The Synthesis of Hydroxyphenylthiophenes

Larry J. Baldwin, Sudabeh Pakray and Raymond N. Castle*

Department of Chemistry, University of South Florida,
Tampa, Florida 33620

Milton L. Lee

Department of Chemistry, Brigham Young University,
Provo, Utah 84602

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The synthesis of the five isomeric methoxyphenylthiophenes is described. The methoxy compounds were hydrolyzed to yield the hydroxyphenylthiophenes.

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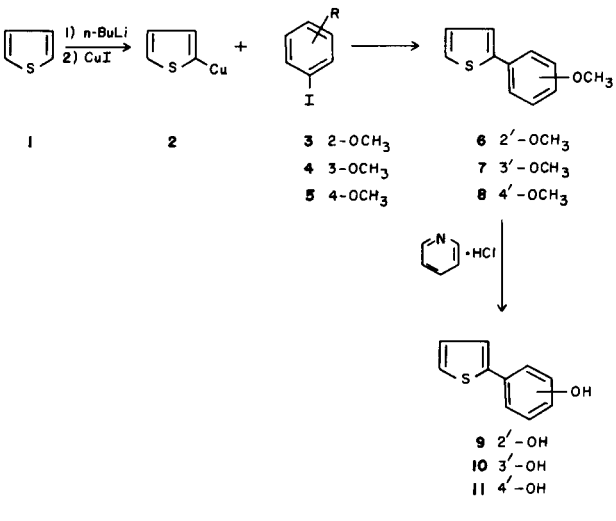
In this paper we report the synthesis of the hydroxyphenylthiophenes as a part of our continuing studies [2-27] directed toward the synthesis of the potentially mutagenic unsubstituted thiophenes and polycyclic thiophenes. Included are many of the hydroxy-substituted derivatives which occur or are suspected of occurring in coal liquids, shale oils and coal-derived products. Recently some of the hydroxyphenylthiophene isomers were found to occur in coal liquids [28].

As shown in Scheme 1 the Ullman reaction of 2-thienylcopper (**2**) [29] and **3** gave 2-(2'-methoxyphenyl)thiophene (**6**) in 37% yield. The methyl ether **6** was cleaved with pyridine hydrochloride to yield 2-(2'-hydroxyphenyl)thiophene (**9**) in 64% yield. Similarly, 2-thienylcopper reacts with 3-iodoanisole (**4**) and 4-iodoanisole (**5**) to give the 2-(3'-methoxyphenyl)thiophene (**7**) in 48% yield and 2-(4'-methoxyphenyl)thiophene (**8**) in 50% yield. Pyridine hydrochloride was used to cleave methyl ethers **7** and **8** to give 2-(3'-hydroxyphenyl)thiophene (**10**) and 2-(4'-hydroxyphenyl)thiophene (**11**) in 54% and 65% yields respectively.

Attempts to extend this chemistry by forming 3-thienylcopper led only to recovery of the starting material. An alternative synthesis for 3-(3'-hydroxyphenyl)thiophene (**16**) is shown in Scheme 2. 3-(3'-Thienyl)-2-cyclohexen-1-one (**15**) was prepared by condensing 3-lithiothiophene (**13**) [prepared by lithiation of 3-bromothiophene (**12**) with *n*-butyllithium] with 1,4-dioxaspiro[4.5]decan-7-one (**14**) [29] followed by hydrolysis. This sequence produced 3-(3'-thienyl)-2-cyclohexen-1-one (**15**) in 41% yield. Compound **16** was obtained in 51% yield by heating a mixture of **15** and sulfur in diphenyl ether at 200° for 1 hour.

3-(4'-Hydroxyphenyl)thiophene (**24**) and 3-(2'-hydroxyphenyl)thiophene (**25**) were prepared by a reaction se-

