Synthesis of Substituted Benzo[*b*]thiophenes by Acid-Catalyzed Cyclization of Thiophenylacetals and Ketones

Patrick A. Plé and Lawrence J. Marnett*

435 Chemistry Building, Wayne State University,
Detroit, MI, 48202

Received March 2, 1988

Benzo[*b*]thiophenes substituted at the 3 position with methyl or carboxymethyl and at the 5 position with methyl, methoxy, chloro, bromo and nitro were prepared by cyclization of thiophenyl-acetals and ketones using a suspension of polyphosphoric acid in refluxing chlorobenzene. The overall efficiency of this method is superior to literature procedures because of the lower temperature and the limited amount of PPA used.

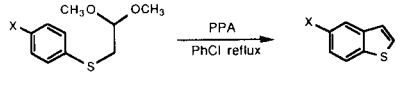
J. Heterocyclic Chem., **25**, 1271 (1988).

Studies in our laboratory of the enzyme-catalyzed reduction of hydroperoxides by aryl sulfides required the preparation of substituted benzo[*b*]thiophenes. Construction of the thiophene ring can be accomplished by cyclization of thiophenylacetals and ketones in neat polyphosphoric acid (PPA) at 180°. The starting material is injected directly into the PPA at 1-10 mm Hg and the resulting benzo[*b*]thiophene is distilled off [1,2]. In our hands, this procedure gave very poor results. Most of the sensitive benzo[*b*]thiophene stays trapped in PPA after its formation and is rapidly degraded. In principle an aromatic solvent should be able to extract the product from PPA as soon as it is formed. The reaction in neat PPA requires temperatures above 120°, so high boiling point aromatic solvents were used; of the solvents tested, chlorobenzene was most effective. We describe here conditions that support cyclization in high yield and are compatible with a range of functional groups.

The amount of PPA used was approximately 2:1 (w/w) with the starting material. Reactions were performed under anhydrous conditions and the starting material was slowly added to refluxing solvent. After 5-24 hours, the corresponding benzo[*b*]thiophenes were obtained following work-up.

Table I

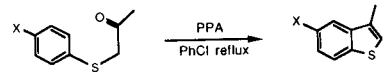
Yields of Benzo[*b*]thiophene Derivatives Obtained by Cyclization of (Arylthio)acetaldehyde Dimethyl Acetals with PPA in Refluxing Chlorobenzene



X	Reaction time (hours)	Yields (%) Observed	Literature
Cl^-	24	80	43; 65 [2,3]
Br^-	24	81	49; 60 [4,3]
Me^-	5	76	48; 61 [2,5]
MeO^-	5, 24	0	0-5 [6]

Table II

Yields of Benzo[*b*]thiophene Derivatives Obtained by Cyclization of (Arylthio)acetones with PPA in Refluxing Chlorobenzene

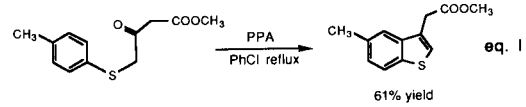


X	Reaction time (hours)	Yields (%) Observed	Literature
Br^-	12	95	31; 70 [7,8]
Me^-	12	96	92 [9]
MeO^-	12	58	18 [10]
NO_2^-	5, 24	12	-

Table I compares the yields of benzo[*b*]thiophenes from phenylthioacetals obtained in the heterogenous system to those obtained in neat PPA. Significantly higher yields were evident in each case. When X = OMe no cyclization occurred and the starting material was quickly degraded.

Higher yields were obtained on cyclization of phenylthioketones (Table II). In this case, even the *para*-methoxy substituted ketone reacted in good yield. Low yields were evident with X = NO_2, variations in the reaction time did not increase the yield. Interestingly, this compound did not react under literature conditions.

A number of potent antiinflammatory agents are arylacetic acids (*e.g.* indomethacin and ibuprofen). Thiophene acetic acids are potentially active antiinflammatory compounds so we attempted to construct them by cyclization in the two phase system (equation I). For synthesis of methyl-5-methylbenzo[*b*]thiophene-3-acetate, the reaction must be carefully monitored to limit decarboxylation. The high yield obtained suggests that the two phase procedure is compatible with a broad range of functional groups.



eq. I

EXPERIMENTAL

General procedure.

