Tetrahedron Letters 50 (2009) 3746–3749

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Mannich reactions of annulated thiophene derivatives

Xin Chen [a], Ronald L. Elsenbaumer [a,b,*]

[a] Department of Materials Science and Engineering, University of Texas at Arlington, Arlington, TX 76019, USA
[b] Department of Chemistry and Biochemistry, University of Texas at Arlington, TX 76019, USA

ARTICLE INFO

Article history:
Received 9 February 2009
Revised 18 March 2009
Accepted 31 March 2009
Available online 8 April 2009

Keywords:
Mannich reaction
Aminoalkylation
Thieno[3,4-*d*]-1,3-dithiole-2-thione
Thieno[3,4-*d*]-1,3-dithiol-2-one
Synthesis
Characterization

ABSTRACT

Aminoalkylation reactions were applied to two annulated thiophene derivatives to successfully prepare mono- and bis-substituted Mannich bases. Compounds were characterized by NMR, FT-IR, and HRMS.

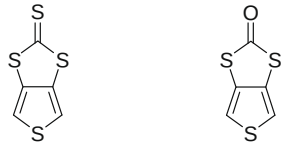
1. Introduction

Thieno[3,4-*d*]-1,3-dithiole-2-thione (**1**) and thieno[3,4-*d*]-1,3-dithiol-2-one (**2**) are structurally similar heterocyclic compounds (Scheme 1), and these two annulated thiophene derivatives share some very interesting features. First, they are easy to convert into dithiolate ligands to form organic metal complexes. Metal-bis-dithiolene complexes, such as $M(dmit)_2$ (dmit = 1,3-dithiole-2-thione-4,5-dithiolate),[1,2] are one class of the most extensively studied hybrid materials owing to their possible applications as organic conductors and/or supperconductor.[3–5] Second, they are readily subjected to coupling reaction with trialkyl phosphite to yield dithiophene–tetrathiofulvalene (DT–TTF) compounds.[6,7] DT–TTFs and their charge transfer salts are another class of electroactive species, which are actively studied worldwide.[8,9] Therefore, functionalization of compounds **1** and **2** would become a crucial step in the process of making new conductive oligomers, polymers, and organic metal complexes.

Mannich reactions applied to the thiophene ring in order to introduce aminoalkyl groups at 2 and/or 5 positions have been well documented.[10,11] Most of the work is focused on thiophenes with electron-donating groups, such as alkyloxythiophenes, but little study has been reported on annulated thiophene derivatives. We report here the synthesis of Mannich bases of thiophene derivatives with fused ring systems, compounds **1** and **2**, in anticipation of extending functionalization of these unique compounds.

Compounds **1** and **2** were prepared according to the reference literature[6,12,13] with corresponding yields of 22% and 48%, respectively. For both starting materials **1** and **2**, using paraformaldehyde and three different secondary amine hydrochlorides at elevated temperature can afford mono-substituted Mannich bases in fairly good yields. The experiments are shown in Scheme 2, and results are summarized in Table 1. Reactions performed in pressure tubes gave marginally better yields, which in the sealed environment helps contain volatile formaldehyde. The results show that the morpholine hydrochloride gives the highest yields, followed by piperidine hydrochloride, and diethylamine hydrochloride.

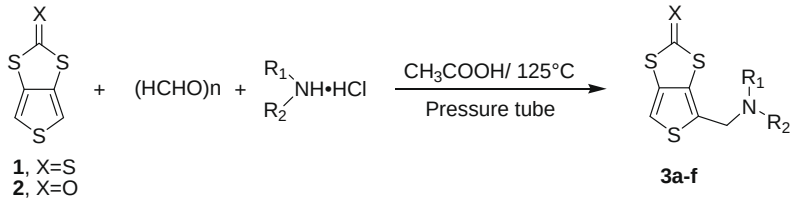
Our successful synthesis of mono-substituted Mannich bases led us to embark upon a study of the preparation of the bis-substituted analogs. Unfortunately, further aminoalkylation on the 6-position has proven to be very difficult, even in the presence of the most active morpholine hydrochloride. Mainly starting materials were recovered with only low yield of anticipated products. Reac-



Scheme 1. Thieno[3,4-*d*]-1,3-dithiole-2-thione (**1**) and thieno[3,4-*d*]-1,3-dithiol-2-one (**2**).

* Corresponding author. Tel.: +1 817 272 1021; fax: +1 817 272 2538.
E-mail address: elsenbaumer@uta.edu (R.L. Elsenbaumer).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.03.222



Scheme 2. Preparation of mono-substituted Mannich bases of **1** and **2** in pressure tube.

