A Facile Synthesis of 3-Alkylthio- (or arylthio-)pyridines and 3,5-Bis(alkylthio)pyridines

Ted K. Chen

Department of Analytical Chemistry, Smith Kline and French Laboratories, P.O. Box 1539 (L960), King of Prussia, PA 19406-0939, U.S.A.

William T. Flowers*

Department of Chemistry, University of Manchester Institute of Science and Technology, P.O. Box 88, Manchester, M60 1QD, England

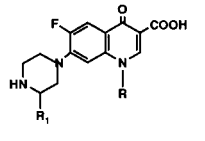
Received October 5, 1989

3-Alkylthio- (or 3-arylthio-)pyridines and 3,5-bis(alkylthio)pyridine can be conveniently prepared by the reaction of 3-thiocyanato- or 3,5-bis(thiocyanato)pyridines with tri-*n*-butylphosphine in the presence of alcohol.

J. Heterocyclic Chem., **27**, 831 (1990).

Sulfur functionalities can readily be introduced to the 2-, 4- or 6-position of the pyridine ring *via* nucleophilic substitution [1,2]. The same strategy is however, less successful when applied to the synthesis of the 3- or 5-analogues, requiring more stringent reaction conditions and producing mixtures of regio-isomers [3-6]. 3- or 5-Alkylthio- as well as arylthiopyridines are usually prepared from the corresponding 3- or 5-aminopyridines *via* diazotization followed by decomposition of the diazonium salt with thiourea [7], sodium methylmercaptan [8], dimethyl- (or diphenyl-) disulfide [9], potassium xanthate [10], sodium dimethyldithiocarbamate [11], or potassium *O*-ethyldithiocarbonate [12]. However, the yields in these reactions are generally low to moderate. Apart from the potential explosion hazards involved in heating diazonium salts with potassium xanthates or sodium dimethyldithiocarbamates, side reactions [7, 10] leading to the formation of diaryl dithiocarbonate, alkyl alkyl xanthates as well as aryl aryl disulfides could also occur in these reactions. 3,5-Diaminopyridine on the other hand, has been reported not to undergo bis(diazotization), and attempted synthesis of 3,5-dimercaptopyridine *via* this route failed [13]. 3,5-Dimercaptopyridine was synthesized *via* the treatment of 3,5-dihydroxypyridine with diethylthiocarbamyl chloride which afforded the corresponding 3,5-bis(diethylthiocarbamyloxy)pyridine followed by thermal rearrangement to 3,5-bis(diethylcarbamylthio)pyridine and subsequent hydrazinolysis [13]. Earlier attempts in introducing a thiol group to the 3-position of the pyridine ring by forceful treatment of 3-hydroxypyridin-2-one with phosphorus pentasulfide was also unsuccessful [14].

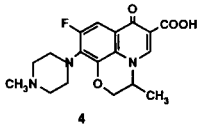
As the reaction between arylthiocyanates and alcohols under the influence of triphenylphosphine has been reported to afford alkyl aryl sulfides [15], we have investigated the utility of this reaction in the heterocyclic series. We report here a facile synthesis of 3-alkylthio- (or 3-arylthio-) and 3,5-bis(alkylthio)pyridines by the tri-*n*-butylphosphine-mediated reaction of halogenated pyridylthiocyanates with alcohols (Scheme 1). The starting materials for these reactions can readily be prepared in good yield from 2,6-diaminopyridine *via* thiocyanation and bis(diazotization) [16].