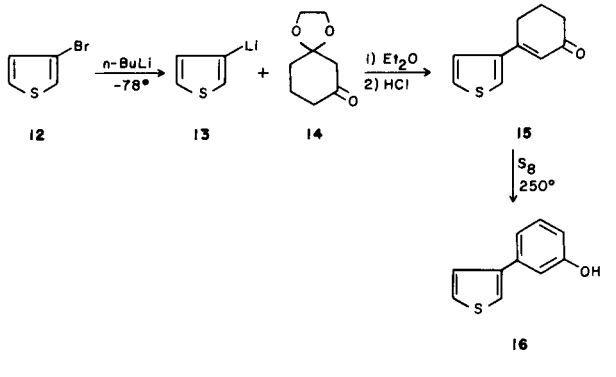
Scheme 1



1 2 3 2-OCH_3 4 3-OCH_3 5 4-OCH_3 6 2'-OCH_3 7 3'-OCH_3 8 4'-OCH_3

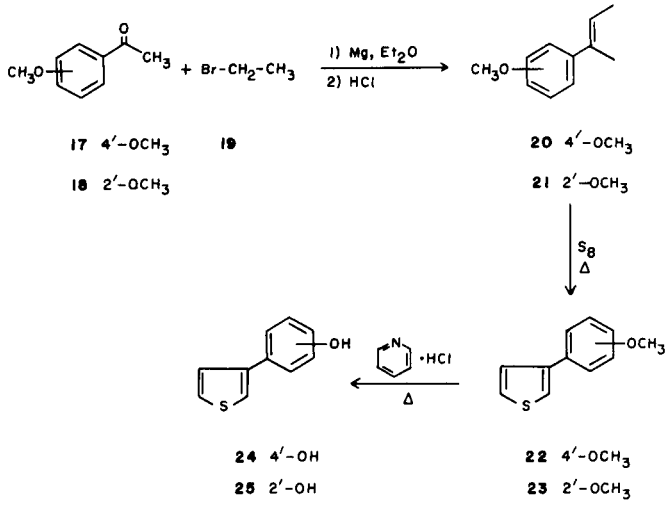
9 2'-OH 10 3'-OH 11 4'-OH

Scheme 2



12 13 14 15 16

Scheme 3



17 4'-OCH_3 18 2'-OCH_3 19 20 4'-OCH_3 21 2'-OCH_3

24 4'-OH 25 2'-OH 22 4'-OCH_3 23 2'-OCH_3

quence outlined by Fringuelli [31] as shown in Scheme 3. 2-(4'-Methoxyphenyl)-2-butene (**20**) was prepared by reacting 4-methoxyacetophenone (**17**) with ethyl magnesium bromide and dehydrating the resulting alcohol. 3-(4'-Methoxyphenyl)thiophene (**22**) was obtained by heating a mixture of sulfur and **20** at 250° for 8 hours. The methyl ether **22** was hydrolyzed with pyridine hydrochloride to give **24**. Similarly, 2-methoxyphenylacetophenone (**18**) was allowed to react with ethyl magnesium bromide followed by dehydration to yield 2-(2'-methoxyphenyl)-2-butene (**21**). A mixture of sulfur and **21** was heated at 250° for 8 hours to yield 3-(2'-methoxyphenyl)thiophene (**23**). The 3-(2'-hydroxyphenyl)thiophene (**25**) was prepared by pyridine hydrochloride hydrolysis of **23**.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were obtained on a Perkin-Elmer Model 337 spectrometer. The ^{1}H-nmr spectra were recorded on a Varian EM-360 spectrometer. Chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. Mass spectra were obtained on a Hewlett-Packard model 5980-A mass spectrometer. The spectra were run using electron impact ionization. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona.

2-(2'-Methoxyphenyl)thiophene (**6**).

Thienylcopper was prepared as described by Nilsson and Ullenius [32]. A solution of thiophene (14.4 g, 0.170 mole) was dissolved in 30 ml of anhydrous ether and it was cooled to 0° in an ice bath. The thiophene was lithiated at 0° by adding dropwise 53.1 ml of a 1.6 *M* *n*-butyllithium solution in hexane. After the addition, the solution was stirred at 0° for 30 minutes to assure complete lithiation. Cuprous iodide (16.2 g, 0.085 mole) was added and the mixture was allowed to warm to room temperature over the period of one hour. After one additional hour, 20 g (0.085 mole) of **3** and 150 ml of anhydrous quinoline were added and the ether was distilled off. The reaction mixture was heated to 150° for 3 hours. The mixture was then cooled and 200 ml of ether was added. The insoluble salts were filtered off and washed with ether. The ether was extracted with 10% aqueous hydrochloric acid solution. The ether layer was then washed with water, dried and evaporated to yield a solid residue. The product was isolated by chromatographic separation on a neutral alumina column using benzene-hexane (50:50) as the eluent. This method produced 5.9 g (37%) of product, bp 130°/1 mm (lit [31] 124-125°/2 mm); nmr (deuteriochloroform): 3.7 (s, 3H), 6.7-7.5 (m, 7H).

2-(3'-Methoxyphenyl)thiophene (**7**).

This compound was prepared in a manner similar to the preparation of **5**. Reaction of 15 g (0.064 mole) of *m*-iodoanisole (**4**) and an equal molar amount of **2** gave 5.8 g (48%) of **6**, bp 120°/1 mm (lit [31,33,34] 100-102°/0.3 mm); nmr (deuteriochloroform): 3.7 (s, 3H), 6.7-7.4 (m, 7H).

