An Efficient Synthesis of 3-Aminoisothiazolo[5,4-*b*]-Quinoline from Quinoline

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Treatment of readily available 3-formylquinoline-2-thiol (**1**) with ammoniacal sodium hypochlorite directly afforded isothiazolo[5,4-*b*]quinoline (**3**) in high yield, probably *via* 3-formylquinoline-2-sulfenamide (**2**). Facile conversion of **3** to the corresponding 3-amino derivative (**7**) was accomplished by the following sequence: base induced opening of the isothiazole ring to 3-cyanoquinoline-2-thiol (**5**), oxidation of **5** to the corresponding stable sulfenamide (**6**) and sodium ethoxide catalysed reclosure of the isothiazole ring which provided 3-aminoisothiazolo[5,4-*b*]quinoline (**7**).

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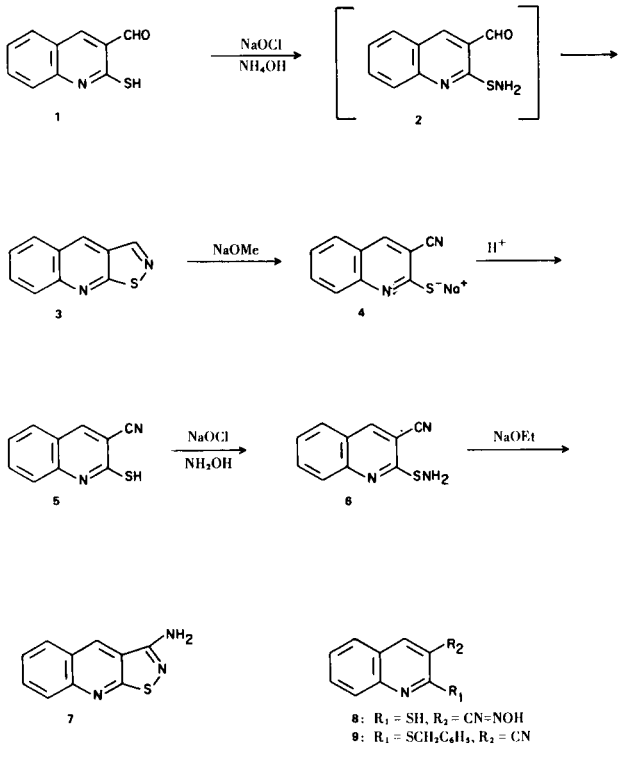
In connection with another program (2), we required relatively large quantities of 3-aminoisothiazolo[5,4-*b*]-quinoline (**7**). An examination of the literature revealed that only three examples (3-5) of this system have been described, none of which were functionalized at the 3-position. The parent heterocycle **3** was however, described by Hull (3) who showed that quinoline could readily be converted to the thiol **1** in two steps (3,6). Subsequent conversion of thiol **1** to the oxime **8** followed by treatment of **8** with acetic anhydride gave isothiazolo-[5,4-*b*]quinoline (**3**) (3).

We would now like to report facile preparation of **3** directly from **1** and efficient conversion of **3** to the required **7**. The method for direct conversion of **1** to **3** should be useful for preparation of congeners of **3** and other fused isothiazoles of this type with functional groups stable to the relatively mild reaction conditions employed.



Reaction of thiols with sodium hypochlorite and ammonia is well known (7) to provide the corresponding sulfenamides and Fries (8,9) has shown that aromatic sulfenyl bromides with *ortho* carbonyl substituents react with liquid ammonia to give 1,2-benzisothiazoles. It therefore seemed probable to us that thiol **1** could initially be converted to the sulfenamide **2** by treatment with ammoniacal sodium hypochlorite and that **2** would cyclize directly to isothiazolo[5,4-*b*]quinoline (**3**).

We found the oxidation of an alkaline ammoniacal solution of thiol with sodium hypochlorite smoothly produced **3** in 78% yield after recrystallization. Although a number of methods (10) exist for synthesis of fused ring isothiazoles, to our knowledge the transformation of **1** to **3** is the first example of direct conversion of an *ortho* carbonyl substituted thiophenol to a fused ring isothiazole. Treatment of **3** with a refluxing solution of methanolic sodium methoxide followed by acidification then gave nitrile **5** in high yield. This ring opening was observed by Hull (3), however in that study, nitrile **5** was not isolated, but was directly converted to the *S*-benzyl derivative **9** by alkylation of the initially formed anion **4** with benzyl chloride. Oxidation of thiol **5** with ammoniacal sodium hypochlorite under essentially the same conditions used for formation of **3** gave the sulfenamide **6**, readily isolated by simply filtering the reaction mixture. Treatment of **6** under essentially the same conditions employed by Gewald (11) for cyclization of 3-cyanopyridine-2-sulfenamides to 3-aminoisothiazolo[5,4-*b*]-pyridines then provided the required **7** in 80% yield after purification.