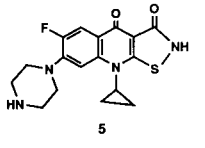
1 R=C_2H_5 R_1=H

2 R=c-C_3H_5 R_1=H

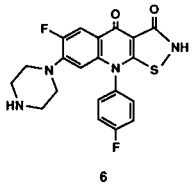
3 R=o.p-$C_6H_3F_2$ R_1=CH_3



4

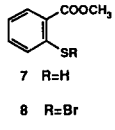


5



6

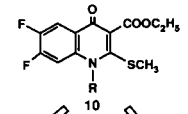
9



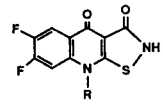
7 R=H

8 R=Br

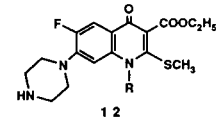
Scheme 1



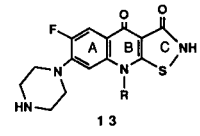
10



11



12



13

Thus under dry nitrogen atmosphere, 2,6-dichloro-3,5-dithiocyanatopyridine (1 mole) was reacted with tri-*n*-butylphosphine (2 moles) in the presence of dry benzyl alcohol to give a single product of 2,6-dichloro-3,5-bis-(benzylthio)pyridine (**1a**) in 82% yield. The reaction is convenient, manipulatively simple, uses only stoichiometric amount of reagents and is completed within an hour at room temperature. Similarly prepared were 2,6-dichloro-3,5-bis(methylthio)pyridine (**1b**), 2,3,6-trichloro-5-methylthiopyridine (**1c**), 2,6-dichloro-3-bromo-5-benzylthiopyridine (**1d**) and 2-chloro-3-(2′-chloro)benzylthiopyridine (**1e**). The results are summarized in Table 1. Replacement of triphenylphosphine with tri-*n*-butylphosphine [17] in these reactions also make the isolation of the product pyridylthioethers considerably easier since the by-product, tri-*n*-butylphosphine is water-soluble and can be easily removed by stirring the crude products in water.

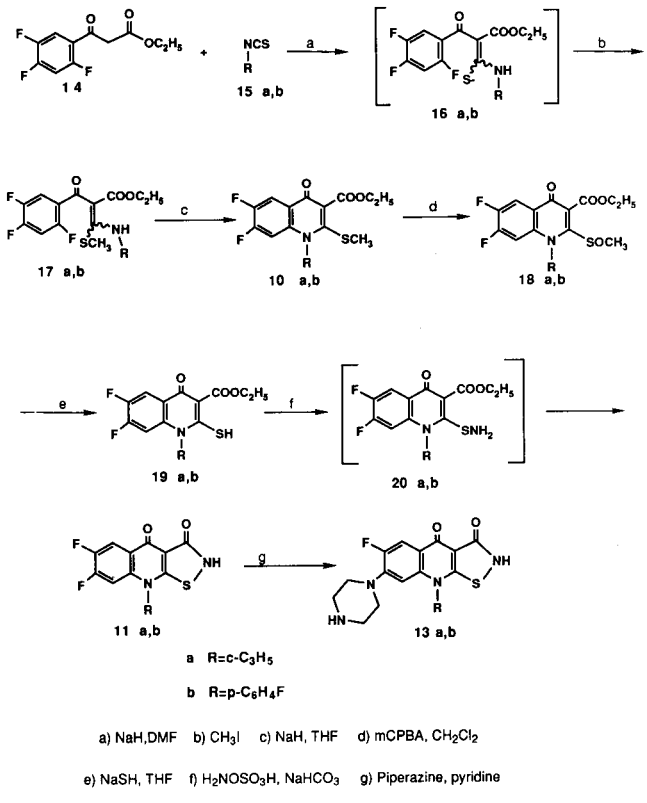
Table 1: Preparation of 3- and 3,5-bis(alkylthio-) or arylthiopyridines

