Preparation of 5-Nitro-2-amino[*b*]thiophenes and 1-(2-Amino-5-nitrophenyl)ethanones *via* Microwave Irradiation

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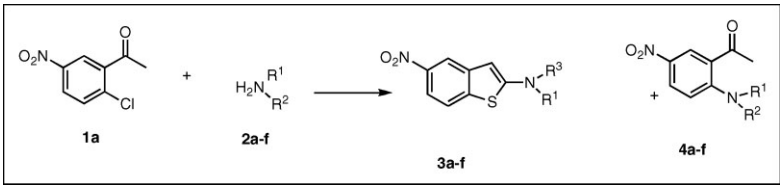

1-(2-Chloro-5-nitrophenyl)ethanone) reacts with various amines in the presence of sulfur under microwave radiation to give the corresponding 2-aminobenzo[*b*]-thiophenes **3a–f** in good yields. The yields of **3a–f** are vastly superior to those obtained using conventional heating. Additionally, 1-(2-amino-5-nitrophenyl)ethanones **4a–f** were also obtained. A mechanism is proposed in which 2-amino thiophenes **3a–f** are formed by a S_NAr mechanism involving an intramolecular addition of sulfur of the intermediate thioamide to the 2-substituted carbon to give a Meisenheimer complex, which collapses to 2-aminothiophenes **3a–f**, and 2-amino ketones (**4a–f**) are formed by a parallel pathway involving nucleophilic addition amine to the 2-chloro position of **1** to form a Meisensheimer complex, which collapses to the amino ethanones.

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INTRODUCTION

In our continuing research on microwave-assisted synthesis of heterocycles [1], we directed our attention to preparing 2-aminobenzo[*b*]-thiophenes. Our interest in these heterocycles was piqued by their extensive use in the chemical and pharmaceutical industries. For example, 2-aminothiophenes are important precursors or intermediates in the preparation of coumarin dyes, biologically active chemicals, other fused heterocycles, *etc*. [2–4].

Before this study, 2-aminothiophenes were prepared primarily by the Gewald reaction [5], which involves treating an activated ketone, an activated nitrile and sulfur in the presence of morpholine as catalyst. Recently, the Gewald reaction was carried out using KF-alumina as catalyst [6] and microwave irradiation for heating. Cyclohexanone and cyclopentanone gave 2-amino products in very good yields (85–92%), whereas other cyclic ketones and various acyclic ketones gave modest yields (55–66%). All reactions were completed in 3.5–8.0 min. On the other hand, when the reactions were carried out using conventional heating (CH), the 2-aminothiphenes were obtained in comparable yields but a much longer time (3.5–7 h) was required [6].

Neckers and coworkers [7] reported a one-pot synthesis of 5-nitro-2-aminobenzo[*b*]thiophenes *via* a Willgerodt–Kindler (W-K) [8] using CH. Although the thiophenes were formed quickly (6–20 min), the yields were generally mediocre (4–47%). Furthermore, 2-chlorophenyl)ethanones that lacks a 5-nitro group failed to react. To see if these yields could be increased, we subjected the reactions to microwave irradiation and report the results herein.

RESULTS AND DISCUSSION

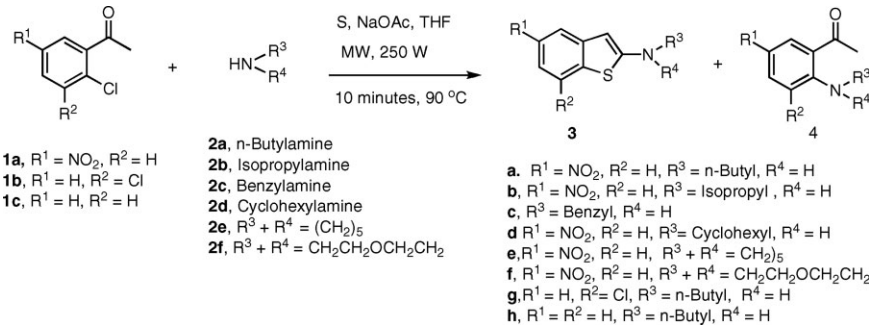
Equation (1) outlines the microwave-assisted reactions carried out in our laboratories for preparation of several 5-nitro-2-amino-benzo[*b*]thiophenes (**3a–f**). As shown, the reaction 5-nitro-1-(2-chlorophenyl)ethanone (**1**) with the appropriate amine **(2a–f)**, elemental sulfur, NaOAc and DMF using microwave irradiation at 90–100°C for 10 min yielded thiophene analogs (**3a–f**) as major products along with minor amounts of 2-amino-5-nitroethanones (**4a–f**). The microwave yields as well as the yields of **3a–f** reported previously using CH [7] are listed in Table 1.