Anhydrous chlorobenzene (20 ml) was placed in a 25 ml flask equipped with a condenser and a magnetic stirring bar. The apparatus was flushed with nitrogen and about 1 ml of polyphosphoric acid was added. The mixture was brought to gentle reflux and 0.58 g (2.5 mmol) of 2,2-dimethoxyethyl-4-chlorophenyl sulfide was slowly added (1 hour) and the solution was refluxed overnight with vigouous stirring. The course of the reaction was monitored by thin layer chromatography (silica gel F, ethyl acetate - hexanes 1/9). The reaction mixture was allowed to cool to ambient temperature and the organic phase was separated from the PPA. Residual PPA was decomposed with water and the resulting aqueous phase was washed with 2 x 10 ml of dichloromethane. The dichloromethane was dried over magnesium sulfate, the organic phases were combined, and the solvent evaporated. Chromatographic purification (silica gel/pentane) gave 0.34 g (80%) of 5-chlorobenzo[*b*]thiophene as an oil.

All compounds listed in Tables I and II had identical spectroscopic properties to literature values.

Methyl-5-Methylbenzo[*b*]thiophene-3-acetate.

This compound had ^{1}H nmr (deuteriochloroform) 300 MHz, δ 2.47 (s, 3H), 3.70 (s, 3H), 3.83 (s, 2H), 7.20 (d, J = 8.2 Hz, 1H), 7.30 (s, 1H), 7.52 (s, 1H), 7.72 (d, J = 8.2 Hz, 1H) ppm; ^{13}C nmr (deuteriochloroform): 75.4 MHz, δ 21.5, 34.2, 52.1, 121.6, 122.5, 124.7, 126.2, 127.8, 134.0, 137.4, 138.8, 171.1 ppm; ir (neat): 3008, 2951, 2860, 1728, 1605, 1433, 1261, 1162, 1015, 801 cm^{-1}; ms: m/e, Calcd. for $C_{12}H_{12}O_2S$ (M^+) 220.0558. Found: 220.0559.

5-Nitrobenzo[*b*]thiophene.

This compound had ^{1}H nmr (deuteriochloroform) 300 MHz, δ 7.51 (d, J = 5.5 Hz, 1H), 7.67 (d, J = 5.5 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 8.20 (dd, J = 8.9, 2.0 Hz, 1H), 8.72 (d, J = 2.0 Hz, 1H) ppm; ^{13}C nmr (deuteriochloroform): 75.4 MHz, δ 118.5, 119.2, 122.9, 124.7, 129.9, 139.3, 145.5, 184.4 ppm; ir (potassium bromide): 3005, 1599, 1514, 1339, 1051, 927, 803 cm^{-1}; ms: m/e, Calcd. for $C_8H_5NO_2S$ (M^+) 179.0041. Found: 179.0041.

Acknowledgments.

This work was supported by a research grant from the National Institutes of Health (GM23642).

REFERENCES AND NOTES

* Author to whom correspondence should be addressed.

[1] K. Rabindran and B. D. Tilak, *Curr. Sci. (India)*, **20**, 205 (1951).

[2] A. V. Sunthankar and B. D. Tilak, *Proc. Indian Acad. Sci.*, **32A**, 396 (1950).

[3] M. S. El Shanta and R. M. Scrowston, *J. Chem. Soc.*, C 2084 (1967).

[4] J. E. Banfield, W. Davies, B. C. Ennis, S. Middleton and Q. N. Porter, *J. Chem. Soc.*, 2603 (1956).

[5] N. B. Chapman, K. Clarke, S. N. Sawhney and B. Gore, *J. Chem. Soc.* (C), 514 (1968).

[6] A. V. Sunthankar and B. D. Tilak, *Proc. Indian Acad. Sci.*, **33A**, 35 (1951).

[7] Y. Matsuki and I. Ito, *Nippon kagaku Zasshi*, **88**, 758 (1967); *Chem. Abstr.*, **69**, 59018 (1968).

[8] N. B. Chapman, K. Clarke and S. N. Sawhney, *J. Chem. Soc.* (C), 518 (1968).

[9] G. D. Gal'pern, I. M. Numanov and M. I. Nasyrov, *Dokl. Akad. Nauk. Tadzh. SSR*, **7**, 34 (1964); *Chem. Abstr.*, **64**, 3452 (1965).

[10] R. Royer, P. Demerseman, J. P. Lechartier, A. M. Laval-Jeantet, A. Cheutin and M. L. Desvoye, *Bull. Soc. Chim. France*, 315 (1964).