Table 1
Mono-substituted Mannich bases of compounds **1** and **2**

Compound	X	$R_1 = R_2 =$	Yield (%)	Yield * (%)	Mp (°C)
3a	S	$-CH_2CH_2OCH_2CH_2-$	75	81	94–95
3b	S	$-CH_2CH_2CH_2CH_2CH_2-$	72	83	90–91
3c	S	$-CH_2CH_3$	48	55	N/A, amber oil
3d	O	$-CH_2CH_2OCH_2CH_2-$	43	60	61–62
3e	O	$-CH_2CH_2CH_2CH_2CH_2-$	15	30	N/A, colorless oil
3f	O	$-CH_2CH_3$	12	22	N/A, colorless oil

Yield * were collected from reactions performed in pressure tubes.

tions performed in pressure tube give bis-substituted Mannich bases **4a** and **4d** at yields of 35% and 43%, respectively, which are illustrated in Scheme 3. In addition, small amounts of acetate derivatives (**5a** and **5d**) were also isolated and characterized. Equilibrium reactions plus strong polar solvent might be the cause for low yields of desired symmetrical Mannich bases. Additionally, excess morpholine hydrochloride does not significantly improve the yield of bis-substituted products. Aminoalkylation reactions of mono-substituted Mannich bases with less active piperidine hydrochloride or diethylamine hydrochloride do not proceed to yield symmetrical bis-substituted compounds. Instead reactions give asymmetrical acetate derivatives with very low yields, and most starting materials were recovered. The formation of these acetate derivatives might occur for the same reason as that observed in the reactions of morpholine analogs. All asymmetrical acetate derivatives are summarized in Table 2, and their schematic presentation is depicted in Scheme 4.

In summary, a series of mono-substituted Mannich bases of annulated thiophene derivatives thieno[3,4-*d*]-1,3-dithiole-2-thione (**1**) and thieno[3,4-*d*]-1,3-dithiol-2-one (**2**) have been successfully synthesized with good yields. Bis-substituted Mannich bases were prepared in low yields owing to possible equilibrium reactions and competitive substitution reactions with the solvent. Reactivities of **1** and **2** undergoing Mannich reactions under identical condition gave similar results.

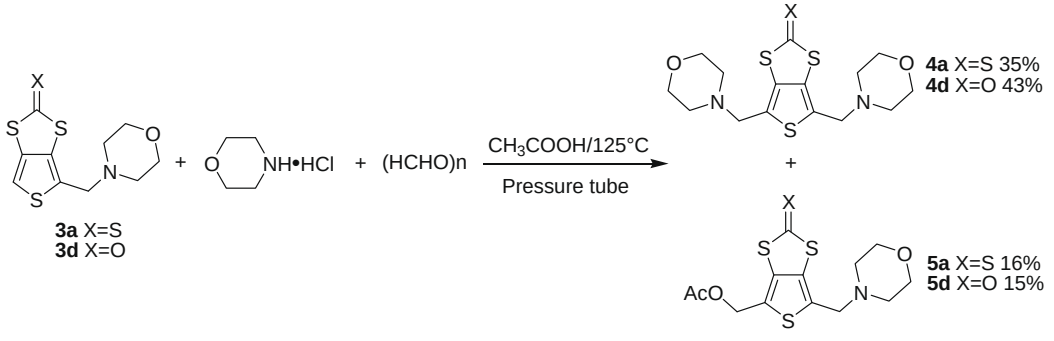
2. General procedure for preparation of mono-substituted Mannich bases of annulated thiophene derivatives in pressure tube

A mixture of compound **1** (or compound **2**, 5 mmol), paraformaldehyde (5.5 mmol), secondary amine hydrochloride (5.5 mmol), and 20 mL glacial acetic acid was heated to 125 °C in a sealed pressure tube. The solution was stirred at 125 °C for 24 h. After it was cooled to room temperature, 20 mL of H_2O was added. The solution was basified with aqueous sodium hydroxide solution (4 M) and extracted with chloroform (3 × 50 mL). The organic phase was washed with brine, dried over sodium sulfate, and

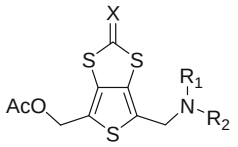
Table 2
Asymmetrical Mannich bases

Compound	X	$R_1 = R_2 =$	Yield * (%)	Mp (°C)
5a	S	$-CH_2CH_2OCH_2CH_2-$	16	N/A, amber oil
5b	S	$-CH_2CH_2CH_2CH_2CH_2-$	13	N/A, amber oil
5c	S	$-CH_2CH_3$	14	N/A, amber oil
5d	O	$-CH_2CH_2OCH_2CH_2-$	15	57–58
5e	O	$-CH_2CH_2CH_2CH_2CH_2-$	11	N/A, colorless oil
5f	O	$-CH_2CH_3$	9	N/A, colorless oil

Yield * were collected from reactions performed in pressure tubes.