Considering first the relative yields of **3a–f** using microwave radiation (MV) *versus* CH, one sees that the yields from the former are significantly higher than those of the latter. For example, the ratio of the yields of **3b** and **3d** (entries 2 and 4) using MV *versus* CH was 60:14 and 52:19, respectively. Additionally, the ratio of the yields of the morpholino derivative **3f** was essentially the same (10 *vs*. 12%) (entry 6) in DMF. However, the MW reaction using NMM (entry 7) increased to 45%.

A possible mechanism for the formation of **3** and **4** is shown in Scheme 1. As shown, there are two parallel

Table 1

Reaction conditions and yields of compound **3a–f** and **4a–f.**



	Ketone	Amine	Yield (%)					
			2-Aminothiophene			2-Aminoethanone		
	1	**2**	**3**	MW[a]	Conventional[b]	**4**	MW[a]	Conventional[b]
1	**a**	**a**	**a**	71	36 (8, 60)	**a**	60	31 (8, 60)
2	**a**	**b**	**b**	60	14 (10,60)	**b**	62	30 (10, 60)
3	**a**	**c**	**c**	62	30 (10, 60)	**c**	52	52 (10, 60)
4	**a**	**d**	**d**	52	19 (6, 35)	**d**	65	65 (6, 35)
5	**a**	**e**	**e**	65	31 (15, 60)	**e**	10	12 (15, 60)
6	**a**	**e**	**f**	10	12 (20, 100)	**f**	48	10 (20, 100)
7	**a**	**e**	**f**	45[c]	–	**f**	25[c]	
8	**b**	**a**	**g**	0	0	**g**	0	0
9	**c**	**a**	**h**	0	0	**h**	0	0

[a] DMF used as solvent unless indicated otherwise. MW reactions were carried out at 90°C for 10 min.
[b] Respective time (minutes) and temperature (°C) for conventional reactions are given in parenthesis and ranged between 6 and 20 min and 35 and 100°C.
[c] NMM used as solvent.

pathways to the two products. One involves the reaction of 5-nitro-2-chloro ketone (**1**), amine (**2**), and sulfur proceeds *via* a W-K reaction to give the corresponding thioamide (**5**). Compound **5** then undergoes a substitution nucleophilic aromatic (S_NAr) intramolecular addition of sulfur to the 2-chloro-substituted carbon to give a Meisenheimer complex **6**, which then collapses to **3**. However, the starting ketone **1** can also proceed *via* a S_NAr pathway in which amine **2** adds intramolecularly to the 2-chloro carbon atom of **1** to form the resonance-stabilized Meisenheimer complex **7** and **8**. The complex then collapses to **4**. The stability of this complex probably allows this pathway to compete successfully with the addition of amine **2** to the C═O group in **1** giving an enamine, which is most likely the first step in the W-K mechanism [8,9].

In support of our proposed mechanism, the starting acetophenones **1b** and **Ic** (entries 8 and 9), which lack a 5-nitro group, failed to react by either pathway. Further, we were able to isolate the direct amination products **4a–f** by carrying out microwave-assisted reactions of **1a** with the amines **2a–f** in the absence of sulfur and solvent. As shown in Table 2, compounds **4a–f** were obtained in excellent yields (93–97%) using microwave irradiation at 90°C for only 5 min.

An added feature of this reaction is that various 2-aminoacetophenones are excellent precursors to various

Scheme 1

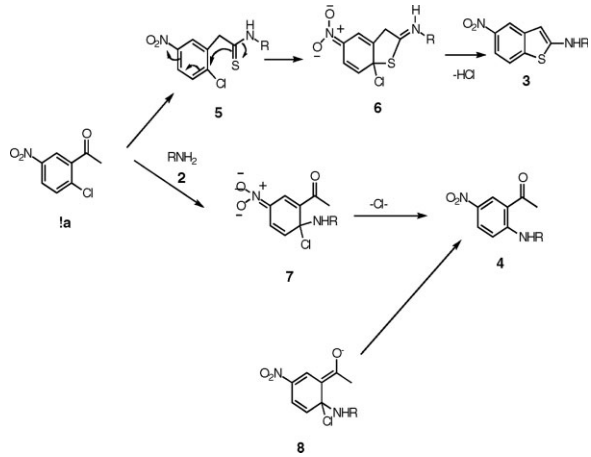
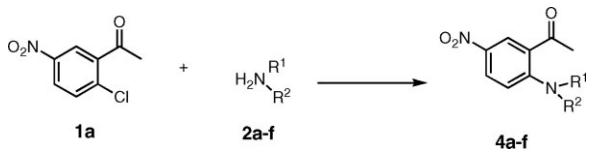


