated and stirred for 6−180 min at 35−100 °C. DMF was removed under reduced pressure, and the residue was purified via column chromatography (SiO_2, hexane/ethyl acetate 8/1) affording corresponding 2-aminobenzo[*b*]thiophenes **3a−k** (4−47% yield; see Table 1).

Methyl-(5-nitrobenzo[*b*]thiophen-2-yl)amine (3a): Yellow solid, 96 mg (46%), mp 138−139 °C; ^{1}H NMR ($CDCl_3$) δ 3.01 (s, 3H), 4.10 (br s, 1H), 6.16 (s, 1H), 7.84 (d, J = 9.0 Hz, 1H), 8.16 (dd, J = 9.0, 2.4 Hz, 1H), 8.48 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 32.2, 97.0, 115.6, 118.8, 123.6, 132.4, 143.5, 144.7, 145.5; *m*/*z* (EI$^+$ mode) 208 (M$^+$, 49%), 162 (100), 134 (44), 89 (21), 63 (30); HRMS (EI$^+$ mode) calcd for M$^+$ 208.0307, found 208.0306.

Allyl-(5-nitrobenzo[*b*]thiophen-2-yl)amine (3b): Red solid, 111 mg (47%), mp 105−107 °C; ^{1}H NMR ($CDCl_3$) δ 3.89 (d, J = 5.7 Hz, 2H), 4.19 (br s, 1H), 5.26 (dd, J = 10.2, 1.2 Hz, 1H), 5.38 (dd, J = 17.4, 1.5 Hz, 1H), 5.98−6.12 (m, 1H), 6.18 (s, 1H), 7.81 (d, J = 9.0 Hz, 1H), 8.13 (dd, J = 9.0, 2.1 Hz, 1H), 8.48 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 48.2, 98.1, 115.6, 117.2, 118.8, 123.5, 132.54, 134.6, 141.8, 144.7, 145.2; *m*/*z* (EI$^+$ mode) 234 (M$^+$, 81%), 193 (34), 173 (23), 161 (43), 147 (100), 120 (21), 89 (17), 63 (31); HRMS (EI$^+$ mode) calcd for M$^+$ 234.0463, found 234.0461.

Butyl-(5-nitrobenzo[*b*]thiophen-2-yl)amine (3c): Red solid, 90 mg (36%), mp 109−110 °C; ^{1}H NMR ($CDCl_3$) δ 1.01 (t, J = 7.5 Hz, 3H), 1.45−1.57 (m, 2H), 1.69−1.79 (m, 2H), 3.23 (t, J = 7.2 Hz, 2H), 6.13 (s, 1H), 7.82 (d, J = 8.7 Hz, 1H), 8.14 (dd, J = 8.7, 2.1 Hz, 1H), 8.48 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 20.4, 31.4, 45.4, 96.9, 115.6, 118.7, 123.5, 132.5, 142.5, 144.6, 145.4; *m*/*z* (EI$^+$ mode) 250 (M$^+$, 59%), 207 (88), 161 (100), 147 (26), 133 (15), 89 (19); HRMS (EI$^+$ mode) calcd for M$^+$ 250.0776, found 250.0774.

Benzyl-(5-nitrobenzo[*b*]thiophen-2-yl)amine (3d): Red solid, 86 mg (30%), mp 123−126 °C; ^{1}H NMR ($CDCl_3$) δ 4.43 (br s, 3H), 6.16 (s, 1H), 7.29−7.45 (m, 5H), 7.82 (d, J = 8.7 Hz, 1H), 8.15 (dd, J = 8.7, 2.1 Hz, 1H), 8.50 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 50.0, 98.2, 115.6, 118.8, 123.6, 127.7, 127.75, 128.8, 132.5, 138.2, 141.9, 144.7, 145.3; *m*/*z* (EI$^+$ mode) 284 (M$^+$, 47%), 282 (11), 147 (18), 91 (100), 77 (8), 65 (44), 51 (20); HRMS (EI$^+$ mode) calcd for M$^+$ 284.0620, found 284.0624.

