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Thieno[2,3-*c*]pyridine has been converted to 6-benzoyl- and 6-carbethoxy-7-cyano-6,7-dihydrothieno[2,3-*c*]pyridine. Alkylation, condensation, Michael addition, and cyclo addition reactions of these Reissert type compounds have been carried out.

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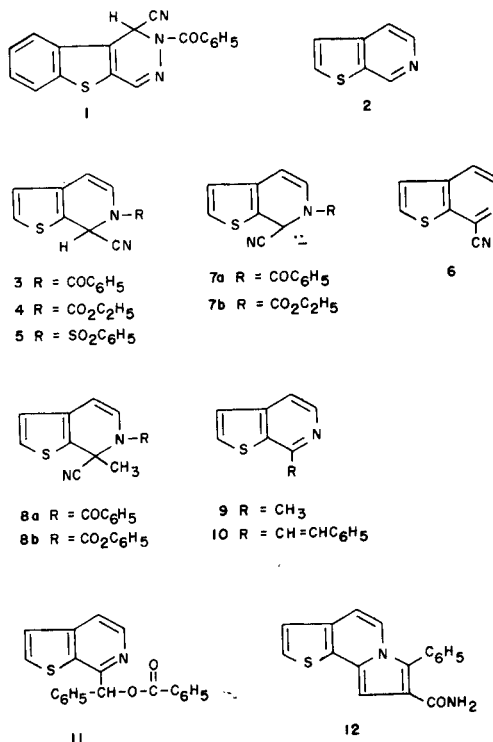
The conversion of various azaaromatic systems to Reissert compounds is a well known reaction [2]. Apparently, the only report of the conversion of a sulfur containing azaaromatic system to a Reissert compound is the conversion of [1]-benzothieno[2,3-*d*]pyridazine to **1** [3]. We wish to now report our studies with thieno[2,3-*c*]pyridine (**2**).

Thieno[2,3-*c*]pyridine (**2**) reacted with benzoyl chloride and aqueous potassium cyanide in methylene chloride to give the expected Reissert compound, 6-benzoyl-7-cyano-6,7-dihydrothieno[2,3-*c*]pyridine (**3**), in only 20% yield. Use of trimethylsilylcyanide resulted in only a slight improvement of yield to 25%. Reaction of ethyl chloroformate and trimethylsilylcyanide with **2** gave the Reissert analog **4** in 57% yield. Reaction of **2** with benzene-sulfonyl chloride and potassium cyanide did not give the Reissert analog **5**, as is observed with isoquinoline, but instead gave directly, as is observed with quinoline [4], the nitrile **6**. The conversion of the other three isomeric thienopyridines to cyanothienopyridines *via* the two step Reissert-Henze reaction has recently been reported [5].

Acid hydrolysis of the Reissert compound **3** gave, as is typical for Reissert compounds [2], benzaldehyde which was isolated as its 2,4-dinitrophenylhydrazone in only 51% yield.

Treatment of **3** or **4** with methyl iodide and sodium hydride in dimethylformamide gave, *via* the carbanion **7**, an oil **8** which was hydrolyzed in moderate yield to 7-methylthieno[2,3-*c*]pyridine (**9**). Confirmation of the structure **9** was had by conversion to the known styryl compound **10** [6]. The conjugate base **7a**, generated by *n*-butyllithium, reacted in the expected manner, with benzaldehyde to give the ester **11** in good yield. The conjugate base **7a** of the Reissert compound **3** reacted with acrylonitrile to give, *via* an initial Michael type addition [2], the pyrrolothienopyridine **12**. An attempt to obtain the rearrangement product of **7a** failed.

Although the yields are somewhat lower than normal both in its preparation and its reactions the thieno[2,3-*c*]pyridine Reissert compound does appear to behave as a relatively normal Reissert compound.



## EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 710 B spectrophotometer and proton magnetic resonance spectra were measured on a Hitachi Perkin-Elmer R24B spectrophotometer using tetramethylsilane as an internal standard. Mass spectra was determined at the Midwest Center for Mass Spectrometry and microanalyses by Spang Microanalytical Laboratory.

6-Benzoyl-7-cyano-6,7-dihydrothieno[2,3-*c*]pyridine (**3**).

To a well stirred solution of 4.0 g (0.029 mole) of thieno[2,3-*c*]pyridine (**2**), 4.08 g (0.041 mole) of trimethylsilylcyanide in 35 ml of anhydrous methylene chloride was added 6.0 g (0.043 mole) of freshly distilled benzoyl chloride in methylene chloride over an hour. The reaction mixture was stirred overnight at room temperature and the solution was washed with water (2 × 10 ml), 5% hydrochloric acid (1 × 10 ml), water (1 × 10 ml), 5% sodium hydroxide (1 × 10 ml) and water (1 × 10 ml). The organic layer was dried (magnesium sulfate), evaporated and the residue crystallized from 95% ethanol to give 1.95 g (25%) of **3**, mp 132-133°; ir (po-

tassium bromide): 3070, 2950, 1660, 1605, 1440, 1340, 1280, 1180  $\text{cm}^{-1}$ ; pmr (deuteriochloroform): 8.60 (d, H4), 6.53 (d, H5), 6.7 (d, s H7), 6.91 (d, H3), 7.33 (d, H2), 7.5 (s, aromatic 5H).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{10}\text{N}_2\text{OS}$ : C, 67.64; H, 3.78; N, 10.52. Found: C, 67.77; H, 3.89; N, 10.26.

Use of a catalytic amount of aluminum chloride in the above procedure increased the yield of **3** by only 3%.

Use of potassium cyanide in an aqueous-methylene chloride solvent system gave **3** in 20% yield.

#### 6-Carboxy-7-cyano-6,7-dihydrothieno[2,3-c]pyridine (**4**).

Using the procedure described for the preparation of **3**, 2.0 g (0.014 mole) of **1**, 2.08 g (0.02 mole) of trimethylsilylcyanide, and 2.17 g (0.02 mole) of ethyl chloroformate gave a 57% yield of **4**, mp 91-92° (from 95% ethanol); ir (potassium bromide): 1700  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$ : C, 56.39; H, 4.30. Found: C, 56.55; H, 4.30.

#### 7-Cyanothieno[2,3-c]pyridine (**6**).

Reaction of **2** with potassium cyanide in water and benzenesulfonyl chloride in methylene chloride gave, after sublimation, a 20% yield of **6**, mp 113-115°; ir (potassium bromide): 2220  $\text{cm}^{-1}$ ; ms: m/e 160.

*Anal.* Calcd. for  $\text{C}_8\text{H}_4\text{N}_2\text{S}$ : C, 59.98; H, 2.52; N, 17.49. Found: C, 59.88; H, 2.52; N, 17.61.

#### Acid Hydrolysis of (**3**).

Equimolar amounts of Reissert compounds **3** and 2,4-dinitrophenylhydrazine in concentrated hydrochloric acid were heated on a steam bath for 10 minutes and then stirred at room temperature for 2 hours. The yellow solid was filtered and crystallized from aqueous ethanol to give 51% yield of benzaldehyde 2,4-dinitrophenyl hydrazone, having superimposable infrared spectra and undepressed melting point with an authentic sample.

#### 7-Methylthieno[2,3-c]pyridine (**9**).

To a stirred solution of (0.001 mole) of **3** or **4** and 0.28 g (0.002 mole) of methyl iodide in 10 ml of anhydrous dimethyl formamide at 0° under argon atmosphere was added 0.10 g (0.002 mole) of sodium hydride (50% in oil). The contents were stirred for 4 hours and poured onto 150 g of ice. The oily product obtained after extracting the aqueous layer with chloroform was subjected to hydrolysis without further characterization by refluxing it with 30% potassium hydroxide in a 1:1 ethanol-water system. The liquid product was isolated by removing ethanol and extracting the aqueous layer with ether several times. The combined extract was washed with water, dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give the dark color liquid which was further purified by vacuum distillation to give **9**, bp 102-105/2.5 mm (reported bp 102-103°/2.5 mm [6]). The ir and pmr spectra were consistent with the assigned structure and the same as those reported [6].

