DOI: 10.1002/ejoc.200700779

Oxidation of 3,4-Diaryl-2,5-dihydrothiophenes to 3,4-Diarylthiophenes Using $CuBr_2$: Simple and Efficient Preparation of 3,4-Diarylthiophenes

Yizhe Dang[a] and Yi Chen*[a]

Keywords: Sulfur heterocycles / Copper / Oxidation

A class of 3,4-diarylthiophenes was prepared in excellent yield (80–91 %) by oxidation of 3,4-diaryl-2,5-dihydrothiophenes with $CuBr_2$. The approach is also available for the synthesis of 3,4-diarylpyrroles and 3,4-diarylfuran.

Introduction

3,4-Disubstituted thiophenes are one of the most important class of heterocyclic compounds, not only as building blocks in the synthesis of natural products or as key structural units[1] of compounds with interesting biological activities but also in the field of materials chemistry.[2] In particular, 3,4-diarylthiophenes and analogs (Figure 1) have interesting pharmacologic properties and are used as anti-inflammatory agents.[3]

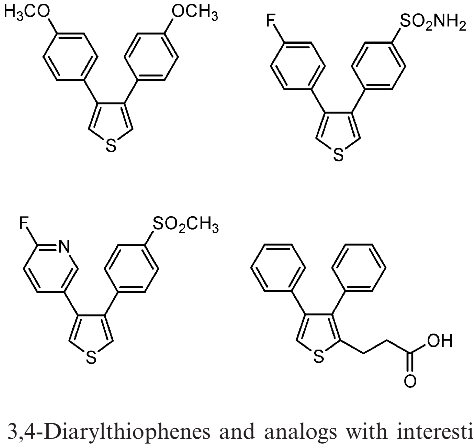


Figure 1. 3,4-Diarylthiophenes and analogs with interesting pharmacologic properties.

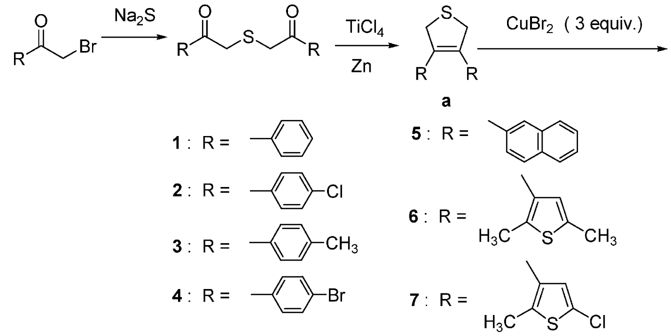
Synthesis of 3,4-disubstituted heterocyclic compounds is challenging due to the fact that selective substitution at one or more of the β positions is not easy because of the tendency of these systems to undergo aromatic substitution reactions at the more electronically favorable α positions of the heterocyclic ring. Several approaches to the preparation of 3,4-disubstituted thiophene derivatives including Hinsburg condensation,[4] modification of 3,4-dibromothiophene,[5] and others,[6] are available, but most syntheses require expensive reagents or strict reaction conditions. Dehydrogenation of 2,5-dihydrothiophenes to thiophenes was reported with a variety of reagents such as hydrogen peroxide,[7] perbenzoic acid,[8] phosphorus pentachloride,[9] chloranil,[10] 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[11] and sulfuryl chloride,[12] but many problems were encountered with these reagents: difficult isolation, low yield, long reaction time, expensive reagents, and polluted gas as a byproduct. Recently, we found[13] that 3,4-diaryl-2,5-dihydrothiophenes could be oxidized and brominated to 3,4-diaryl-2,5-dibromothiophenes by a one-pot reaction with the use of Br_2 in excellent yields, but the reaction could not be stopped at the oxidation step and we could not obtain 3,4-diarylthiophenes. Therefore, the development of an efficient and convenient synthesis of 3,4-diarylthiophenes continues to be an active research area.[14] In this paper, we found $CuBr_2$ to be a highly efficient reagent for the dehydrogenation of 3,4-diaryl-2,5-dihydrothiophenes to 3,4-diarylthiophenes. Using $CuBr_2$ as the dehydrogenation reagent has some advantages: it is an inexpensive reagent, it is easy to handle, and it provides excellent yields of the products. The reaction is complete within 3–4 h, and the product is isolated by normal work up procedures.

