Chemoselective Reactions of 3-Chloroisonicotinonitrile

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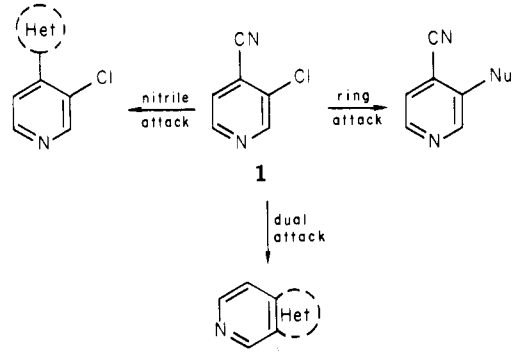
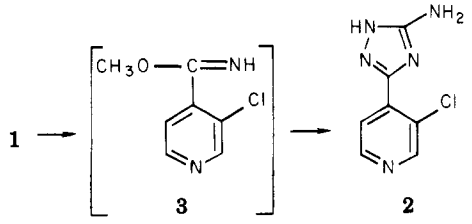
Chemoselective reactions of 3-chloroisonicotinonitrile (1) with nucleophiles are described. Treatment of 1 with sodium methoxide/methanol results in formation of the imino ether, which can be further elaborated into a triazole ring. However, when 1 is reacted with sodium methoxide/DMF, exclusive formation of 3-methoxyisonicotinonitrile (via aromatic nucleophilic substitution) occurs. Extrapolation of this chemoselectivity allows entry into a variety of 3,4-disubstituted pyridines, as well as novel heterocycles such as the thieno[2,3-*c*]pyridine ring system.

Rokach and Girard recently reported a synthesis of 3-chloroisonicotinonitrile (1) in one step from commercially available isonicotinonitrile *N*-oxide, thus making quantities of 1 readily available.[1] The structure of 1 is interesting from a synthetic standpoint due to the potential sites for nucleophilic addition. The nitrile function, for example, would be expected to be susceptible to attack by Grignard reagents[2] and alkoxide[3] to afford ketones and imino ethers, respectively. Yet, due to activation by the nitrile, the chloride moiety may be envisioned as being displaced by nucleophiles via an aromatic nucleophilic substitution reaction. Clearly, chemoselective reactions of nucleophiles with 1 would allow entry into a variety of novel heterocyclic



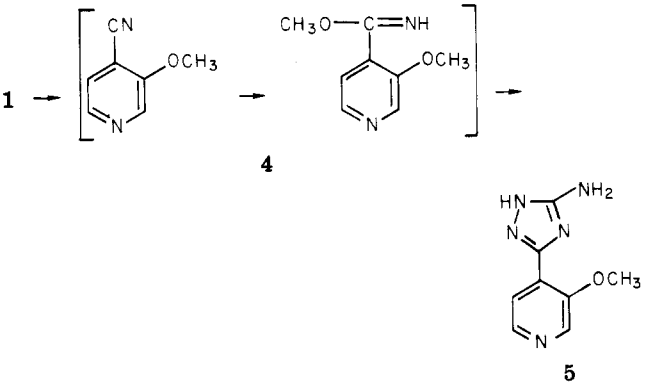
compounds, thereby making 1 a valuable heterocyclic synthon. The following results demonstrate that, despite the juxtaposition of the chloro and cyano moieties, chemospecificity is possible, thus affording a variety of 3,4-disubstituted pyridines and other heterocycles not readily accessible by conventional literature procedures.

When heated at reflux in methanol with 1 equiv of sodium methoxide, 1 was consumed in less than 0.5 h as determined by thin-layer chromatography. Treatment of this solution with aminoguanidine led to isolation of the 3-aminotriazole **2** in 41% yield. Presumably, imino ether **3** is the intermediate in this reaction. No 3-methoxyisonicotinonitrile (**4**) was detected.