2-(4'-Methoxyphenyl)thiophene (**8**).

This compound was prepared in the same manner as **5**. Reaction of 2.0 g (0.0085 mole) of *p*-iodoanisole (**5**) and an equal molar amount of **2** gave 1.0 g (67%) of **8**, mp 105-106° (lit [19,31,32,35,36] 104-107°; nmr (deuteriochloroform): 3.7 (s, 3H), 6.8 (d, 3'-H, 5'-H, 2H, J = 7 Hz), 7.1 (m, 3-H, 4-H, 5-H, 3H), 7.5 (d, 2'-H, 6'-H, 2H, J = 7 Hz).

2-(2'-Hydroxyphenyl)thiophene (**9**).

Compound **6** (1.0 g, 0.053 mole) was mixed with 10 g of pyridine hydrochloride and the mixture was heated at 200° for 12 hours. After the mixture cooled, 50 ml of water was added and the resultant precipitate was isolated by filtration. The solid was dissolved in 20% aqueous sodium hydroxide solution. The solution was filtered and neutralized with 4 *M* aqueous hydrochloric acid. The white solid was filtered and purified by sublimation at reduced pressure (1 mm) to yield colorless needles in 64% yield, mp 40-42°; nmr (deuteriochloroform): 5.2 (bs, 1H, OH), 6.8-7.5 (m, 7H).

Anal. Calcd. for $C_{10}H_8OS$: C, 68.15; H, 4.58; S, 18.20. Found: C, 68.31; H, 4.63; S, 18.31.

2-(3'-Hydroxyphenyl)thiophene (**10**).

2-(3'-Methoxyphenyl)thiophene (**7**) (1.0 g, 0.0053 mole) was cleaved with 10.0 g of pyridine hydrochloride. The product was isolated and purified in the same manner as **9**. This hydrolysis produced **10**, 0.5 g (54%) as colorless needles, mp 80-81° (lit [31] 86-88°); nmr (deuteriochloroform): 7.0-8.0 (m, 8H).

2-(4'-Hydroxyphenyl)thiophene (**11**).

A mixture of 1.0 g (0.0053 mole) of **8** was cleaved with 10 g of pyridine hydrochloride using the method described for the production of **9**. The purified hydroxy compound was isolated as colorless needles, 0.6 g (75%) mp 148° (lit [31,35,36,37] 143-146°); nmr (DMSO-d_6): 7.5-8.3 (m, 7H), 9.5 (br s, OH).

3-(3'-Thienyl)-2-cylohexen-1-one (**15**).

A solution of 3.13 g (0.019 mole) of 3-bromothiophene (**12**) dissolved in 50 ml of dry ether was cooled to −78°. The 3-bromothiophene (**12**) was lithiated by slowly adding 12.4 ml of a 1.55 *M* solution of *n*-butyllithium in hexane. After the addition was complete, the solution was stirred at −78° for 30 minutes. A solution of 3.0 g (0.019 mole) of 1,4-dioxaspiro-[4.5]decan-7-one [30] in 25 ml of dry ether was added over a period of 20 minutes. The solution was allowed to warm to room temperature overnight. The solution was then neutralized with 10% aqueous ammonium chloride solution. The ether layer was separated, dried and the solvent was evaporated. The residue was then refluxed in aqueous 1.4 *M* hydrochloric acid for 1 hour. The organic product was isolated by extraction with ether. The ether was dried and evaporated to yield an oil which was crystallized from benzene-hexane as yellow needles, 1.4 g (41%), mp 100-102°; nmr (deuteriochloroform): 2.0-3.0 (m, 6H), 6.3 (s, 1H), 7.3 (m, 2H), 7.5 (m, 1H); ms: 180 (3.0), 179 (6.4), 178 (54), 150 (95), 122 (100), 121 (84), 39 (86).

Anal. Calcd. for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99. Found: C, 67.06; H, 5.75; S, 17.69.

3-(3'-Hydroxyphenyl)thiophene (**16**).

A mixture of 1.0 g (0.0056 mole) of **15** and 0.5 g of sulfur in 20 g of diphenyl ether was heated at 240° for 1 hour. The diphenyl ether was distilled off under reduced pressure. The residue was dissolved in ether, filtered and extracted wtih 10% aqueous sodium hydroxide. The aqueous layer was neutralized with 4 *N* aqueous hydrochloric acid and extracted with ether. The ether layer was separated, dried and evaporated. The residue was then sublimed under reduced pressure to yield white prisms, mp 90-92°, in 51% yield (lit [31] 100-102°); nmr (deuteriochloroform): 6.6-7.6 (m, 7H, OH).