Table 2

Microwave-assisted synthesis of 5-nitro-2-aminoacetophenones (**4a–f**) using primary and secondary amines.[a]



Entry	Amine	Products [yield (%)][b]
1	*n*-Butylamine (**2a**)	**4a** (93)
2	Isopropylamine (**2b**)	**4b** (97)
3	Benzylamine (**2c**)	**4c** (92)
4	Cyclohexylamine (**2d**)	**4d** (94)
5	Pyrrolidine(**2e**)	**4e** (97)
6	Morpholine (**2f**)	**4f** (93)

[a] Reaction mixtures were subjected to microwave radiation at 90°C for 5 min.

[b] Product yields were determined by gravimetric analysis. Products were identified by NMR, IR, and elemental analyses.

biologically important compounds, such as azines [10], heterocyclic compounds [10], and repaglinide and related hypoglycemic benzoic acid derivatives [11].

EXPERIMENTAL

The ^{1}H and ^{13}C NMR were recorded on a 500 MHz Joel multinuclear NMR spectrometer; chemical shifts were referenced to TMS as internal standard. Microwave experiments were carried out in CEM-Driver microwave. All chemicals were purchased from Aldrich Chemicals and were used without further purification. Elemental analyses were performed by the SMU Analytical Services.

General procedure for the preparation of 5-nitro-2-amino[*b*]thiophenes (3a–f). In a typical experiment, 1-(2-chloro-5-nitrophenyl)-ethanone (**1**) (1 equiv) was mixed with amine 2 (2 equiv), sulfur (3 equiv), DMF or *N*-methylpyrrolidine as solvent, and base (sodium acetate or methylpyrrolidine) in a microwavable test tube. The tube was then capped and charged into a CEM microwave instrument, and the mixture was irradiated with 250 psi pressure and at a temperature for several minutes (see Table 1 for conditions). After cooling, the reaction mixture was dissolve in ethyl acetate and then washed with brine. The ethyl acetate layer was separated, dried over sodium sulfate, and evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography using ethyl acetate–hexane (9:1, v/v) as eluent, and the compounds were identified by comparison of their ^{1}H and ^{13}C NMR spectral data with those previously reported [7].

General procedure for the preparation of 1-(2-amino-5-nitrophenyl)ethanones (4a–f). In a typical experiment, 1 equiv 1-(2-chloro-5-nitrophenyl)ethanone (**1**) and 2 equiv of the appropriate amine **2a–f** were placed in a microwavable test tube and then capped. The mixture was then placed in a CEM-driven microwave and heated at 90°C for 10 min. After cooling, the reaction mixture was worked up as described in the general procedure for the preparation of **3a–f**. The ^{1}H and ^{13}C NMR, IR spectral data, and elemental analyses for these novel compounds are shown later.

1-(2-(n-Butylamino)-5-nitrophenyl)ethanone (4a). This compound was obtained as light yellow solid, mp (46.8–48.3°C); IR: 637.1, 748.2, 904.3, 953.4, 1213.8, 1322.2, 1496.8, 1608.9, 1633.8, 2960.6, 3284.9 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 0.96 (t, J = 7.45 Hz, 3H, CH_3), 1.42–1.49 (m, 2H, CH_2), 1.64–1.71 (m, 2H, CH_2), 2.63 (s, 1H, CH_3), 3.26–3.30 (m, 2H, CH_2), 6.68 (d, J = 9.75 Hz, 1H, aromatic), 8.17 (dd, J = 2.3 Hz, 9.15 Hz, 1H, aromatic), 8.70 (d, J = 2.5 Hz, 1H, aromatic), 9.63 (br, 1H, NH). ^{13}C NMR (deuteriochloroform): δ 13.8 (CH_3), 20.2 (CH_2), 27.8 (CH_3), 30.8 (CH_2), 42.8 (CH_2), 111.5 (C), 115.7 (CH), 130.0 (CH), 130.1 (CH), 135.1 (C), 154.7 (C), 200.5 (CO). *Anal*. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.86; H, 7.01; N, 12.05.

