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Synthesis of Dipyridyl Sulfides from Pyridyl-Pyridinium Halides

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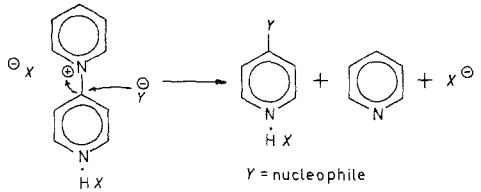
Reactions of pyridyl-pyridinium halides with thiolpyridines and thiourea were investigated. New dipyridyl sulfides were obtained by this method.

[Keywords: Di-(4-pyridyl)-sulfides; Pyridyl-pyridinium chlorides; Thiolpyridines; Thiourea]

Synthese von Dipyridil-sulfiden aus Pyridil-pyridinium-halogeniden

Reaktionen von Pyridil-pyridinium-halogeniden mit Thiolpyridinen und Thioharnstoff werden untersucht. Auf diesem Weg wurde eine Reihe neuer Dipyridil-sulfide synthesiert.

Pyridyl-pyridinium halides are very susceptible to react with nucleophilic agents. Several authors have reported[1,2] that 1-(4-pyridyl)-pyridinium chloride readily reacts with phenols, amines or hydrogen sulfide giving derivatives substituted at position 4, the quanternary pyridinium moiety leaving as pyridine hydrochloride.



The possibility of application of these pyridinium salts to the synthesis of dipyridyl sulfides is the subject of this paper. Our attention to dipyridyl sulfides was prompted by biological activity of these compounds[5,7,9].

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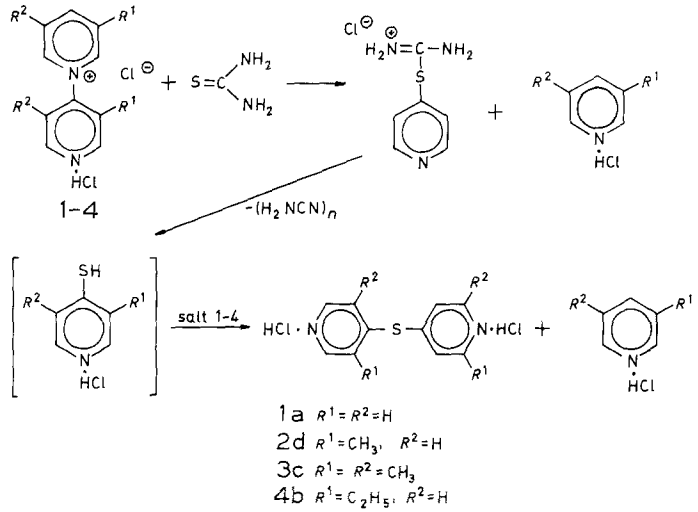
Pyridyl-pyridinium chlorides **1** and **2** were obtained by treating pyridine or 3-picoline with thionyl chloride at room temperature for 3 days[2]. Adapting this method to other 3-, or 3,5-dialkylpyridines two new pyridyl-pyridinium salts **3** and **4** were obtained. 2-, and 4-alkylpyridines failed to react with thionyl chloride to produce the corresponding pyridinium salts. 1-(2-pyridyl)-pyridinium iodide (**5**) was obtained by treatment of pyridine hydrochloride with iodine chloride[3].

These pyridinium salts easily reacted with thiolpyridines to form dipyridyl sulfides and corresponding pyridines in high yield. In the case of salt **5** the yield of sulfides was considerably lower; this may be explained by the fact that **5** is more resistant against nucleophilic agents than 4-pyridyl salts[10].

The free sulfides were obtained by treatment of the reaction mixture with an excess of aqueous potassium carbonate.

An interesting reaction was observed, when salts **1**-**4** were treated with thiourea. Under the same conditions as in the case of thiolpyridines, symmetrical di-(4-pyridyl)sulfides were obtained, with formation of thiolpyridines as by-products. Yields of the sulfides were highest when the molar ratio of pyridinium salts and thiourea was 2 : 1. With an excess of thiourea sulfides were also formed but with lower yield.



The reaction of thiourea with pyridyl-pyridinium salts proceeds analogously to the reaction of thiourea with alkyl halides[14]. So formed *S*-(4-pyridyl)-thiouronium salts may under the reaction conditions decompose to thiolpyridines, which react with unreacted pyridinium salts forming the corresponding symmetrical sulfides.