Anal. Calcd. for $C_{10}H_8OS$: C, 68.15; H, 4.58; S, 18.20. Found: C, 68.04; H, 4.58; S, 18.31.

2-(4'-Methoxyphenyl)-2-butene (**20**).

Compound **20** was prepared by the Grignard reaction of *p*-methoxyacetophenone (**17**) (40.0 g, 0.26 mole) and 0.3 mole of ethyl magnesium bromide. The grignard reagent was prepared by reacting 7.2 g (0.3 mole) of magnesium and bromoethane (32.4 g, 0.3 mole) in 100 ml of dry tetrahydrofuran. After refluxing the reaction mixture for 3 hours, the magnesium complex formed was decomposed by adding 10% aqueous hydrochloric acid. The product was isolated by extraction of the resulting solution with ether. The ether layer was separated, dried and the solvent was evaporated. The residue was refluxed in 100 ml of benzene containing

0.1 g of *p*-toluenesulfonic acid for 1 hour. The benzene was then dried and evaporated. The oily residue was distilled under reduced pressure to yield 25.9 g (57%) bp 118-120°/1 mm (lit [31] 120-124°/14 mm); nmr (deuteriochloroform): 1.6 (d, 3H, J = 2.5 Hz), 1.95 (s, 3H), 3.60 (s, 3H), 5.45 (q, 1H, J = 2.5 Hz), 6.65 (dd, 4H, J = 10 Hz, J' = 24 Hz).

3-(4'-Methoxyphenyl)thiophene (**22**).

A mixture of **20** (10.0 g, 0.06 mole) and sulfur (9.8 g, 0.3 mole) was heated to 250° for 8 hours. The hydrogen sulfide gas that was generated during the reaction was trapped in a solution of 35% aqueous sodium hydroxide solution. The residue was extracted with 100 ml of hot benzene. The volume of the benzene was reduced and cold hexane was added. The yellow solution was decanted and the solvents were evaporated. The residue was then chromatographed on a column of neutral alumina eluting with hexane to yield the crystalline solid product, 2.4 g (21%) mp 130-131° (lit [31] 126-129°); nmr (deuteriochloroform): 3.7 (s, 3H), 6.35-7.40 (m, 7H).

3-(4'-Hydroxyphenyl)thiophene (**24**).

3-(4'-Methoxyphenyl)thiophene (**17**) (0.5 g, 0.051 mole) and pyridine hydrochloride (3.0 g) were heated in an oil bath at 180° for 10 hours. The resulting residue was washed with ether and a yellow solid was obtained. The solid was recrystallized from benzene and sublimed at reduced pressure to give 0.18 g (56%) of colorless needles mp 189-190° (lit [31] 200-202°, 192-193°); nmr (acetone-d_6): 6.75-7.25 (m, 7H), 8.60 (s, 1H).

Anal. Calcd. for $C_{10}H_8OS$: C, 68.15; H, 4.58; S, 18.20. Found: C, 68.22; H, 4.63; S, 18.13.

2-(2'-Methoxyphenyl)-2-butene (**21**).

o-Methoxyacetophenone (**18**) (40.0 g, 0.26 mole) was allowed to react with 0.3 mole of ethyl magnesium bromide and the product was treated in the same manner as in the preparation of **20**. This reaction afforded **21**, in 65% yield (8 g), bp 110°/10 mm (lit [38] 219°); nmr (deuteriochloroform): 1.75 (d, 3H, J = 3 Hz), 1.75 (s, 1H), 5.45 (q, 1H, J = 3 Hz), 3.60 (s, 3H), 6.70 (m, 4H).

3-(2'-Methoxyphenyl)thiophene (**23**).

Compound **21** (28.8 g, 0.17 mole) and sulfur (28.4 g, 0.88 mole) were heated at 250° for 10 hours. The product was isolated in the same manner as was **22**. The product **23** was distilled to give 3.8 g (12%), bp 108-110°/10 mm; nmr (deuteriochloroform): 3.65 (s, 3H), 6.75 (m, 4H), 7.30 (m, 3H). This compound was used in the next reaction without further purification.

3-(2'-Hydroxyphenyl)thiophene (**25**).

Compound **25** was prepared by hydrolyzing **23** (0.1 g, 0.52 mmole) in 1.5 g of pyridine hydrochloride in the same manner as **8** was hydrolyzed to **11** to yield 0.05 g (50%) of a colorless oil bp 120°/10 mm; nmr (deuteriochloroform): 5.15 (bs, 1H), 6.7-7.0 (m, 4H), 7.0-7.2 (m, 3H).