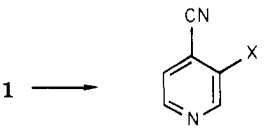
However, **4** could be readily prepared by stirring a solution of 1 with 1 equiv of sodium methoxide in dimethylformamide (DMF) as solvent. Thus, depending on the choice of solvent, one can generate the imino ether **3** or the product resulting from aromatic nucleophilic displacement (**4**). This solvent effect is probably due to the fact that imino ether formation requires a protic solvent (i.e., alcohol), whereas nucleophilic aromatic substitution is abetted by a polar aprotic solvent (i.e., DMF).

Subsequent treatment of **4** with sodium methoxide/methanol also resulted in imino ether formation (in situ). Further reaction with aminoguanidine yielded the 3-aminotriazole **5**. It was later found that **5** could be prepared directly from 1 in a one-pot procedure by first carrying out the aromatic nucleophilic displacement and then generating the imino ether, followed by reaction with aminoguanidine.



It is interesting to note that the 3-chloro moiety of **2** was inert to sodium methoxide in either methanol or DMF, and, consequently, **2** could not be utilized to prepare **5**. This emphasizes the need of a strong electron-withdrawing function (cyano) in the 4-position of the pyridine ring for aromatic nucleophilic substitution.

Attention was next turned to extending these chemoselective substitution reactions to other nucleophiles. As expected, good nucleophiles such as potassium phenoxide, sodium benzyl oxide, and sodium *n*-butylmercaptide reacted with 1 in DMF to afford good yields of **6**–**8**, respectively.



6, X = OC_6H_5
7, X = $OCH_2C_6H_5$
8, X = SC_4H_9-*n*

When sodium amide was reacted with 1, multiple products were detected by thin-layer chromatography, and this did not appear to be a worthwhile route to 3-aminoisonicotinonitrile (**9**). However, **9** could be prepared in

(1) Rokach, J.; Girard, Y. *J. Heterocycl. Chem.* **1978**, *15*, 683.
(2) Prasad, K.; Al-Jallo, H.; Al-Dulaimi, K. *J. Chem. Soc. C* **1969**, 2134.
(3) Schaefer, F. C.; Peters, G. A. *J. Org. Chem.* **1961**, *26*, 412.

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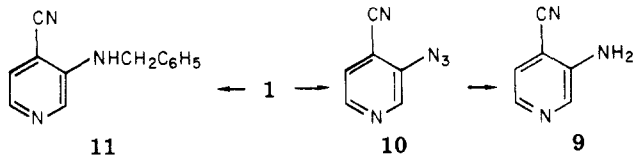
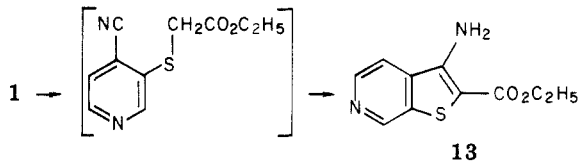
good overall yield by first reacting 1 with sodium azide thus giving azide 10, which was reduced via catalytic hydro-



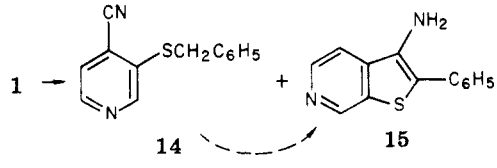
genation. In view of the well documented utility of *o*-aminonitriles in heterocyclic synthesis, 9 may be a particularly valuable intermediate.[4] Weaker nucleophiles such as sodium cyanide (with or without 18-crown-6) and potassium phthalimide in DMF did not react with 1. Some reaction was observed with benzylamine, and the corresponding 11 could be isolated, albeit in poor yield.

