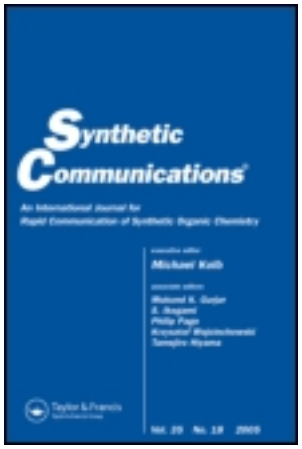


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Solvent-Free Synthesis of Thiophenol Using Uncatalyzed Transfer Hydrogenation

Shaodong Zhou [a], Chao Qian [a] & Xinzhi Chen [a]

[a] Department of Chemical and Biological Engineering, Zhejiang University, Hangzhou, China

Available online: 15 Dec 2011

To cite this article: Shaodong Zhou, Chao Qian & Xinzhi Chen (2012): Solvent-Free Synthesis of Thiophenol Using Uncatalyzed Transfer Hydrogenation, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:16, 2432-2439

To link to this article: http://dx.doi.org/10.1080/00397911.2011.559317

Synthetic Communications®, 42: 2432–2439, 2012

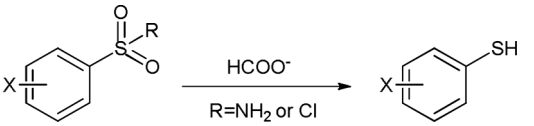
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.559317

Taylor & Francis
Taylor & Francis Group

SOLVENT-FREE SYNTHESIS OF THIOPHENOL USING UNCATALYZED TRANSFER HYDROGENATION

Shaodong Zhou, Chao Qian, and Xinzhi Chen
Department of Chemical and Biological Engineering, Zhejiang University, Hangzhou, China

GRAPHICAL ABSTRACT



Abstract *Clean and sustainable transfer hydrogenation for aryl sulfonamides and sulfonyl chlorides is described. The protocol is chemoselective and uses neither catalyst nor solvent.*

Keywords Solvent-free; thiophenol; uncatalyzed transfer hydrogenation

INTRODUCTION

Thiophenols constitute an important class of compounds in chemistry and biology. They are widely used as intermediates in printing, dyeing, and pharmaceutical industry.[1–3] Among the reported methods for synthesis of thiophenol, reduction of aryl sulfonyl compounds has been well investigated.[4–8] The reductants include metal, sodium borohydride, lithium aluminum hydride, phosphorus trichloride, and iodine, most of which contaminate the environment.

Catalytic transfer hydrogenation (CTH) is an alternative reduction method that can be used in the synthesis of many organic compounds. With supported noble-metal catalyst, CTH has been used for the reduction of nitro compounds and azides to amines and dehalogenation of mono- and polychlorinated aryl compounds.[9–12] As an ecofriendly reductive method, CTH has attracted increasing attention. However, CTH can hardly be used in the reduction of sulfo compounds, because thiophenols (H_2S, SO_2, et al.), which may be produced in the reaction, are toxic to the catalyst. Only Chen and Gong have reported synthesis of thiophenols using CTH.[13] Dockner found that benzenesulfonyl chloride can be reduced via uncatalyzed transfer hydrogenation with a combination of hydrocarbons (refinery products such as vacuum residue or white oil) and active carbon as hydrogen donor.

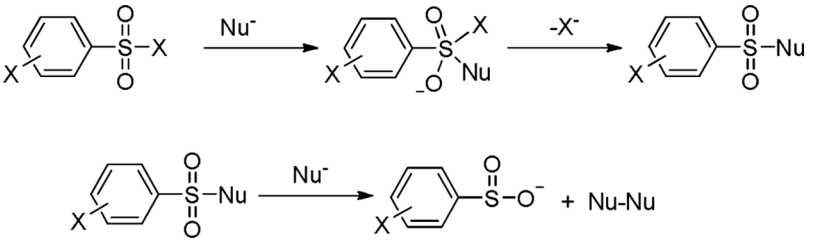
Received April 22, 2010.