Isopropyl-(5-nitrobenzo[*b*]thiophen-2-yl)amine (3e): Red-orange solid, 32 mg (14%), mp 148−150 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (d, J = 6.3 Hz, 6H), 3.62−3.69 (m, 1H), 3.87 (br s, 1H), 6.14 (s, 1H), 7.85 (d, J = 8.7 Hz, 1H), 8.18 (dd, J = 8.7, 2.1 Hz, 1H), 8.49 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.8, 46.4, 97.2, 115.6, 118.8, 123.5, 132.8, 141.0, 144.7, 145.3; *m*/*z* (EI$^+$ mode) 236 (M$^+$, 43%), 221 (100), 175 (37), 148 (29), 121 (15); HRMS (EI$^+$ mode) calcd for M$^+$ 236.0620, found 236.0618.

Cyclopentyl-(5-nitrobenzo[*b*]thiophen-2-yl)amine (3f): Red solid, 104 mg (40%), mp 142−145 °C; ^{1}H NMR ($CDCl_3$) δ 1.72−1.87 (m, 6H), 2.05−2.12 (m, 2H), 3.81−3.88 (m, 1H), 4.02 (br s, 1H), 6.14 (s, 1H), 7.81 (d, J = 9.0 Hz, 1H), 8.17 (dd, J = 9.0, 2.1 Hz, 1H), 8.45 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.3, 33.4, 56.4, 97.6, 115.6, 118.7, 123.5, 132.7, 141.7, 144.6, 145.3; *m*/*z* (EI$^+$ mode) 262 (M$^+$, 90%), 233 (68), 220 (29), 194 (100), 173 (32), 159 (18), 148 (55), 121 (21), 69 (34); HRMS (EI$^+$ mode) calcd for M$^+$ 262.0776, found 262.0774.

Cyclohexyl-(5-nitrobenzo[*b*]thiophen-2-yl)amine (3g): Orange solid, 52 mg (19%), mp 121−123 °C; ^{1}H NMR ($CDCl_3$) δ 1.44−1.49 (m, 5H), 1.68−1.72 (m, 1H), 1.81−1.86 (m, 2H), 2.15−2.19 (m, 2H), 3.29 (tt, J = 3.6, 9.6 Hz, 1H), 3.90 (br s, 1H), 6.13 (s, 1H), 7.82 (d, J = 8.7 Hz, 1H), 8.15 (dd, J = 8.7, 2.1 Hz, 1H), 8.49 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.0, 25.9, 33.1, 53.8, 96.9, 115.6, 118.7, 123.5, 132.8, 140.9, 144.6, 145.3; *m*/*z* (EI$^+$ mode) 276 (M$^+$, 89%), 233 (55), 194 (58), 173 (31), 159 (18), 148 (46), 89 (14), 55 (100); HRMS (EI$^+$ mode) calcd for M$^+$ 276.0933, found 276.1928.

Dimethyl-(5-nitrobenzo[*b*]thiophen-2-yl)amine (3h): Orange solid, 9 mg (4%), mp 130−132 °C; ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 6H), 6.68 (s, 1H), 7.88 (d, J = 8.7 Hz, 1H), 8.19 (dd, J = 8.7, 2.4 Hz, 1H), 8.73 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 44.4, 108.4, 118.3, 118.7, 123.7, 134.7, 144.9, 145.4, 149.0; *m*/*z* (EI$^+$ mode) 222 (M$^+$, 100%), 176 (86), 160 (62), 148 (21), 134 (42), 89 (40), 63 (33); HRMS (EI$^+$ mode) calcd for M$^+$ 222.0463, found 222.0460.

1-(5-Nitrobenzo[*b*]thiophen-2-yl)pyrrolidine (3i): Red solid, 78 mg (31%), mp 134−137 °C; ^{1}H NMR ($CDCl_3$) δ 2.04−2.12 (m, 4H), 3.49−3.52 (m, 4H), 6.20 (s, 1H), 7.82 (d, J = 9.0 Hz, 1H), 8.12 (dd, J = 9.0, 2.1 Hz, 1H), 8.87 (d, J = 2.1 Hz, 1H); ^{13}C

(13) Poupaert, J. H.; Duarte, S.; Colacino, E.; Depreux, P.; McCurdy, C. M.; Lambert, D. L. *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *179*, 1959−1973.