Scheme 3. Synthesis of bis-substituted Mannich bases.



5a-f

Scheme 4. Schematic presentation of asymmetrical Mannich bases.

concentrated under vacuum to give crude Mannich bases. Further purification was performed by column chromatography on basic silica gel with EtOAc/hexanes as eluent solvents.

3. General procedure for preparation of bis-substituted Mannich bases in pressure tube

A mixture of mono-substituted Mannich base (compound **3a**–**f**, 1.0 equiv), paraformaldehyde (1.2 equiv), and secondary amine hydrochloride (1.2 equiv) in glacial acetic acid (1 mL/mmol) was heated to 125 °C in a sealed pressure tube. The solution was stirred at 125 °C for 24 h. The cooled reaction mixture was basified with aqueous sodium hydroxide (4 M) and extracted with $CHCl_3$. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography (basic silica gel, EtOAc/hexanes).

4. Spectral data for selected compounds

Compound **3a**: 4-(morpholinomethyl)thieno[3,4-*d*]-1,3-dithiole-2-thione, yellow needles. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (s, 1H), 3.77 (t, J = 4.6 Hz, 4H), 3.62 (s, 2H), 2.53 (t, J = 4.6 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 221.1, 137.1, 135.0, 128.5, 111.0, 66.6, 56.0, 53.4; FT-IR (KBr): 3098, 2971, 2858, 2804, 1454, 1346, 1330, 1288, 1173, 1112, 1056, 997, 910, 862, 765, 734, 619, 543, 543, 500 cm^{-1}; HRMS: MH$^+$ 289.9810, expected 289.9796.

Compound **3b**: 4-((piperidin-1-yl)methyl)thieno[3,4-*d*]-1,3-dithiole-2-thione, amber solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (s, 1H), 3.54 (s, 2H), 2.45 (m, 4H), 1.64 (m, 4H), 1.46 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 222.1, 137.0, 135.0, 130.0, 110.6, 56.6, 54.6, 25.7, 24.2; FT-IR (KBr): 3100, 2935, 2851, 2800, 2758, 1441, 1367, 1346, 1299, 1157, 1109, 1060, 994, 858, 824, 775, 713, 496, 469 cm^{-1}; HRMS: MH$^+$ 288.0016, expected 288.0004.

Compound **3c**: 4-((diethylamino)methyl)thieno[3,4-*d*]-1,3-dithiole-2-thione, amber oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (s, 1H) 3.66 (s, 2H), 2.60 (q, J = 7.3 Hz, 4H), 1.07 (t, J = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 222.3, 136.9, 134.7, 131.3, 110.4, 51.0, 47.0, 11.5; FT-IR (KBr): 3103, 2969, 2932, 2817, 1454, 1373, 1309, 1201, 1166, 1060, 994, 857, 827, 712, 496, 465 cm^{-1}; HRMS: MH$^+$ 276.0007, expected 276.0004.

Compound **3d**: 4-(morpholinomethyl)thieno[3,4-*d*]-1,3-dithiol-2-one, pale-yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (s, 1H), 3.75 (t, J = 4.6 Hz, 4H), 3.65 (s, 2H), 2.52 (t, J = 4.6 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.1, 130.7, 125.6, 113.4, 66.7, 56.4, 53.4; FT-IR (KBr): 31296, 2964, 2852, 2812, 1632, 1452, 1351, 1294, 1111, 1029, 995, 949, 924, 857, 824, 761, 616, 462 cm^{-1}; HRMS: MH$^+$ 274.0031, expected 274.0025.

Compound **3e**: 4-((piperidin-1-yl)methyl)thieno[3,4-*d*]-1,3-dithiol-2-one, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (s, 1H), 3.57 (s, 2H), 2.44 (br s, 4H), 1.58–1.63 (m, 4H), 1.45 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.7, 132.0, 127.7, 125.5, 112.9, 56.7, 54.4, 25.7, 24.1; FT-IR (KBr): 3109, 2935, 2852, 2800, 2758, 1700, 1647, 1442, 1346, 1300, 1157, 1111, 1038, 994, 947, 821, 776, 460 cm^{-1}; HRMS: MH$^+$ 272.0244, expected 272.0232.