Address correspondence to Chao Qian, Department of Chemical and Biological Engineering, Zhejiang University, No. 38, Zheda Road, Hangzhou, China. E-mail: supmoney@163.com

However, all the reactions have to be carried out at very high temperatures (as high as 350 °C), so too much by-product will be produced[14] and the reaction procedures are unsafe. Engels and Singer found that aryl sulfonyl chloride can be reduced using uncatalyzed transfer hydrogenation with hydrazine as hydrogen donor, producing thiophenol.[15] The reaction occurs in milder conditions (60–120 °C), though the hydrogen donor is expensive. More economical transfer hydrogenation systems for the synthesis of thiophenol need to be developed.

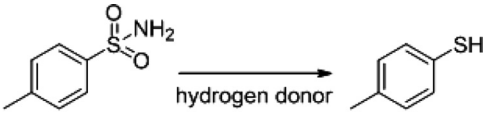
In our recent study on transfer hydrogenation with different hydrogen donors, we focused on the reduction of sulfonyl compounds/sulfonates. As the products are toxic to the noble-metal catalyst, new catalysts or uncatalyzed techniques should be explored. We chose to develop one uncatalyzed transfer hydrogenation reaction system for reduction of sulfonyl compounds/sulfonates. Among all the hydrogen donors, formic acid/formates are active and less expensive, so they are used as the hydrogen donor. Reduction of sulfonic acid was initially investigated. Unfortunately, no thiophenols were produced at reaction temperatures from 25 °C to 200 °C. It has been reported that reduction of sulfonyl compounds is a nucleophilic process in which the initial step is substitution of the –X group by nucleophile, as shown in Scheme 1.[16] The sulfinic acid is reactive and easy to reduce. According to the previous mechanism shown in Scheme 1, –X should be a good leaving group and give rise to the reduction product. The sulfonic acid is so strong that it can be almost fully deprotonated, and the sulfonate anion has three negatively charged oxygen atoms on which the charge is almost averaged. The charged oxygen atoms repel nucleophiles to approach the central sulfur atom. The averaging of charge on the three oxygen atom makes them nearly identical and the S-O bond is thus difficult to rupture. The poor leaving ability of –OH may be also responsible for the failure of reduction by formats. Considering that the amino in sulfonamide and the chloride in sulfonyl chloride are better leaving groups, our attention turned to the reduction of sulfonamides and sulfonyl chlorides.

In the reaction of sulfonamides and sulfonyl chlorides with formates, thiophenols were produced. The reactions takes place at a temperature range of 160–210 °C, and solvent is not needed. The by-products are water and carbonates; it is thus a clean method to synthesize thiophenols. During the experiments, we found that ammonium formate was the most effective hydrogen donor for the reduction of sulfonyl chlorides, whereas potassium formate was better for reduction of sulfonamides.



Scheme 1. Initial step in the reduction of sulfonyl compounds.

Table 1. Uncatalyzed reduction of 4-methylbenzenesulfonamide[a]



2a

Entry	Hydrogen donor (equiv)	Yield[b] (%)
1	$HCOONH_4$ (4)	73
2	HCOOK (4)	79
3	HCOONa (4)	50

[a]Reaction conditions: 4-methylbenzenesulfonamide (0.02 mol), hydrogen donor, solvent (15 mL or none), temperature (185 °C), reaction time (5 h).
[b]Determined by GC methods using hexadecane as an internal standard.

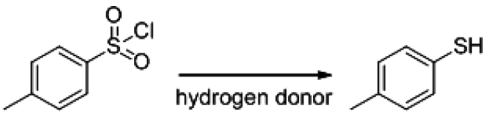
RESULTS AND DISCUSSION

Uncatalyzed Reduction of 4-Methylbenzenesulfonamide and 4-Methylbenzene Sulfonyl Chloride

First, reduction of 4-methylbenzene sulfonamide (**1a**) with different formates was investigated to optimize the reaction parameters (Table 1). Similarly good yields of 4-methylthiophenol (**2a**) were obtained using ammonium formate and potassium formate as hydrogen donors (Table 1, entries 1 and 2), whereas sodium formate resulted in lower product yield (Table 1, entry 8). Potassium formate was thus selected for further investigation on reduction of aryl sulfonamides.