Starting Material	Alcohol used R^3OH		Product	Yield
R^1 = SCN, R^2 = Cl	$R^3 = C_6H_5CH_2$-	1a	$R^1 = C_6H_5CH_2$-S- R^2 = Cl, $R^3 = C_6H_5CH_2$-	82%
R^1 = SCN, R^2 = Cl	$R^3 = CH_3$	1b	R^1 = SCH_3, R^2 = Cl, $R^3 = CH_3$	82%
$R^1 = R^2$ = Cl	$R^3 = CH_3$	1c	$R^1 = R^2$ = Cl, $R^3 = CH_3$	87%
R^1 = Br, R^2 = Cl	$R^3 = C_6H_5CH_2$-	1d	R^1 = Br, R^2 = Cl $R^3 = C_6H_5CH_2$-	85%
$R^1 = R^2$ = H	R^3 = o-Cl-$C_6H_4CH_2$-	1e	$R^1 = R^2$ = H R^3 = o-Cl-$C_6H_4CH_2$-	40%

The mechanism of this tri-*n*-butylphosphine-mediated reaction of pyridylthiocyanates with alcohol (Scheme 2) may be similar to the carbocyclic analogues of Flowers *et al.* [11], which was well characterized. Nucleophilic attack of trivalent phosphorus on divalent sulfur resulting as in Scheme 2, in the formation of a phosphonium ion and the displacement of an anion, *e.g.*, CN^-, has been reported [18] and reviewed [19]. Support for the intermediacy of the phosphonium salt **A** can be found in the reaction of diphenyl disulfide with triphenylphosphine in the presence of water [20] and methanol [21] where thiophenol and methylphenyl sulfide were obtained respectively. The formation of the oxythiophosphorane analogues of **B** and its subsequent ionization has also been observed by Barton *et al.* [22] in the reaction of benzylmethyl sulfenate with tri-*n*-butylphosphine where benzylmethyl sulfide and tri-*n*-butylphosphine oxide were the exclusive products.

Treatment of **1b** with lithium aluminum hydride removed both of the chlorines, and the resultant 3,5-bis(methylthio)pyridine was isolated via its methiodide in 95% yield, the free base being very difficult to purify. Oxidation of **1b** with *meta*-chloroperbenzoic acid gave quantitatively, 2,6-dichloro-3,5-bis(methylsulphonylthio)pyridine (**1f**).

Scheme 2



EXPERIMENTAL

Melting points were obtained in open capillary tubes in a Thomas-Hoover melting point apparatus and are reported uncorrected. The ^{1}H nmr spectra were recorded on a Perkin Elmer R32 spectrometer. Chemical shifts were measured as value from internal tetramethylsilane reference. The starting materials, 2,6-dichloro-3,5-dithiocyanatopyridine, 2,6-dichloro-5-bromo-3-thiocyanatopyridine and 2-chloro-3-thiocyanatopyridine were prepared according to published methods [8,16].

General Procedure for the Reaction of Halogenated Pyridylthiocyanates with Alcohol in the presence of Tri-*n*-butylphosphine.

A typical synthetic procedure is illustrated with the preparation of 2,6-dichloro-3,5-bis(benzylthio)pyridine (**1a**): To a dry 3-necked flask fitted with a magnetic pedal and nitrogen inlet as well as outlet tubes, 2,6-dichloro-3,5-dithiocyanatopyridine (1.4 g, 5.4 mmoles) was introduced. The flask was then closed with a rubber cap and flushed with dry nitrogen. The flow rate of dry nitrogen was lowered, and tri-*n*-butylphosphine (2.4 g, 10.8 mmoles) was injected. After stirring at room temperature for 15 minutes, dry benzyl alcohol (15 ml) was injected and the resultant reaction mixture stirred at room temperature for a further hour. Excess benzyl alcohol was next removed by distillation under reduced pressure, leaving a thick brown oil. Distilled water (100 ml) was next added and the mixture was stirred for 30 minutes.

After decanting the water layer, methanol (10 ml) was added to the organic layer and the resultant precipitates were filtered and recrystallised from aqueous methanol to give 1.6 g (82%) of **1a**, mp 101°; ^{1}H nmr (deuteriochloroform): δ 3.94 (s, 4H), 7.18 (s, 1H)

and 7.3 (s, 10H); ms: (m/e) 395 (5.5), 393 (23.2), 391 (30.8), 267 (1.1), 265 (1.9), 181 (1.7), 91 (100), 65 (42.8).