Compound **3f**: 4-((diethylamino)methyl)thieno[3,4-*d*]-1,3-dithiol-2-one, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (s, 1H), 3.70 (s, 2H), 2.58 (t, J = 7.3 Hz, 4H), 1.06 (t, J = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.8, 133.4, 127.8, 125.0, 112.8, 51.5, 46.9, 11.6; FT-IR (KBr): 3108, 2969, 2933, 2814, 1699, 1641, 1456, 1373, 1309, 1202, 1167, 1060, 947, 839, 715, 632, 473, 457 cm^{-1}; HRMS: MH$^+$ 260.0226, expected 260.0232.

Compound **4a**: 4,6-bis(morpholinomethyl)thieno[3,4-*d*]-1,3-dithiole-2-thione, yellow needle, melting point: 150–153 °C (decomposed). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.77 (t, J = 4.6 Hz, 8H), 3.57 (s, 4H), 2.53 (t, J = 4.6 Hz, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 223.0, 134.5, 126.0, 66.8, 56.2, 53.5; FT-IR (KBr): 2956, 2851, 2817, 1451, 1348, 1276, 1114, 1063, 1006, 927, 861, 789 cm^{-1}; HRMS: MH$^+$ 389.0493, expected 389.0486.

Compound **4d**: 4,6-bis(morpholinomethyl)thieno[3,4-*d*]-1,3-dithiol-2-one, pale-orange needle, melting point: 128–132 °C (decomposed). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.74 (t, J = 4.6 Hz, 8H), 3.60 (s, 4H), 2.52 (t, J = 4.6 Hz, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.9, 128.6, 125.3, 66.8, 56.5, 53.4 FT-IR (KBr): 2972, 2915, 2865, 2803, 1645, 1451, 1349, 1332, 1302, 1113, 1065, 1032, 1008, 919, 859, 802, 625 cm^{-1}; HRMS: MH$^+$ 373.0718, expected 373.0709.

Compound **5a**: (4-morpholinomethyl)-2-thioxothieno[3,4-*d*]-1,3-dithiol-6-yl)methyl acetate, amber oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.14 (s, 2H), 3.77 (t, J = 4.6 Hz, 4H), 3.58 (s, 2H), 2.54 (t, J = 4.1 Hz, 4H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 220.3, 170.4, 137.4, 134.6, 128.9, 122.6, 66.7, 59.0, 56.1, 53.5, 20.7; FT-IR (KBr): 2957, 2857, 2820, 1740, 1453, 1223, 1108, 1067, 1008, 953, 923, 859, 826, 788, 750, 625, 531 cm^{-1}; HRMS: MH$^+$ 362.0019, expected 362.0008.

Compound **5b**: (4-(piperidin-1-yl)methyl)-2-thioxothieno [3,4-*d*]-1,3-dithiol-6-yl)methyl acetate, amber oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.13 (s, 2H), 3.51 (s, 2H), 2.46 (br s, 4H), 2.11 (s, 3H), 1.62–1.67 (m, 4H), 1.46 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 221.2, 170.4, 134.4, 130.4, 122.0, 59.1, 56.4,54.7, 25.7, 24.1, 20.7 FT-IR (KBr): 2935, 2853, 2802, 1743, 1661, 1441, 1374, 1221, 1109, 1067, 962, 857, 776 cm^{-1}; HRMS: MH$^+$ 360.0224, expected 360.0215.

Compound **5c**: (4-(diethylamino)methyl)-2-thioxothieno [3,4-*d*]-1,3-dithiol-6-yl)methyl acetate, amber oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.14 (s, 2H), 3.62 (s, 2H), 2.60 (q, J = 7.3 Hz, 4H), 2.12 (s, 3H), 1.07 (t, J = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 221.1, 170.5, 137.3, 134.3, 131.7, 122.0, 59.2, 51.0, 47.1, 20.7, 11.5 FT-IR (KBr): 2969, 2817, 1743, 1659, 1452, 1376, 1221, 1115, 963, 826, 758, 617, 496 cm^{-1}; HRMS: MH$^+$ 348.0216, expected 348.0215.