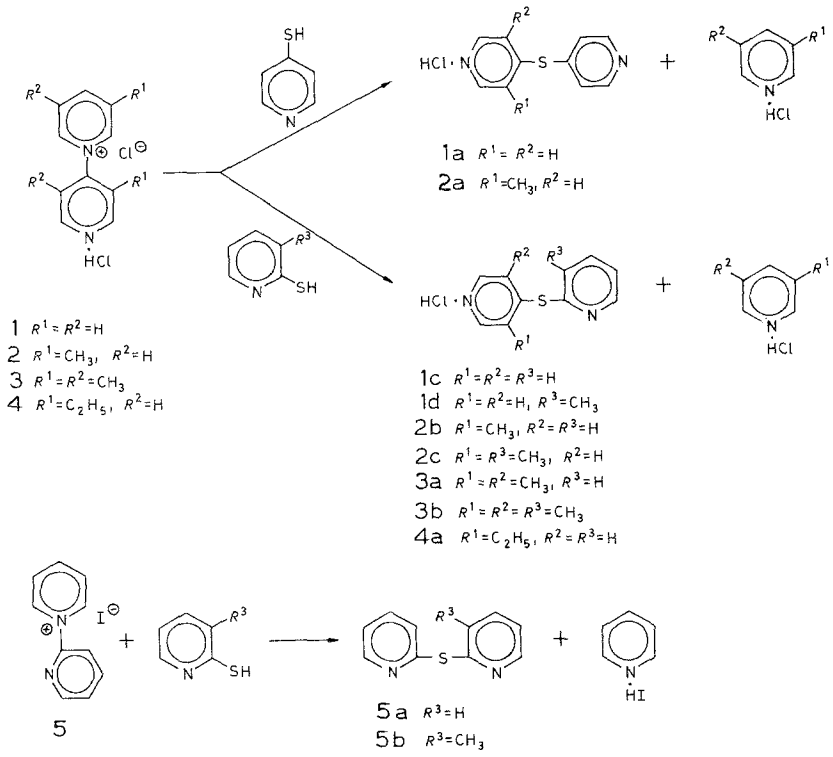


Table 1. *Data for 1-(4-pyridyl)-pyridinium salts*

Compound No.	Yield %	M.p. °C	^{1}H-NMR (D_2O) δ/ppm
1	80-85	172 173 lit.[1] 172-174	9.62 (m, 4 H), 9.28 (m, 1 H), 8.82 (m, 4 H)
2	55-60	202-203 lit.[2] 175	9.26 (m, 5 H), 8.64 (m, 2 H) 2.97 (s, 3 H), 2.75 (s, 3 H)
3	50-60	310 dec.	9.30 (s, 2 H), 9.05 (s, 2 H) 8.93 (s, 1 H), 2.95 (s, 6 H, CH_3) 2.60 (s, 6 H, CH_3)
4	35	196-197	9.25 (m, 5 H), 8.60 (m, 2 H), 3.35 (q, 2 H, CH_2CH_3), 3.05 (q, 2 H, CH_2CH_3), 1.66 (t, CH_3, 3 H), 1.52 (t, 3 H, CH_3)

Table 2. *Data for dipyridyl sulfides*

Compound No.	Yield %	M. p. °C	^{1}H-NMR (CCl_4) δ/ppm
1a	85	66-67 lit[2] 69	8.66 (d, 4H), 7.33 (d, 4H)
1b	65	oil 192-194[a]	8.54 (d, 4H), 8.15-7.40 (m, 4H)
1c	80	oil 167-168[a]	8.66 (d, 2H), 8.17-7.25 (m, 6H)
1d	90	oil 166-168[a]	8.60 (d, 2H), 8.10-7.10 (m, 5H), 2.60 (s, 3H, $ArCH_3$)
2a	85	67-68 207-209[a]	8.64 (d, 2H), 8.50 (d, 2H), 7.35 (m, 2H), 7.15 (m, 1H), 2.60 (s, 3H, $ArCH_3$)
2b	78	oil 159-160[a]	8.60 (m, 3H), 7.82 (m, 1H), 7.44 (m, 3H), 2.60 (s, 3H, $ArCH_3$)
2c	95	74-75 224-225[a]	8.30 (s, 2H), 8.15 (d, 2H), 6.87 (d, 2H), 2.40 (s, 6H, $ArCH_3$)
3a	67	85-87 162-163[a]	8.56 (m, 3H), 7.68 (m, 1H), 7.12 (m, 2H), 2.63 (s, 6H, $ArCH_3$)
3b	92	99-101 167-168[a]	8.52 (s, 2H), 8.22 (d, 1H), 7.56 (d, 1H), 7.12 (m, 1H), 2.67 (s, 3H, $ArCH_3$), 2.56 (s, 6H, $ArCH_3$)
4a	90	oil 130-132[a]	8.56 (m, 3H), 7.69 (m, 1H), 7.35 (m, 3H), 3.00 (q, 2H, CH_2CH_3), 1.50 (t, 3H, CH_2CH_3)
5a	22	oil 120[a], lit.[7] 120[a]	8.56 (d, 2H), 7.62 (m, 4H), 7.24 (m, 2H)
5b	28	oil 143-145[a]	8.50 (m, 2H), 7.65 (m, 3H), 7.25 (m, 2H), 2.63 (s, 3H, $ArCH_3$)

[a] M. p. of picrate.

The obtained sulfides (as hydrochlorides) were preliminarily tested on a number of microorganisms. Sulfides which contain two or more methyl groups strongly inhibit the growth of gram-positive bacteria and also the growth of some funguses in a concentration of 1-10 mg per liter.