#### 7-Styrylthieno[2,3-c]pyridine (**10**).

A solution of 0.06 g of 7-methylthieno[2,3-c]pyridine (**9**), 0.05 g of benzaldehyde and 2 ml of acetic anhydride was heated to 160° and stirred for five minutes to give an oil which solidified after seven days at room temperature. The solid collected, washed with water and recrystallized from

ethanol (absolute) to give 7-styrylthieno[2,3-c]pyridine (**10**), mp 68-70° (reported 69-70° [6]). The ir and pmr were consistent with the assigned structure.

#### Phenyl-7-thieno[2,3-c]pyridinoyl Benzoate (**11**).

To a solution of 0.25 g (0.009 mole) of **3** in 10 ml of anhydrous ether and 3 ml of dry tetrahydrofuran at -78° was added a solution of *n*-butyllithium (0.0018 mole) in ether under argon atmosphere. To the resultant deep red mixture was added a solution of 0.19 g (0.0018 mole) of benzaldehyde in ether. The mixture was stirred under inert atmosphere at a temperature of less than -78° for one hour and then allowed to warm slowly to room temperature. After an additional sixteen hour stirring, 10 ml of fresh ether was added and the contents were washed with water, 0.5 *M* hydrochloric acid and water (1 × 10 ml). After removal of the solvent *in vacuo*, the product was obtained as an oil which was subjected to column chromatography using silica and benzene as an eluent to give 0.20 g (67%) of **11** (95% ethanol), mp 123-124°; ir (potassium bromide): 3050, 1705, 1600, 1560, 1440, 1260, 1285  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{13}\text{NO}_2\text{S}$ : C, 73.02; H, 4.38; N, 4.06. Found: C, 73.15; H, 4.34; N, 4.00.

#### 3-Phenylpyrrolo[6,7-a]thieno[2,3-c]pyridine-2-carboxamide (**12**).

To a well stirred solution of 0.5 g (0.0018 mole) of **3** and 0.14 g (0.0027 mole) of acrylonitrile in 15 ml of anhydrous dimethylformamide at 0° under argon atmosphere was added 0.12 g (0.0027 mole) of 50% sodium hydride in oil. After stirring for four hours, the mixture was poured over ice. The aqueous layer was extracted with chloroform several times. The combined extract was washed with water, dried (anhydrous magnesium sulfate) and evaporated *in vacuo* to give an oil which solidified on cooling. The solid was washed with water and recrystallized from 95% ethanol to give 0.4 g (77%) of **12**, mp 186-189°; ir (potassium bromide): 3400, 3300, 3050, 2950, 1600, 1560, 1475, 1375, 1270  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ : C, 69.83; H, 4.14; N, 9.58. Found: C, 69.77; H, 4.23; N, 9.51.

## REFERENCES AND NOTES

- [1] This is paper XLVI in the UMKC series on Reissert Compound Studies.
- [2] W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 511 (1955); F. D. Popp, *Adv. Heterocyclic Chem.*, **9**, 1 (1968); *idem.*, *ibid.*, **24**, 187 (1979); *idem.*, *Heterocycles*, **14**, 1033 (1980).
- [3] G. Dore, M. Bonhomme and M. Robba, *Tetrahedron*, **28**, 2553 (1972).
- [4] J. M. Wefer, A. Catala and F. D. Popp, *J. Org. Chem.*, **30**, 3075 (1965).
- [5] L. M. Klemm and D. R. Muchiri, *J. Heterocyclic Chem.*, **20**, 213 (1983).
- [6] M. L. Dressler and M. M. Joullie, *ibid.*, **7**, 1257 (1970).