Compound **5d**: (4-(morpholinomethyl)-2-oxothieno[3,4-*d*]-1,3-dithiol-6-yl)methyl acetate, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.17 (s, 2H), 3.75 (t, J = 4.6 Hz, 4H), 3.62 (s, 2H), 2.53 (m, 4H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.1, 170.5, 131.6, 128.6, 125.2, 125.1, 66.7, 59.3, 56.3, 53.4, 33.4, 20.7; FT-IR(KBr): 2964, 2942, 2856, 2810, 1738, 1661, 1450, 1374, 1353, 1291, 1230, 1144, 1107, 1065, 1022, 1005, 957, 924, 905, 855, 820, 789, 753, 620, 597, 555,458, 428 cm^{-1}; HRMS: MH$^+$ 346.0231, expected 346.0236.

Compound **5e**: (4-(piperidin-1-yl) methyl)-2-oxothieno [3,4-*d*]-1,3-dithiol-6-yl)methyl acetate, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.16 (s, 2H), 3.55 (s, 2H), 2.45 (br s, 4H), 2.15 (s, 3H), 1.60–1.64 (m, 4H), 1.45 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.7, 170.4, 133.0, 128.4, 124.8, 124.5, 59.3, 56.7, 54.5, 25.6, 24.1, 20.6; FT-IR (KBr): 2936, 2854, 2801, 1744, 1668, 1442, 1374, 1222, 1110, 1038, 962, 918, 813, 460, 435 cm^{-1}; HRMS: MH$^+$ 344.0452, expected 344.0443.

Compound **5f**: (4-(diethylamino)methyl)-2-oxothieno[3,4-*d*]-1,3-dithiol-6-yl)methyl acetate, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.17 (s, 2H), 3.66 (s, 2H), 2.58 (q, J = 7.3 Hz, 4H), 2.11 (s,

3H), 1.06 (t, J = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.8, 170.6, 134.5, 128.6, 124.5, 124.5, 59.5, 51.5, 47.0, 20.8, 11.6 FT-IR (KBr):2970, 2816, 1744, 1669, 1454, 1376, 1116, 1021, 963, 913, 809, 773, 543, 460 cm^{-1}; HRMS: MH^+ 332.0447, expected 332.0443.

Acknowledgments

This work was partially supported by the Robert A. Welch Foundation (Y-1291). The authors would like to thank Scripps Center for Mass Spectrometry for HRMS measurements.

Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of all new compounds are included) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.222.

References and notes

1. Valade, L.; Bousseau, M.; Gleizes, A.; Cassoux, P. *J. Chem. Soc., Chem. Commun.* **1983**, 110.
2. Kato, R. *Chem. Rev.* **2004**, *104*, 5319.
3. *Organic Superconductors*; Ishiguro, T., Yamaji, K., Saito, G., Eds., 2nd ed.; Springer: Berlin Heidelberg, 1998.
4. Belo, D.; Alves, H.; Lopes, E. B.; Duarte, M. T.; Gama, V.; Henriques, R. T.; Almeida, M.; Perez-Benitez, A.; Rovira, C.; Veciana, J. *Chem. Eur. J.* **2001**, *7*, 511.
5. Belo, D.; Figueira, M. J.; Mendonca, J.; Santos, I. C.; Almeida, M.; Henriques, R. T.; Duarte, M. T.; Rovira, C.; Veciana, J. *Eur. J. Inorg. Chem.* **2005**, 3337.
6. Chiang, L. Y.; Shu, P.; Holt, D.; Cowan, D. *J. Org. Chem.* **1983**, *48*, 4713.
7. Skabara, P. J.; Mullen, K.; Bryce, M. R.; Howard, J. A. K.; Batsanov, A. S. *J. Mater. Chem.* **1998**, *8*, 1719.
8. Mas-Torrent, M.; Durkut, M.; Hadley, P.; Ribas, X.; Rovira, C. *J. Am. Chem. Soc.* **2004**, *126*, 984.
9. Mas-Torrent, M.; Hadley, P.; Bromley, S. T.; Ribas, X.; Tarres, J.; Mas, M.; Molins, E.; Veciana, J.; Rovira, C. *J. Am. Chem. Soc.* **2004**, *126*, 8546.
10. Barker, J. M.; Huddleston, P. R.; Wood, M. L. *Synth. Commun.* **1975**, *5*, 59.
11. Halfpenny, J.; Rooney, P. B.; Sloman, Z. S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2595.
12. Gronowitz, S.; Moses, P. *Acta Chem. Scand.* **1962**, *16*, 105.
13. Rasheed, K.; Warkentin, J. D. *J. Heterocycl. Chem.* **1981**, *18*, 1581.