Second, reduction of 4-methylbenzene sulfonyl chloride was investigated using different formates. It can be found in Table 2 that reaction with ammonium formate as the hydrogen donor was dramatically superior to the others (Table 2, entry 1).

Table 2. Uncatalyzed reduction of 4-methylbenzenesulfonyl chloride[a]



2a

Entry	Hydrogen donor (equiv)	Yield[b] (%)
1	$HCOONH_4$ (5)	82
2	HCOOK (5)	58
3	HCOONa (5)	37

[a]Reaction conditions: 4-methybenzenesulfonyl (0.02 mol), hydrogen donor, solvent (15 mL or none), temperature (100 °C for 1 h and 180 °C for another 5 h).
[b]Determined by GC methods using hexadecane as an internal standard.

Ammonium formate was selected for further investigation on reduction of aryl sulfonamides.

Extended Study on Synthesis of Thiophenols

Our investigation was expanded to the synthesis of different thiophenols from aryl sulfonamides and sulfonyl chlorides. As expected, most sulfonamides and sulfonyl chlorides can be reduced with good yields of corresponding thiophenols (Table 3). It can be concluded that reductions of aryl sulfonamides and sulfonyl chlorides with electron-withdrawing substituent on benzene ring (Table 3, entries 2 and 3) proceed in better yields than those with electron-donating substituent (Table 3, entries 1, 4, 5, 7, and 9). The reductions of sulfonamides and sulfonyl chlorides with both electron-withdrawing and electron-donating substituents result in different yields depending on the combined effect of the substituents. The substituting site also has considerable effect on the yield. Reductions 11 and 12, in which the sulfonamides have electron-withdrawing substituents, should have given better yields. The probable reason for the poor yields is that the electron-withdrawing substituents on *meta*-position increase the electron density around the sulfur atom so that it is more difficult to be nucleophilically attacked. Generally, the reduction of sulfonamides and sulfonly chlorides give similar yields.

Table 3. Reduction of aryl sulfonamides and sulfonyl chlorides with potassium formate and ammonium formate as hydrogen donor[a]

Entry	X	Product	Yield[b] (R=NH_2) (%)	Yield (R=Cl) (%)
1	4-Me	**2a**	77	80
2	4-Br	**2b**	79	78
3	4-F	**2c**	82	80
4	2,5-Dihydroxyl	**2d**	60	—
5	2-OEt	**2e**	59	61
6	2-Me-4-F	**2f**	72	72
7	3,5-Dimethyl	**2g**	63	59
8	3-F-4-OMe	**2h**	61	57
9	2-Me-5-Cl	**2i**	63	65
10	2,5-Difluoro	**2j**	66	68
11	3,5-Bis(trifluoromethyl)	**2k**	50	51
12	3-CF_3	**2l**	55	58
13	3-Me-4-F	**2m**	64	63

[a]Reaction conditions: Sulfonamide (0.1 mol), potassium formate (0.5 mol), without solvent, 200 °C, 7 h; sulfonyl chloride (0.1 mol), ammonium formate (0.5 mol), without solvent, 100 °C for 1 h and 200 °C for 6 h.

[b]Yield of isolated product.

CONCLUSION

In summary, we have explored an uncatalyzed transfer hydrogenation of aryl sulfonamides and sulfonyl chlorides to thiophenols with formates as the hydrogen donor. Most reductions gave good yields of corresponding thiophenols. The whole process is clean and solvent free. Further investigation is needed both theoretically and experimentally to improve the reaction system.

EXPERIMENTAL

Typical Procedure for the Reduction of Aryl Sulfonamides

Potassium formate (0.5 mol) was added to a flask containing 4-bromobenzene sulfonamide (0.1 mol). The mixture was heated, melted, and stirred at 200 °C for 7 h. Then the reaction mixture was cooled to 120 °C and acidified using formic acid. The organic componets can be separated from the acidified reaction mixture via steam distillation. After cooling down the distillate, 4-bromothiophenol was obtained over filtration, with yield of 79% and purity of 99.3% (justified with gas chromatography, GC).