Anal. Calcd. for $C_{19}H_{15}Cl_2NS_2$: C, 58.16; H, 3.85; N, 3.57; Cl, 18.07; S, 16.34. Found: C, 57.9; H, 3.7; N, 3.4; Cl, 18.0; S, 16.0.

2,6-Dichloro-3,5-bis(methylthio)pyridine (**1b**).

This compound was obtained as colorless needles (aqueous methanol), mp 161.5-163°; ^{1}H nmr (deuteriochloroform): δ 2.5 (s, 6H) and 7.25 (s, 1H); ms: (m/e) 243 (16.0), 241 (72.3), 239 (100), 228 (1.3), 226 (6.5), 224 (9.1), 213 (0.9), 211 (3.8), 209 (5.2), 191 (6.2), 189 (13.0), 181 (1.2), 179 (3.6), 177 (5.3), 176 (1.6), 174 (4.2), 139 (0.3).

Anal. Calcd. for $C_7H_7Cl_2NS_2$: C, 35.01; H, 2.94; N, 5.83; Cl, 29.52; S, 26.67. Found: C, 34.8; H, 2.9; N, 5.7; Cl, 29.7; S, 26.2.

2,3,6-Tichloro-5-methylthiopyridine (**1c**).

This compound was recrystallized from aqueous methanol, mp 81°; ^{1}H nmr (deuteriochloroform): δ 2.47 (s, 3H) and 7.47 (s, 1H).

Anal. Calcd. for $C_6H_4Cl_3NS$: C, 31.54; H, 1.76; N, 6.13; S, 14.03; Found: C, 31.3; H, 1.8; N, 6.3; S, 13.7.

2,6-Dichloro-3-bromo-5-benzylthiopyridine (**1d**).

This compound was recrystallized from aqueous ethanol, mp 108-109°; ^{1}H nmr (deuteriochloroform): δ 4.16 (s, 2H), 7.38 (s, broad 5H) and 7.68 (s, 1H); ms: (m/e) 353 (3.0), 351 (17.1), 349 (37.2), 347 (21.7), 262 (0.5), 260 (2.5), 258 (5.3), 256 (3.2), 225 (0.5), 223 (2.1), 181 (1.9), 179 (10.4), 177 (15.4), 144 (1.2), 142 (2.9), 91 (100).

Anal. Calcd. for $C_{12}H_8BrCl_2NS$: C, 41.29; H, 2.31; N, 4.01; S, 9.18. Found: C, 41.3; H, 2.1; N, 3.9; S, 9.3.

2-Chloro-3-(2′-chloro)-benzylthiopyridine (**1e**).

This compound was isolated by column chromatography on silica gel with chloroform as eluent, mp 51-52°; ms: (m/e) 272 (2.6), 270 (13.9), 268 (19.8), 146 (1.0), 144 (2.3), 125 (100), 109 (1.8), 82 (3.0).

Anal. Calcd. for $C_{12}H_9Cl_2NS$: C, 53.35; H, 3.36; N, 5.18. Found: C, 53.6; H, 3.3; N, 5.2.

Preparation of 3,5-Bis(methylthio)pyridine *N*-Methiodide (**1f**).