Anal. Calcd. for $C_{10}H_8OS \cdot \frac{1}{4}H_2O$: C, 66.45; H, 4.75; N, 17.74. Found: C, 66.11; H, 4.74; S, 17.74.

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REFERENCES AND NOTES

[1] To whom correspondence should be addressed at the University of South Florida.

[2] M. Iwao, M. L. Lee and R. N. Castle, *J. Heterocyclic Chem.*, **17**, 1259 (1980).

[3] Y. Tominaga, M. L. Lee and R. N. Castle, *J. Heterocyclic Chem.*, **18**, 967 (1981).

[4] R. Pratap, Y. Tominaga, M. L. Lee and R. N. Castle, *J. Heterocyclic Chem.*, **18**, 973 (1981).

[5] Y. Tominaga, M. L. Lee and R. N. Castle, *J. Heterocyclic Chem.*, **18**, 977 (1981).

[6] R. D. Thompson, M. Iwao, M. L. Lee and R. N. Castle, *J. Heterocyclic Chem.*, **18**, 981 (1981).

[7] R. Pratap, M. L. Lee and R. N. Castle, *J. Heterocyclic Chem.*, **18**, 1457 (1981).

[8] R. Pratap, M. L. Lee and R. N. Castle, *J. Heterocyclic Chem.*, **19**, 219 (1981).

[9] R. Pratap, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **19**, 439 (1982).

[10] Y. Tominaga, R. Pratap, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **19**, 859 (1982).

[11] R. Pratap, Y. Tominaga, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **19**, 865 (1982).

[12] Y. Tominaga, R. Pratap, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **19**, 871 (1982).

[13] Y. Tominaga, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **19**, 1125 (1982).

[14] Y. Tominaga, M. L. Tedjamulia, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **20**, 487 (1983).

[15] M. L. Tedjamulia, Y. Tominaga, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **20**, 861 (1983).

[16] M. L. Tedjamulia, Y. Tominaga, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **20**, 1143 (1983).

[17] M. L. Tedjamulia, Y. Tominaga, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **20**, 1149 (1983).

[18] M. Sugiura, M. L. Tedjamulia, Y. Tominaga, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **20**, 1453 (1983).

[19] M. L. Tedjamulia, Y. Tominaga, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **20**, 1485 (1983).

[20] H. Kudo, M. L. Tedjamulia, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **21**, 185 (1984).

[21] M. L. Tedjamulia, H. Kudo, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **21**, 321 (1984).

[22] M. L. Tedjamulia, J. G. Stuart, Y. Tominaga, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **21**, 1215 (1984).

[23] H. Kudo, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **21**, 1761 (1984).

[24] L. J. Baldwin, M. L. Tejamulia, J. G. Stuart, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **21**, 1775 (1984).

[25] H. Kudo, M. L. Tedjamulia, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **21**, 1833 (1984).

[26] H. Kudo, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **22**, 211 (1985).

[27] H. Kudo, R. N. Castle and M. L. Lee, *J. Heterocyclic Chem.*, **22**, 215 (1985).

[28] M. Nishioka, M. L. Lee, H. Kudo, D. R. Muchiri, L. J. Baldwin, S. Pakray, J. G. Stuart and R. N. Castle, *Anal. Chem.*, **57**, 1327 (1985).

[29] M. Nilsson and C. Ullenius, *Acta Chem. Scand.*, **24**, 2379 (1970).

[30] M. P. Mertes, *J. Org. Chem.*, **26**, 5236 (1961).

[31] F. Fringuelli, G. Marino and A. Taticchi, *J. Chem. Soc. (B)*, 1595 (1970).

[32] M. Nilsson and C. Ullenius, *Acta Chem. Scand.*, **22**, 1998 (1968).

[33] L. Benati and M. Tiecco, *Boll. Sci. Fac. Chim. Ind. Bologna, Suppl.*, **24**, 225 (1966); *Chem. Abstr.*, **67**, 90193a (1966).

[34] G. Martelli, P. Spagnolo and M. Tiecco, *J. Chem. Soc. (B)*, 901 (1968).

[35] M. A. Al'perovich and L. T. Bogolyubskaya, *J. Gen. Chem. USSR*, **34**, 647 (1964).

[36] T. Sone, O. Shiromaru, S. Igarashi, E. Kato and M. Sawara, *Bull. Chem. Soc. Japan*, **52**, 1126 (1979).

[37] F. D. King and D. R. M. Walton, *Synthesis*, 40 (1976).

[38] M. J. S. Dewar and N. A. Puttnam, *J. Chem. Soc.*, 4080 (1959).