Typical Procedure for the Reduction of Aryl Sulfonyl Chlorides

Aqueous ammonium formate (0.6 mol) was added to a flask containing 4-bromobenzene sulfonyl chloride (0.1 mol). The mixture was heated and refluxed for 1 h. Then the water was distilled out, and the mixture was heated to 200 °C and kept for 5 h. Then the reaction mixture was cooled to 120 °C and acidified using formic acid. The organic componets can be separated from the acidified reaction mixture via steam distillation. After cooling down the distillate, 4-bromothiophenol was obtained over filtration, with yield of 82% and purity of 98.8% (justified with GC).

GC conditions: flame ionization detector, initial temperature 100 °C, detector temperature 260 °C, heating rate 25 °C/min. Note: Liquid thiophenols can be separated by splitting from the distillates.

Product Characterization Data

4-Methylthiophenol (2a). White solid, mp: 41–43 °C (lit.[17] mp: 43 °C). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.27$ (s, 3H), 3.36 (s, 1H), 7.02 (d, 2H, $J = 8.2$ Hz),[18] 7.15 (d, 2H, $J = 7.9$ Hz); MS (EI): m/z (rel. int.) 124 (91), 91 (100), 79 (9), 45 (13).

4-Bromothiophenol (2b). White solid, mp: 70–73 °C (lit.[18] mp: 72–74 °C). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.46$ (s, 1H), 7.15 (d, 2H, $J = 8.6$), 7.38 (d, 2H, $J = 8.4$)[18]; MS (EI): m/z (rel. int.) 190 (40), 188 (40), 109 (100), 69 (26), 50 (19), 33 (10), 15 (3).

4-Fluorothiophenol (2c). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.43$ (s, 1H), 6.94 (t, 2H, $J = 8.0$ Hz), 7.23–7.27 (m, 2H)[19]; MS (EI): m/z (rel. int.) 128 (100), 108 (49), 95 (7), 84 (31), 69 (14), 57 (13), 45 (10), 31 (2).

2,5-Dihydroxylthiophenol (2d). White solid, mp: 117–118 °C (lit.[20] mp: 118 °C). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.10$ (s, 1H), 4.53 (s, 1H), 5.70 (s, 1H), 6.69–7.26 (m, 3H)[21]; MS (EI): m/z (rel. int.) 142 (100), 113 (26), 97 (6), 81 (23), 69 (5), 53 (10), 39 (2).

2-Ethoxythiophenol (2e). Light yellow liquid, ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.48$ (t, 3H), 3.88 (s, 1H), 4.04–4.11 (q, 2H), 6.80–6.85 (m, 2H), 7.04–7.10 (m, 1H), 7.22–7.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 17.5$, 63.4, 126.2, 120.3, 112.1, 118.5, 129.8, 155.4; MS (EI): m/z (rel. int.) 154 (100), 139 (5), 126 (97), 109 (5), 97 (88), 84 (10), 69 (14), 53 (12), 39 (5), 29 (4). EI-HRMS calcd. for $C_8H_{10}OS$ (M^+): 154.0452; found: 154.0454.

2-Methyl-4-fluorothiophenol (2f). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.32$ (s, 3H), 3.20 (s, 1H), 6.75–6.81 (m, 1H), 6.86–6.90 (m, 1H), 7.20–7.25 (m 1H);^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 20.0$, 112.4, 116.2, 129.2, 131.1, 143.5, 159.1; MS (EI): m/z (rel. int.) 142 (98), 109 (100), 97 (9), 83 (9), 69 (6), 57 (6), 45 (7). EI-HRMS calcd. for C_7H_7FS (M^+): 142.0252; found: 142.0255.

3,5-Dimethylthiophenol (2g). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.33$ (s, 6H), 3.44 (s, 1H), 6.86 (s, 1H), 6.98 (s, 2H)[18]; MS (EI): m/z (rel. int.) 138 (65), 123 (9), 105 (100), 91 (14), 77 (23), 63 (9), 39 (17).

3-Fluoro-4-methoxythiophenol (2h). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.43$ (s, 1H), 3.84 (s, 3H), 6.82 (t, 1H, $J = 11.4$ Hz), 7.04–7.12 (m, 2H)[22]; MS (EI): m/z (rel. int.) 158 (100), 143 (97), 126 (3), 115 (28), 95 (6), 83 (5), 69 (6), 57 (4), 45 (5).