Results and Discussion

The starting 3,4-diaryl-2,5-dihydrothiophenes (Scheme 1) were prepared according to the literature[15] starting from acetophenone and its derivatives, which were brominated at the 2-position with Br_2 in $CHCl_3$. After sulfuration of bromoacetophenone and its derivatives with Na_2S in EtOH, the sulfides were coupled through a McMurry coupling reaction to afford **1a**–**7a** in good yields (70–83 %).

---

[a] Laboratory of Organic Optoelectronic Functional Materials and Molecular Engineering, Technical Institute of Physics and Chemistry, Chinese Academy of Science,
Beijing 100080, China
Fax: +86-10-6254-4049
E-mail: yichencas@yahoo.com.cn



Scheme 1. The synthetic route of 3,4-diaryl-2,5-dihydrothiophenes and 3,4-diarylthiophenes.

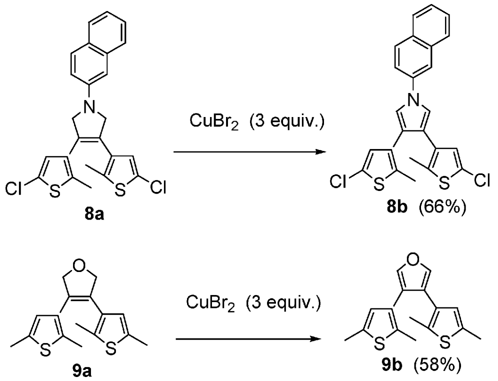
3,4-Diarylthiophenes **1b**–**7b** were obtained by treatment of 3,4-diaryl-2,5-dihydrothiophenes **1a**–**7a** with $CuBr_2$ in a solution of ethyl acetate/chloroform (Scheme 1). The reaction was simple and quick: the mixture was heated at reflux until no further starting material was detected by TLC (2–4 h). After the reaction mixture was cooled down to room temperature, the grey powder was filtered off, and the solution was then washed with water, $NaHCO_3$ (10%), and a saturated solution of NaCl and extracted with dichloromethane. The combined organic layer was dried with $MgSO_4$. After evaporation of the solvent, target compounds **1b**–**7b** were obtained without further purification in excellent yields (80–91%).

The effect of $CuBr_2$ and solvent was examined in an effort to improve the yields of the 3,4-diarylthiophenes. As presented in Table 1, without the $CuBr_2$ reagent, no conversion of **1a** into **1b** was detected in the reaction and starting material **1a** was recovered quantitatively. The yield of **1b**, however, greatly improved from 25 to 85% when the number of equivalents of $CuBr_2$ was increased from one to three, but no increase in the yield of **1b** was obtained when the number of equivalents of $CuBr_2$ was greater than three. It is worth noting that the conversion of **1a** into **1b** did not occur when other copper reagents such as $CuCl_2$, CuI, or $Cu(OOCCH_3)_2$ were used to replace $CuBr_2$, although the mechanism is not clear. Additionally, it was found that solvents have little influence on both the yield and the conversion of **1b**, and no significant changes were detected when different solvents were employed in the reaction. Similar results were obtained when 3,4-diaryl-2,5-dihydrothiophenes **2a**–**7a** were converted into corresponding 3,4-diarylthiophenes **2b**–**7b** with the use of the $CuBr_2$ reagent.

To extend the scope of the oxidation reaction with $CuBr_2$, 1,3,4-triaryl-2,5-dihydropyrrole **8a**[15e] and 3,4-diaryl-2,5-dihydrofuran **9a**[15d] were employed as templates. It was found that both **8a** and **9a** could also be oxidized into 1,3,4-triarylpyrrole **8b** and 3,4-diarylfuran **9b** in reasonable yields of 66 and 58%, respectively (Scheme 2). This suggests that $CuBr_2$ may also be efficient for the preparation of 1,3,4-triarylpyrroles and 3,4-diarylfurans, and a more detailed study on the conversion of 1,3,4-triaryl-2,5-dihydropyrroles and 3,4-diaryl-2,5-dihydrofuran to 1,3,4-triarylpyrroles and 3,4-diarylfurans, respectively, is currently under investigation.

Table 1. The effects of $CuBr_2$ and the solvent on the preparation of **1b**.