1-(2-(Isopropylamino)-5-nitrophenyl)ethanone (4b). This compound was obtained as light orange solid, mp (68.3–71.4°C); IR: 676.1, 634.8, 831.2, 1172.3, 1114.5, 1236.4, 1338.0, 1440.3, 1486.9, 1527.8, 1580.9, 1604.4, 1642.7, 1690.2, 1708.9, 2973.5, 3249.2 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 1.29 (d, J = 6.30 Hz, 6H, —CH_3 X 2), 2.61 (S, 3H, CH_3), 3.78–3.82 (m, 1H, CH), 6.68 (d, J = 9.15 Hz, 1H, aromatic), 8.13 (dd, J = 2.3 Hz, 9.15 Hz, 1H, aromatic), 8.67 (d, J = 2.3 Hz, 1H, aromatic), 9.60 (br, 1H, NH). ^{13}C NMR (deuteriochloroform): δ 22.5 (CH_3), 27.9 (CH_3), 44.2 (CH), 111.8 (CH), 126.3 (C), 129.9 (CH), 130.3 (CH), 132.0 (CH), 153.8 (C), 200.4 (CO). *Anal*. Calcd. for $C_{15}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 10.36. Found: C, 60.86; H, 5.27; N, 10.45.

1-(2-(Benzyl)-5-nitrophenyl)ethanone (4c). This compound was obtained as light yellow solid, mp (89.1–91.5°C); IR: 696.7, 746.4, 819.7, 965.4, 1118.4, 1224.9, 1326.0, 1493.7, 1579.0, 1605.7, 1643.7, 3068.7, 3280.9 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 2.69 (s, 3H, CH_3), 4.54 (d, J = 5.65 Hz, 1H, CH_2), 6.68 (d, J = 9.20 Hz, 1H, aromatic), 7.28–7.37 (m, 5H, aromatic), 8.15 (d, J = 9.75 Hz, 1H, aromatic), 8.73 (d, J = 2.25 Hz, 1H, aromatic), 10.0 (br, 1H, NH). ^{13}H NMR (deuteriochloroform): δ 27.9 (CH_3), 47.1 (CH_2), 112.2 (CH), 116.3 (C), 127.0 (CH), 127.9 (CH), 129.1 (CH), 129.9 (CH), 130.0 (CH), 135.7 (C), 136.7 (C), 154.6 (C), 200.7 (CO). *Anal*. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.86; H, 5.27; N, 10.45.

1-(2-Cyclohexylamino-5-nitrophenyl)ethanone (4d). This compound was obtained as light yellow solid, mp (124.3–126.1°C); IR: 654.97, 757.7, 834.5, 907.4, 953.2, 1115.3, 1225.0, 1315.7, 1442.2, 1492.5, 1529.5, 1579.4, 1603.7, 1649.2, 1708.0, 2852.8, 2927.2, 3254.1 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 1.31–1.46 (m, 5H, CH_2), 1.63–1.65 (m, 1H, CH_2), 1.78–1.79 (m, 2H, CH_2), 1.99–2.03 (m, 2H, CH_2), 2.65 (s, 3H, CH_3), 3.51–3.52 (m, 1H, CH), 6.71 (d, J = 9.70 Hz, 1H, aromatic), 8.15 (dd. J = 2.90 Hz, 9.70 Hz, 1H, aromatic), 8.71 (d, J = 2.90 Hz, 1H, aromatic), 9.75 (br, 1H, NH). ^{13}C NMR (deuteriochloroform): δ 24.4 (CH_2), 25.5 (CH_2), 27.9 (CH_3), 32.4 (CH_2), 51.1 (CH_2), 111.8 (CH), 115.6 (C), 129.9 (CH), 130.4 (CH), 134.8 (C), 153.8 (C), 200.5 (CO). *Anal*. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.16; H, 6.77; N, 10.48.