2-Methyl-5-chlorothiophenol (2i). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.27$ (s, 3H), 3.33 (s, 1H), 7.00–7.07 (m, 2H), 7.24 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 21.6$, 125.0, 130.2 (2C), 130.8, 134.9, 140.3; MS (EI): m/z (rel. int.) 158 (100), 125 (77), 99 (3), 89 (30), 77 (11), 63 (10), 53 (3), 45 (11). EI-HRMS calcd. for C_7H_7ClS (M^+): 157.9957; found: 157.9959.

2,5-Difluorothiophenol (2j). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.70$ (s, 1H), 6.79–6.84 (m, 1H), 6.97–7.07 (m, 2H);^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 114.0$, 116.4, 117.2, 121.3, 158.7, 160.1; MS (EI): m/z (rel. int.) 146 (100), 126 (68), 101 (39). EI-HRMS calcd. for $C_6H_4F_2S$ (M^+): 146.0002; found: 146.0003.

3,5-Bis(trifluoromethyl)thiophenol (2k). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.70$ (s, 1H), 7.64 (s, 1H), 7.68 (s, 2H)[23]; MS (EI): m/z (rel. int.) 246 (100), 226 (56), 207 (5), 182 (41), 157 (28), 132 (19), 114 (5), 99 (8), 69 (53), 45 (21), 20 (2).

3-Trifluoromethylthiophenol (2l). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.57$ (s, 1H), 7.24–7.43 (m, 3H), 7.51 (s, 1H)[18]; MS (EI): m/z (rel. int.) 178 (100), 158 (60), 145 (12), 133 (9), 114 (36), 95 (8), 82 (7), 69 (36), 57 (10), 45 (22), 28 (5).

3-Methyl-4-fluorothiophenol (2m). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.21$ (s, 3H), 3.38 (s, 1H), 6.84–6.90 (m, 1H), 7.04–7.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 15.1$, 115.4, 124.0, 126.3, 127.8, 128.0, 158.7; MS

(EI): m/z (rel. int.) 142 (91), 121 (6), 109 (100), 95 (7), 83 (12), 89 (7), 57 (5), 45 (8). EI-HRMS calcd. for C_7H_7FS (M^+): 142.0252, found: 142.0255.

ACKNOWLEDGMENTS

This work has been supported by the National Natural Science Foundation of China (20776127), the National Key Technology Research and Development Program (2007BAI34B07), and the Natural Science Foundation of the Zhejiang Province (Y4090045 and R4090358).