Entry	$CuBr_2$ [equiv.]	Solvent	Time [h]	Yield of **1b** [%]	Recovery of **1a** [%]
1	0	$CHCl_3$	4	0	100
2	1	$CHCl_3$	4	25	60
3	2	$CHCl_3$	4	50	35
4	3	$CHCl_3$	4	85	<5
5	4	$CHCl_3$	4	82	<5
6	3	DCM	4	85	<5
7	3	THF	4	80	<5
8	3	CH_3CN	4	84	<5
9	3	Cyclohexane	4	78	<5



Scheme 2. The oxidation of 3,4-diaryl-2,5-dihydropryyole **8a** and 3,4-diaryl-2,5-dihydrofuran **9a** into 3,4-diarylpyrrole **8b** and 3,4-diarylfuran **9b**.

Conclusions

A new synthetic approach for the preparation of 3,4-diarylthiophenes by oxidation of 3,4-diaryl-2,5-dihydrothiophenes with the use of $CuBr_2$ was developed. This reaction sequence is advantageous, as the procedure is simple and offers excellent yields of the products with the use of cheap reagents.

Experimental Section

General Methods: ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, with TMS as an internal reference and $CDCl_3$ as the solvent. HRMS spectra were recorded with a GCT-

MS spectrometer. All chemicals for synthesis were purchased from commercial suppliers, and the solvents were used without further purification. Reactions were monitored by TLC silica gel plates (60F-254). Column chromatography was performed on silica gel (Merck, 70–230 mesh).

General Procedure for the Conversion of 1a–9a into 1b–9b: To a mixture of $CuBr_2$ (0.67 g, 3.0 mmol) in ethyl acetate (30 mL) heated at reflux was added compound **1a**–**9a** (1.0 mmol) in $CHCl_3$ (30 mL), and the mixture was heated at reflux until the starting material disappeared (TLC detection). The mixture was cooled down to ambient temperature, and the grey powder was filtered. The solution was washed with water (50 mL), $NaHCO_3$ (10%, 50 mL), and a saturated solution of NaCl (50 mL) and then extracted with CH_2Cl_2. The combined organic layer was dried with $MgSO_4$. After evaporation of the solvent, target compounds **1b**–**9b** were obtained without further purification.

1b: Yield: 201 mg (85%). M.p. 115–116 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (s, 2 H), 7.29–7.27 (m, 6 H), 7.22–7.20 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9, 136.7, 129.2, 128.3, 127.0, 124.2 ppm. HRMS: calcd. for $C_{16}H_{12}S$ 236.0660; found 236.0663. $C_{16}H_{12}S$ (236.34): calcd. C 81.41, H 5.12; found C 81.48, H 5.06.

2b: Yield: 268 mg (88%). M.p. 136–137 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31 (s, 2 H), 7.25 (d, J = 8.6 Hz, 4 H), 7.11 (d, J = 8.4 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.5, 134.8, 133.2, 130.4, 128.7, 124.7 ppm. HRMS: calcd. for $C_{16}H_{10}Cl_2S$ 303.9880, found 303.9882 (100%). $C_{16}H_{10}Cl_2S$ (305.23): calcd. C 63.22, H 3.31; found C 63.31, H 3.28.

3b: Yield: 240 mg (91%). M.p. 70–72 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 (s, 2 H), 7.13–7.08 (m, 8 H), 2.36 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.8, 136.6, 133.9, 129.0, 123.7, 21.3 ppm. HRMS: calcd. for $C_{18}H_{16}S$ 264.0973; found 264.0974. $C_{18}H_{16}S$ (264.39): calcd. C 81.86, H 6.11; found C 81.78, H 6.05.

4b: Yield: 327 mg (83%). M.p. 147–148 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, J = 8.4 Hz, 4 H), 7.31 (s, 2 H), 7.05 (d, J = 8.4 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.4, 135.2, 131.6, 130.7, 124.7, 121.4 ppm. HRMS: calcd. for $C_{16}H_{10}Br_2S$ 393.8849; found 393.8847. $C_{16}H_{10}Br_2S$ (394.13): calcd. C 48.79, H 2.56; found C 48.68, H 2.51.

5b: Yield: 282 mg (84%). M.p. 146–147 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.86 (s, 2 H), 7.80–7.75 (m, 4 H), 7.66 (d, J = 8.5 Hz, 2 H), 7.49 (s, 2 H), 7.48–7.44 (m, 4 H), 7.26 (dd, J = 8.4, 8.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9, 134.3, 134.3, 133.8, 132.5, 128.1, 127.8, 127.7, 127.6, 127.5, 126.2, 126.0, 124.7 ppm. HRMS: calcd. for $C_{24}H_{16}S$ 336.0973; found 336.0975. $C_{24}H_{16}S$ (336.45): calcd. C 85.77, H 4.50; found C 85.68, H 4.53.