1-(5-Nitro-2-(pyrrolidin-1-yl)phenyl)ethanone (4e). This compound was obtained as a colorless solid, mp (149.8–

151.8°C); IR: 747.9, 802.1, 867.4, 914.7, 955.2, 1113.4, 1229.2, 1266.8, 1300.6, 1369.1, 1447.1, 1481.8, 1501.9, 1563.2, 1556.1, 1682.4, 2851.6 cm^{-1}; ^1H NMR (deuteriochloroform): δ1.97−2.0 (m, 4H, NCH_2 X 2), 2.62 (s, 3H, CH_3) 3.17−3.19 (m, 4H, NCH_2 X 2), 6.70 (d, J = 9.75 Hz, 1H, aromatic), 8.08 (dd, J = 2.3 Hz, 9.2 Hz, 1H, aromatic), dd, J = 2.3 Hz, 1H, aromatic). ^{13}C NMR (deuteriochloroform): δ 25.8 (NCH_2), 29.0 (CH_3), 52.3 (OCH_2), 113.7 (CH), 124.2 (C), 126.8 (CH), 127.3 (CH), 135.6 (C), 150.8 (C), 198.4 (CO). *Anal*. Calcd. for $C_{14}H_{12}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.63; H, 6.07; N, 11.89.

1-(2-Morpholino)-5-nitrophenyl)ethanone (4f). This compound was obtained as light yellow solid, mp (61.1–63.6°C); IR: 601.3, 653.7, 739.2, 905.3, 931.3, 1263.7, 1043.5, 1107.8, 1229.4, 1342.6, 1452.6, 1503.8, 1576.2, 1598.0, 1684.7 cm^{-1}; 2859.5 ^1H NMR (deuteriochloroform): δ 2.63 (s, 3H, CH_3)), 3.15−3.17 (m, 4H, NCH_2 X 2), 3.84−3.86 (m, 4H, OCH_2 X 2), 2.63 (s, 3H, CH_3), 7.03 (d, J = 9.2 Hz, 1H, aromatic), 8.22 (dd, J = 2.4 Hz, 9.2 Hz, 1H, aromatic), 8.31 (d, J = 2.4 Hz, 1H, aromatic). ^{13}C NMR (deuteriochloroform): δ 28.7 (CH_3), 52.4 (NCH_2), 66.4 (OCH_2), 117.6 (CH), 127.2 (CH), 127.5 (CH), 131.8 (C), 141.0 (C), 155.3 (C), 200.7 (CO). Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.86; H, 5.67; N, 11.25.

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REFERENCES AND NOTES

[1] See, for example: (a) Kamila, S; Biehl, E. R. J Heterocycl Chem 2007, 44, 407; (b) Kamila, S.; Biehl, E. R. J Heterocycl Chem 2006, 43, 1; (c) Kamila, S.; Koh, B.; Khan, O.; Biehl, E. R. J Heterocycl Chem 2006, 43, 1641; (d) Kamila, S.; Zhang, H.; Biehl, E. R. Heterocycles 2005, 65, 2493.

[2] For an excellent review on 2-aminothiophenes see: Sabnis, R. W.; Rangnekar, D. W.; Sonawane, N. D. J Heterocycl Chem 1999, 36, 333.

[3] Rana, A.; Siddiqui, N.; Khan, S. A. J Indian Pharm Sci 2007, 69, 10.

[4] Steinfeld, G.; Kersting, B. Z Anorg Allg Chem 2006, 32, 2010.

[5] Gewald, K; Schinke, E.; Boettcher, H. Chem Ber 1999, 99, 94.

[6] Sridhar, M.; Rao, R. M.; Baba, H. K.; Kumbhare, R. M. Tetrahedron Lett 2007, 48, 3171.

[7] Solovyev, A. Y.; Androsov, D. A.; Neckers, D. C. J Org Chem 2007, 72, 3122.

[8] Assinger, F.; Offermanns, H. Angew Chem Int Ed 1967, 6, 907.

[9] For reviews, see (a) Brown, E. V. Synthesis 1975, 358 and references cited therein; (b) Asinger, F.; Schafer, K.; Halcour, A.; Triem, H. Angew Chem Int Ed Engl 1964, 3, 19, and references cited therein.

[10] Loghmani-Khouzani, H.; Sadegi, M. M.; Safari, J.; Sabzi-Fini, O. J Sci I R Iran 2001, 12, 233.

[11] Grell, W.; Hurnaus, R.; Griss, G.; Sauter, R.; Rupprecht, E.; Mark, M.; Luger, P.; Nar, H.; Wittneben, H.; Mueller, P. J Med Chem 1998, 41, 5219.