REFERENCES

1. Kajimoto, T.; Ishioka, Y.; Katoh, T.; Node, M. Odorless benzenethiols in synthesis of thioglycosides and its application for glycosylation reactions. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5736–5739.
2. Robins, L. I.; Fettinger, J. C.; Tinti, D. S.; Kurth, M. J. Selective nucleophilic chemistry in the synthesis of 5-carbamoyl-3-sulfanylmethylisoxazole-4-carboxylic acids. *J. Comb. Chem.* **2007**, *9*, 139–142.
3. Rohr, H.; Trieflinger, C.; Rurack, K.; Daub, J. Proton- and redox-controlled switching of photo- and electrochemiluminescence in thiophenyl-substituted boron-dipyrromethene dyes. *Chem.—Eur. J.* **2006**, *12*, 689–700.
4. Field, L.; Grunwald, F. A. Lithium aluminum hydride reduction of certain sulfonic acid derivatives. *J. Org. Chem.* **1951**, *16*, 946–953.
5. Fujimori, K.; Togo, H.; Oae, S. Iodine-catalyzed reduction of arenesulfonic acid to the arenethiol with triphenylphosphine. *Tetrahedron Lett.* **1980**, *21*, 4921–4924.
6. Nose, A.; Kudo, T. Reactions of sodium-borohydride, 4: Reduction of aromatic sulfonyl chlorides with sodium-borohydride. *Chem. Pharm. Bull.* **1987**, *35*, 1770–1776.
7. Pervez, H.; Onyiriuka, S. O.; Rees, L.; Rooney, J. R.; Suckling, C. J. Selective functionalization, 10: The nitration of phenols by pyridine-derivatives carrying a transferable nitro-group. *Tetrahedron* **1988**, *44*, 4555–4568.
8. Uchiro, H.; Kobayashi, S. Non-aqueous reduction of aromatic sulfonyl chlorides to thiols using a dichlorodimethylsilane–zinc–dimethylacetamide system. *Tetrahedron Lett.* **1999**, *40*, 3179–3182.
9. Calo, V.; Nacci, A.; Monopoli, A.; Damascelli, A.; Ieva, E.; Cioffi, N. Palladium-nanoparticles-catalyzed hydrodehalogenation of aryl chlorides in ionic liquids. *J. Organomet. Chem.* **2007**, *692*, 4397–4401.
10. Novakova, E. K.; McLaughlin, L.; Burch, R.; Crawford, P.; Griffin, K.; Hardacre, C.; Hu, P. J.; Rooney, D. W. Palladium-catalyzed liquid-phase hydrogenation/hydrogenolysis of disulfides. *J. Catal.* **2007**, *249*, 93–101.
11. Reddy, P. G.; Baskaran, S. A chemoselective method for the reductive N-formylation of aryl azides under catalytic transfer hydrogenation conditions. *Tetrahedron Lett.* **2002**, *43*, 1919–1922
12. Tike, M. A.; Mahajani, V. V. Studies in catalytic transfer hydrogenation of soybean oil using ammonium formate as donor over 5% Pd/C catalyst. *Chem. Eng. J.* **2006**, *123*, 31–41.
13. Chen, X.; Gong, L. Method for preparing corresponding phenyl-sulfhydrate by reduction of aromatic sulfonic acid or derivatives thereof. CN Patent 101381333, 2009.
14. Dockner, T. Reduktion und Hydrierung mit dem System Kohlenwasserstoff/Kohlenstoff. *Angew. Chem.* **1988**, *100*, 4.

15. Engels, H. D.; Singer, R. J. Process for the preparation of thiophenols. U.S. Patent 4006186, 1977.
16. Oae, S.; Togo, H. Reduction of organic sulfonic acids, sodium sulfonates, and sulfonic esters to the corresponding disulfides with polyphosphoric acid derivatives, potassium iodide, and tetrabutylammonium iodide system. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3813–3817.
17. Mustafa, A.; Harhash, A. H. E.; Kamel, M. Reactions with mercaptans, 2: Action of aromatic thiols on omega-nitrostyrenes, 4-styryl-5-oxazolones, and 2-phenyl-3,1-benzoxaz-4-one. *J. Am. Chem. Soc.* **1955**, *77*, 3860–3862.
18. Jiang, Y. W.; Qin, Y. X.; Xie, S. W.; Zhang, X. J.; Dong, J. H.; Ma, D. W. A general and efficient approach to aryl thiols: CuI-catalyzed coupling of aryl iodides with sulfur and subsequent reduction. *Org. Lett.* **2009**, *11*, 5250–5253
19. Chapman, N. B.; Clarke, K.; Iddon, B. Synthesis of some 5-substituted benzo[B]thiophens related to gramine. *J. Chem. Soc.* **1965**, 774.
20. Nichols, D. E.; Shulgin, A. T. Sulfur analogs of psychotomimetic amines. *J. Pharm. Sci.* **1976**, *65*, 1554–1555.
21. Farzaliev, V. M.; Allakhverdiev, M. A.; Shamkhalova, S. A.; Rzaeva, I. A. Synthesis and antioxidative activity of S-substituted 2-mercapto-1,4-dihydroxybenzenes. *Russ. J. Appl. Chem.* **2004**, *77*, 783–786.
22. Campaigne, E.; Smith, H. A.; Sandhu, J. S.; Kim, C. S. Benzo[B]thiophene derivatives, 26: 5-Methoxy-6-chloro-3-β-acetamidoethylbenzo[B]thiophene, a blocked analog of melatonin. *J. Heterocycl. Chem.* **1983**, *20*, 55–59
23. Waern, J. B.; Turner, P.; Harding, M. M. Synthesis and hydrolysis of thiol derivatives of molybdocene dichloride incorporating electron-withdrawing substituents. *Organometallics* **2006**, *25*, 3417–3421.