6b: Yield: 243 mg (80%). M.p. 88–90 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (s, 2 H), 6.34 (s, 2 H), 2.36 (s, 6 H), 2.15 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.7, 135.6, 133.2, 128.3, 127.1, 121.2, 15.1, 13.5 ppm. HRMS: calcd. for $C_{16}H_{16}S_3$ 304.0414; found 304.0416. $C_{16}H_{16}S_3$ (304.50): calcd. C 63.21, H 5.30; found C 63.30, H 5.21.

7b: Yield: 283 mg (82%). M.p. 113–115 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.21 (s, 2 H), 6.49 (s, 2 H), 2.11 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.9, 134.3, 132.6, 128.1, 125.4, 124.3, 13.9 ppm. HRMS: calcd. for $C_{14}H_{10}Cl_2S_3$ 343.9322; found 343.9325. $C_{14}H_{10}Cl_2S_3$ (345.34): calcd. C 48.89, H 2.93; found C 48.88, H 2.84.

8b: Yield: 300 mg (66%). M.p. 105–106 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, J = 8.8 Hz, 1 H), 7.89 (d, J = 4.2 Hz, 1 H), 7.87 (d, J = 4.3 Hz, 1 H), 7.83 (d, J = 2.0 Hz, 1 H), 7.62 (dd, J = 8.8, 2.2 Hz, 1 H), 7.59 (t, J = 6.7, 7.3 Hz, 1 H), 7.51 (t, J = 7.2, 6.5 Hz, 1 H), 7.20 (s, 2 H), 6.62 (s, 2 H), 2.20 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6, 133.9, 132.9, 131.7, 131.5, 130.0, 128.5, 128.0, 127.8, 127.3, 126.0, 125.1, 120.4, 119.8, 118.7, 117.4, 14.1 ppm. HRMS: calcd. for $C_{24}H_{17}Cl_2NS_2$ 453.0179; found 453.0177. $C_{24}H_{17}Cl_2NS_2$ (454.44): calcd. C 63.63, H 3.78; found C 63.55, H 3.71.

9b: Yield: 167 mg (58%). M.p. 98–100 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43 (s, 2 H), 6.34 (s, 2 H), 2.35 (s, 6 H), 2.15 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.5, 135.3, 133.1, 128.5, 127.4, 121.5, 15.3, 13.9 ppm. HRMS: calcd. for $C_{16}H_{16}OS_2$ 288.0643; found 288.0645. $C_{16}H_{16}OS_2$ (288.43): calcd. C 66.71, H 5.60; found C 66.66, H 5.54.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 60337020).

---

[1] a) W. G. Gribble in *Comprehensive Heterocyclic Chemistry* (Eds: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, **1996**; b) J. B. Press in *The Chemistry of Heterocyclic Compounds: Thiophene and Its Derivatives* (Ed.: S. Gronowitz), John Wiley & Sons, Inc., New York, **1991**; c) J. B. Press, R. K. Russell in *Progress in Heterocyclic Chemistry* (Eds: H. Suschitzky, E. F. V. Scriven), Pergamon, Oxford, **1992**.

[2] a) J. Roncali, *Chem. Rev.* **1992**, *92*, 711–738; b) D. Fichou (Ed.), *Handbook of Oligo- and Polythiophenes*, Wiley-VCH, Weinheim, **1999**; c) H. E. Katz, Z. Bao, S. L. Gilat, *Acc. Chem. Res.* **2001**, *34*, 359–369; d) T. Otsubo, Y. Aso, K. Takimiya, *J. Mater. Chem.* **2002**, *12*, 2565–2575; e) C. R. Newman, C. D. Frisbie, D. A. de Silva Filho, J.-L. Bredas, P. C. Ewbank, K. R. Mann, *Chem. Mater.* **2004**, *16*, 4436–4451; f) A. Facchetti, M.-H. Yoon, T. J. Marks, *Adv. Mater.* **2005**, *17*, 1705–1725; g) H. Rath, V. Prabhuraja, T. K. Chandrashekar, N. Nag, D. Goswami, B. S. Joshi, *Org. Lett.* **2006**, *8*, 2325–2328.