To a suspension of lithium aluminum hydride (0.7 g, 18 mmoles) in dry THF under dry nitrogen atmosphere, a solution of 2,6-dichloro-3,5-bis(methylthio)pyridine (1.2 g, 5 mmoles) in dry THF (90 ml) was added dropwise with stirring and with external cooling in an ice-bath. Upon complete addition of the 2,6-dichloro-3,5-bis(methylthio)pyridine solution, the reaction mixture was allowed to stir at room temperature for a further half hour and then heated to reflux for 12 hour. After cooling to room temperature, excess lithium aluminum hydride was decomposed by dropwise addition of ice-water (10 ml) at 0°. The mixture was filtered and the residue washed with diethyl ether (80 ml). The organic layer was separated, and the aqueous layer extracted twice with diethyl ether (100 ml). The combined ether extract was dried over magnesium sulfate and evaporated under reduced pressure to leave a thick brown oil (0.8 g) which was taken up in dry ethanol (25 ml) and cooled in an ice bath. Iodomethane (24 g, 170 mmoles) was next added and the resultant solution was heated to gentle reflux for 6 hours. Upon slow cooling, 1.4 g (95%) of 3,5-bis-(methylthio)pyridine *N*-methiodide was obtained, mp 217.5-218°; ^{1}H nmr (DMSO-d_6): δ 3.37 (s, 6H), 4.40 (s, 3H), 8.18 (t, 1H, J = 1.3 Hz) and 8.75 (d, J = 1.5 Hz, 2H); ms: (m/e) 186 (0.5), 171 (74.8), 156 (6.3), 155 (4.5), 142 (100), 141 (34.8), 140 (7.6), 139 (7.8), 138 (23.0), 127 (44.2), 125 (15.3), 124 (7.5), 123 (11.2), 114 (18.1), 112 (12.5).

Anal. Calcd. for $C_8H_{12}NS_2I$: C, 30.68; H, 3.86; N, 4.47. Found: C, 30.6; H, 3.8; N, 4.3.

REFERENCES AND NOTES

[1] C. K. Bradsher and D. F. Lohr, *J. Heterocyclic Chem.*, **3**, 27 (1966).

[2] J. S. A. Brunskill, *J. Chem. Soc. (C).*, 960 (1968).

[3] J. A. Zoltewicz and C. Nisi, *J. Org. Chem.*, **34**, 765 (1969).

[4] H. M. Wuest and E. N. Sakal, *J. Am. Chem. Soc.*, **73**, 1210 (1951).

[5] L. B. Bauer and T. E. Dickerhofe, *J. Org. Chem.*, **29**, 2183 (1964).

[6] L. B. Bauer and L. A. Gardella, *J. Org. Chem.*, **28**, 1320 (1963).

[7] J. L. Wardel, in The Chemistry of the Thio Group, S. Patai, ed, John Wiley & Sons, N. Y., 1974, pp 189-191.

[8] G. S. Ponticello, R. D. Hartman, W. C. Lumma and J. J. Badwin, *J. Org. Chem.*, **44**, 3080 (1979).

[9] S. S. Giam and K. Kikukawa, *J. Chem. Soc., Chem. Commun.*, 756 (1980).

[10] J. L. Wardell, in The Chemistry of the Thiol Group, S. Patai, ed, John Wiley & Sons, N.Y., 1974, pp 195-198.

[11] K. Krowicki, *Pol. J. Chem.*, **53**, 889 (1979).

[12] K. Krowicki, *Pol. J. Chem.*, **52**, 2039 (1978).

[13] K. Krowicki, *Pol. J. Chem.*, **53**, 503 (1979).

[14] J. S. Davies, K. Smith and J. Turner, *Tetrahedron Letters*, 2191 (1980).

[15] W. T. Flowers, G. Holt, F. Omogbai and C. P. Poulos, *J. Chem. Soc., Perkin Trans. I*, 1309 (1979).

[16] T. K. Chen and W. T. Flowers, *J. Chem. Soc., Chem. Commun.*, 1379 (1980).

[17] K. M. Walker, *Tetrahedron Letters*, 4475 (1977).

[18] W. A. Shepperd, *J. Org. Chem.*, **24**, 1460 (1961).

[19] J. I. G. Cadogan and R. K. Mackie, *Chem. Soc. Rev.*, 87 (1974).

[20] A. Schonberg, *Chem. Ber.*, **68(B)** 163 (1935).

[21] R. S. Davidson, *J. Chem. Soc. (C).*, 2131 (1967).

[22] D. H. R. Barton, D. P. Manly and D. A. Widdowson, *J. Chem. Soc., Perkin Trans. I*, 1568 (1975).