8: R_1 = SH, R_2 = CN=NOH
9: R_1 = $SCH_2C_6H_5$, R_2 = CN

EXPERIMENTAL

Melting points (corrected) were determined in open capillary tubes using a Thomas-Hoover apparatus. Microanalyses were performed by this Laboratory's Section on Microanalytical Services and Instrumentation. Ir (Perkin-Elmer 257), mass (Hitachi Perkin-Elmer RMU-6E; 70 ev) and nmr (Varian A60;

TMS internal reference) spectra were consistent with the assigned structures. Optimization of yields was not attempted in this study.

Isothiazolo[5,4-*b*]quinoline (**3**).

An aqueous solution of 4.97% sodium hypochlorite was added dropwise to a stirred solution of **1** (3) (11.3 g., 59.7 mmoles) in concentrated ammonium hydroxide (90 ml.) and 3.3% aqueous sodium hydroxide (90 ml.) during 20 minutes at 0-5°. After stirring for 1 hour at the same temperature, the solid which separated during the reaction was filtered, washed with water and dried to give crude material (10.7 g.). Recrystallization from methanol gave **3** (8.71 g., 78%), as yellow plates, m.p. 169-170°. [Lit. (3), m.p. 169-170°]. The picrate was prepared in the usual way as yellow needles from ethanol, m.p. 174° [Lit. (3), m.p. 173-174°].

3-Cyanoquinoline-2-thiol (**5**).

A mixture of **3** (5.59 g., 30.0 mmoles) and sodium methoxide (2.16 g., 40 mmoles) in methanol (300 ml.) was refluxed for 2 hours. The solvent was removed under reduced pressure and the residue dissolved in water. After acidification with 10% aqueous hydrochloric acid, the solid that separated was filtered, washed with water and dried. Recrystallization from dimethylformamide-water gave **5** (4.61 g., 82.5%) as yellow needles m.p. > 290°; ms: m/e 186 (M^+); ir (nujol): 2220 cm^{-1} (CN); nmr (DMSO-d_6): δ 7.21-8.00 (m, 4H), 8.64 (s, 1H, H-4) and 14.10 (br s, 1H, S-H).

Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.49; H, 3.25; N, 15.04. Found: C, 64.30; H, 3.24; N, 14.89.

3-Cyanoquinoline-2-sulfenamide (**6**).

A solution of 4.97% aqueous hypochlorite (123.7 ml., 82.0 mmoles) was added dropwise to a stirred solution of **5** (13.95 g., 75.0 mmoles) in concentrated ammonium hydroxide (250 ml.) and 3% aqueous sodium hydroxide (200 ml.) at 0° during 20 minutes. After stirring for an additional 40 minutes at the same temperature the solid which separated during the reaction was filtered, washed with water and dried to give crude material (13.1 g.). Recrystallization gave **6** (11.50 g., 76.1%) as pale yellow needles from ethyl acetate, m.p. 219°; ms: m/e 201 (M^+), 169 and 153; ir (nujol): 3290, 3200, 2220 (CN) and 1610 cm^{-1}; nmr (DMSO-d_6): δ 4.27 (s, 2H, NH_2), 7.5-8.15 (m, 4H) and 8.88 (s, 1H, H-4).

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.68; H, 3.50; N, 20.88. Found: C, 59.83; H, 3.50; N, 20.45.

3-Aminoisothiazolo[5,4-*b*]quinoline (**7**).

A mixture of **6** (4.02 g., 20.0 mmoles), sodium ethoxide (1.63 g., 24.0 mmoles) in ethanol (150 ml.) was refluxed for 2.0 hours. The solvent was removed under reduced pressure and the residue was treated with water, neutrallized with 10% aqueous hydrochloric acid and the solid was filtered, washed with water and dried to give crude material (3.85 g.). Recrystallization from dimethylformamide gave **7** (3.21 g., 79.9%) as yellow prisms, m.p. 277-279°; ms: m/e 201 (M^+) and 153; ir (nujol): 3360, 3295, 3170, 1643 and 1603 cm^{-1}; nmr (DMSO-d_6): δ 7.20 (br. s, 2H, NH), 7.41-8.43 (m, 4H) and 9.18 (s, 1H, H-4).

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.68; H, 3.50; N, 20.88. Found: C, 59.55; H, 3.56; N, 20.77.

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