[3] a) K. Brown, J. F. Cavalla, U. S. Patent 3,644,399, **1972**; b) K. Brown, J. F. Cavalla, U. S. Patent 3,743,656, **1973**; c) J. J. Talley, S. R. Bertenshaw, P. W. Collins, T. D. Penning, D. B. Reitz, R. S. Rogers, U. S. Patent 7,030,153 B2, **2006**.

[4] a) P. J. Garratt, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1972**, *94*, 7087–7092; b) Y. Miyahara, *J. Heterocycl. Chem.* **1979**, *16*, 1147–1151.

[5] a) P. Spagnolo, P. Zanirato, S. Gronowitz, *J. Org. Chem.* **1982**, *47*, 3177–3180; b) S. Gronowitz, M. Temciuc, A.-B. Hornfeldt, *J. Heterocycl. Chem.* **1993**, *30*, 1111–1116; c) J. L. Reddinger, J. R. Reynolds, *J. Org. Chem.* **1996**, *61*, 4833–4834; d) X.-S. Ye, H. N. C. Wong, *J. Org. Chem.* **1997**, *62*, 1940–1954.

[6] a) Y. Sakamoto, S. Komatsu, T. Suzuki, *J. Am. Chem. Soc.* **2001**, *123*, 4643–4644; b) T. M. Pappenfus, M. W. Burand, D. E. Janzen, K. R. Mann, *Org. Lett.* **2003**, *5*, 1535–1538; c) J. Casado, T. M. Pappenfus, L. L. Miller, K. R. Mann, E. Orti, P. M. Viruela, R. Pou-Amerigo, V. Hernandez, J. T. L. Navarrete, *J. Am. Chem. Soc.* **2003**, *125*, 2524–2534; d) A. Facchetti, M.-H. Yoon, C. L. Stern, H. E. Katz, T. J. Marks, *Angew. Chem. Int. Ed.* **2003**, *42*, 3900–3903.

[7] A. Stoll, R. Suess, *Helv. Chim. Acta* **1974**, *57*, 2487–2492.

[8] T. Takaya, S. Kosaka, Y. Otsuji, E. Imoto, *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2086–2095.

[9] O. Hromatka, D. Binder, *Chem. Abstr.* **1976**, *85*, 5612.

[10] H. Ruschig, W. Meixner, H. G. Alpermann, U. S. Patent 3,445,473, **1969**.

[11] O. Hromatka, D. Binder, U. S. Patent 4,028,373, **1977**.

[12] P. A. Rossy, W. Hoffmann, N. Muller, *J. Org. Chem.* **1980**, *45*, 617–620.

[13] Y. Dang, Y. Chen, *J. Org. Chem.* **2007**, *72*, 6901–6904.

[14] a) T. Izumi, S. Kobashi, K. Takimiya, Y. Aso, T. Otsubo, *J. Am. Chem. Soc.* **2003**, *125*, 5286–5287; b) A. Facchetti, M. Mushrush, M.-H. Yoon, C. L. Stern, G. R. Hutchison, M. A. Ratner, T. J. Marks, *J. Am. Chem. Soc.* **2004**, *126*, 13480–13501; c) K. Takimiya, N. Niihara, T. Otsubo, *Synthesis* **2005**, *10*, 1589–1592; d) S. Ando, J.-I. Nishida, H. Tada, Y. Inoue, S. Tokito, Y. Yamashita, *J. Am. Chem. Soc.* **2005**, *127*, 5336–5337; e) Y. Wang, M. D. Watson, *J. Am. Chem. Soc.* **2006**, *128*, 2536–2537.

[15] a) J. E. McMurry, K. L. Kees, *J. Org. Chem.* **1977**, *42*, 2655–2656; b) J. Nakayama, H. Machida, M. Hoshino, *Tetrahedron Lett.* **1985**, *26*, 1981–1982; c) Y. Chen, D. X. Zeng, M. G. Fan, *Org. Lett.* **2003**, *5*, 1435–1437; d) Z.-N. Huang, B.-A. Xu, S. Jin, M.-G. Fan, *Synthesis* **1998**, 1092–1094; e) N. Xie, Y. Chen, *J. Mater. Chem.* **2006**, *16*, 982–985.

Received: August 23, 2007