Experimental

^{1}H-NMR Spectra were determined on a Tesla BS-487 80 MHz spectrometer. IR spectra were measured on a Perkin Elmer Model 621 spectrometer. Melting points are uncorrected.

Thiolpyridines

4-Thiolpyridine was obtained from 1-(4-pyridyl)-pyridinium chloride **1** and H_2S[2]. 2-Thiolpyridine was obtained from 2-chloropyridine[11]. 3-Thiolpyridine was obtained from 3-chloropyridine[13]. 2-Thiol-3-methylpyridine was obtained by a published method[11] from 2-bromo-3-methylpyridine[12]. Yield 52%, m.p. 163—165 °C.

Table 3. *Dipyridyl sulfides from pyridinium salts and thiourea*

Compound No.	Yield %	M.p. °C	^{1}H-NMR (CCl_4) δ/ppm
1a	69	66-67 lit.[2] 69	8.66 (d, 4H), 7.33 (d, 4H)
2d	65	85-88 lit.[6] 88-89	8.32 (m, 4H), 6.91 (d, 2H), 2.33 (s, 6H, $ArCH_3$)
3c	66	171-173	8.58 (s, 4H), 2.52 (s, 12H, $ArCH_3$)
4b	67	oil 185-186[a]	8.64 (s, 2H), 8.50 (d, 2H), 7.13 (d, 2H), 3.06 (q, 4H, CH_2CH_3), 1.56 (t, 6H, CH_2CH_3)

[a] M.p. of picrate.

C_6H_7NS (125,1). Calc.: C 57.6, H 5.6, N 11.10.
Found: C 57.2, H 5.62, N 11.22.

^{1}H-NMR ($CDCl_3$; δ/ppm): 2.87 (s, 3H, CH_3), 7.25-7.06 (t, 1H, C_5), 8.05-8.84 (m, 2H, C_4, C_6).

1-(4-Pyridyl)-pyridinium Chlorides Hydrochlorides 1-4

Thionyl chloride (300 g, 2.5 mol) was added dropwise to 1.2 mol of dry pyridine or corresponding 3-, 3,5-dialkylpyridine with cooling. The mixture was kept for 3-10 days at room temperature. Then excess $SOCl_2$ was evaporated under reduced pressure, the residue was cooled to 0° and 100 ml absol. C_2H_5OH were added. The mixture was left for 1 h at 0°, and brown crystals were filtered off. Crude crystals of pyridinium salts were purified by warming with charocoal in water solution, then the solvent was evaporated and the residue was crystallized from ethanol or ethanol-acetone (1:1).

Dipyridyl Sulfides **1a–d, 2a–c, 3a–b, 4a, 5a–b**

Pyridinium salt (0.01 mol) and 0.01 mol of corresponding thiolpyridine were mixed and heated for 1–2 h at 140–150 °C. Then the reaction mixture was cooled and dissolved in excess aqueous K_2CO_3 (to *pH* 9–10).

The mixture was extracted with diethyl ether, the ethereal extract was dried over anhydrous K_2CO_3, and the solvent was evaporated to yield crude product.

The products were crystallized from hexane (solid) or purified by column chromatography (oil): Silica gel, eluent diethyl ether or ethanol-chloroform 1:15.

Reaction of Pyridinium Salts **1–4** *with Thiourea*

The pyridinium salt (0.02 mol), 0.01 mol (0.76 g) of thiourea, and 1 ml of pyridine were mixed, and heated for 1 h at 160–180 °C. The reaction mixture was worked up as described above.

The crude products were crystallized from hexane.

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References

[1] *E. Koenigs* and *H. Greiner*, Chem. Ber. **64**, 1049 (1931).
[2] *D. Jerchel, J. Fischer*, and *K. Thomas*, Chem. Ber. **89**, 2921 (1956).
[3] *Z. Rodewald* and *E. Plazek*, Rocz. Chem. **16**, 444 (1936).
[4] *H. King* and *L. Ware*, J. Chem. Soc. **1939**, 873.
[5] US-Pat. 2761866, Chem. Abstr. **51**, 3671a (1957).
[6] *G. Clemo* and *G. Swan*, J. Chem. Soc. **1948**, 198.
[7] *J. Renault*, Ann. Chim. **10**, 135; Chem. Abstr. **50**, 9408c (1956).
[8] *T. Dewing, W. Gray*, and *P. Platt*, J. Chem. Soc. **1952**, 239.
[9] *D. Grassetti, M. Brokke*, and *I. Murray*, J. Med. Chem. **8**, 753 (1965); Chem. Abstr. **63**, 1821 (1965).
[10] *P. Baumgarten* and *E. Damman*, Chem. Ber. **66**, 1633 (1933).
[11] *R. Jones* and *A. Katritzky*, J. Chem. Soc. **1958**, 3612.
[12] *H. Bradlow* and *C. Vanderwerf*, J. Org. Chem. **14**, 512 (1949).
[13] *H. Wuest* and *E. Sakal*, J. Amer. Chem. Soc. **73**, 1215 (1951).
[14] Organic Syntheses III, 363, 440.