(14) Aghapoor, K.; Darabi, H.-R.; Tabar-Heydar, K. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 1183−1187.

(15) Aghapoor, K.; Darabi, H.-R.; Tabar-Heydar, K. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 1189−1192.

(16) Schroth, W.; Andersch, J. *Synthesis* **1989**, 202−204.

NMR ($CDCl_3$) δ 25.3, 51.5, 99.9, 118.2, 119.1, 123.6, 133.7, 144.4, 145.6, 145.8; *m*/*z* (EI^+ mode) 248 (M^+, 100%), 201 (37), 192 (24), 173 (34), 160 (43), 146 (36), 133 (20), 89 (46); HRMS (EI^+ mode) calcd for M^+ 248.0620, found 248.0615.

1-(5-Nitrobenzo[*b*]thiophen-2-yl)piperidine (3j): Yellow-orange solid, 27 mg (10%), mp 143−145 °C; ^1H NMR ($CDCl_3$) δ 1.61−1.69 (m, 2H), 1.81−1.88 (m, 4H), 3.04−3.11 (m, 4H), 6.74 (s, 1H), 7.87 (d, J = 9.0 Hz, 1H), 8.17 (dd, J = 9.0, 2.1 Hz, 1H), 8.62 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.3, 26.2, 54.1, 109.7, 118.0, 118.7, 123.7, 135.0, 145.0, 145.2, 149.3; *m*/*z* (EI^+ mode) 262 (M^+, 100%), 215 (24), 206 (12), 160 (41), 146 (14), 133 (36), 89 (49); HRMS (EI^+ mode) calcd for M^+ 262.0776, found 262.0776.

4-(5-Nitrobenzo[*b*]thiophen-2-yl)morpholine (3k): Orange solid, 31 mg (12%), mp 183−184 °C; ^1H NMR ($CDCl_3$) δ 3.14−3.17 (m, 4H), 3.96−3.99 (m, 4H), 6.83 (s, 1H), 7.90 (d, J = 9.0 Hz, 1H), 8.20 (dd, J = 9.0, 2.1 Hz, 1H), 8.62 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 53.0, 67.0, 110.8, 117.7, 119.0, 123.9, 134.5, 145.0, 145.3, 147.8; *m*/*z* (EI^+ mode) 264 (M^+, 96%), 206 (96), 160 (100), 146 (14), 133 (32), 89 (48); HRMS (EI^+ mode) calcd for M^+ 264.0569, found 264.0571.

3-Methyl-5-nitrobenzo[*d*]isothiazole (4). A mixture of 1-(2-chloro-5-nitrophenyl)ethanone **1** (200 mg, 1.0 mmol), NH_4Cl (160 mg, 3.0 mmol), NaOAc (246 mg, 3.0 mmol), and sulfur (160 mg, 5.0 mmol) was added to 10 mL of DMF and stirred for 10 min at 55−60 °C. The resulting dark solution was cooled to rt, and the DMF was removed under reduced pressure. The residue was purified via column chromatography (SiO_2, hexane/ethyl acetate 5/1) to afford 152 mg (78%) of the light orange product: mp 109−110 °C (lit.[10] mp 114−115 °C); ^1H NMR ($CDCl_3$) δ 2.85 (s, 3H), 8.05 (d, J = 8.7 Hz, 1H), 8.38 (dd, J = 8.7, 2.1 Hz, 1H), 8.84 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.5, 119.6, 120.7, 121.7, 135.1, 145.6, 157.4, 164.1; *m*/*z* (EI^+ mode) 194 (M^+, 42%), 164 (46), 148 (17), 136 (35), 121 (25), 69 (27), 63 (100).

Acknowledgment. The authors sincerely acknowledge the Office of Naval Research (Grant No. N00014-05-1-0372) for summer undergraduate research support (A.Y.S.). We thank NSF (CHE-0234796) for the MALDI-TOF mass spectrometer.

Supporting Information Available: General information and copies of MS, ^1H, and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062141A