In contrast to these results, certain reagents reacted exclusively with the nitrile. For example, methylmagnesium bromide reacted with 1 not via nucleophilic displacement but rather by addition to the nitrile, thereby affording 4-acetyl-3-chloropyridine (12) in excellent yield. Similarly, when the Taylor–Martin procedure[5] for the alkylation of haloheterocycles was applied to 1 by using *n*-propyltriphenylphosphonium bromide, only addition to the nitrile was observed.[6]

Of particular interest was the possibility of reactions of 1 with bifunctional nucleophiles to provide access to a variety of new heterocyclic systems. The chemoselective reactions of 1 with the monofunctional nucleophiles discussed above augured well for this purpose. Treatment of 1 with the sodium salt of ethyl thioglycolate in DMF directly afforded the thieno[2,3-*c*]pyridine (13) in 54% yield. Presumably, the first step in this reaction is aromatic nucleophilic displacement of chloride.

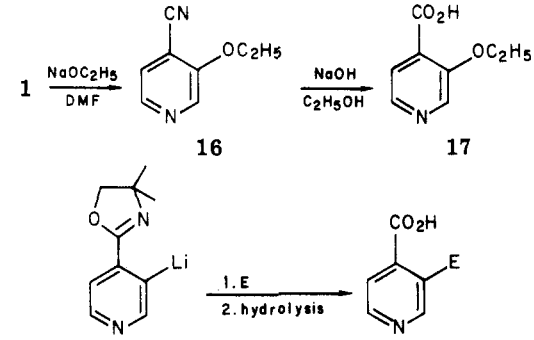


This entry into the thieno[2,3-*c*]pyridine ring system is unique in that it involves building the thiophene ring onto the pyridine moiety. Classical syntheses of this ring system such as the Pomeranz–Fritsch method or the Bischler–Napieralski method deal with building a pyridine ring onto the thiophene nucleus.[7] Thus, this approach complements previous syntheses of these compounds. Furthermore, this reaction is not limited to sodium ethylthioglycolate. Reaction of 1 with sodium benzylmercaptide afforded 69% of the displacement product 14 and 12% thienopyridine



15. The reduced acidity of the methylene group of this reagent relative to that of sodium thioglycolate undoubtably allows for isolation of 14. However, 14 could be converted into 15 in good yield by treatment with sodium methoxide.

3-Chloroisonicotinonitrile can also be used as an entry into 3-substituted isonicotinic acids. Base hydrolysis of 3-ethoxyisonicotinonitrile (16) affords 3-ethoxyisonicotinic acid (17) in nearly quantitative yield. This complements



recent work of Meyers, who has prepared 3-substituted isonicotinic acids via ortho metalation of oxazolines.[8] Thus, entries now exist for the introduction of both electrophiles and nucleophiles into the 3-position of isonicotinic acid.

In conclusion, by choice of the appropriate reaction conditions, one can (a) elaborate the nitrile moiety of 1 into various derivatives via its amino ether, (b) substitute the chloride with certain nucleophiles, thereby affording heretofore inaccessible 3,4-disubstituted pyridines, and (c) prepare thieno[2,3-*c*]pyridines by a combination of reactions at both sites. Thus, 3-chloroisonicotinonitrile should prove valuable in heterocyclic synthesis.

Experimental Section

^{1}H NMR spectra were obtained on a Varian T-60 spectrometer. Chemical shifts from tetramethylsilane are reported on the δ scale. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Melting points are uncorrected and were obtained in open capillaries on a Thomas-Hoover melting point apparatus.

Solvents and reagents were commercially available unless otherwise noted and were used directly. Dimethylformamide (DMF) was dried over 4A molecular sieves before use.

3-Amino-5-(3-chloro-4-pyridyl)triazole (2). A mixture of 1.0 g (7.2 mmol) of 3-chloroisonicotinonitrile (1), 0.39 g (7.2 mmol) of sodium methoxide, and 20 mL of MeOH (dried over 3A molecular sieves) was heated at reflux for 0.5 h, after which time TLC indicated all the starting material had been consumed. To the mixture was added 0.78 g (14.4 mmol) of sodium methoxide and then 1.78 g (7.2 mmol) of aminoguanidine sulfate. The mixture was again heated at reflux, this time for 2 h. The mixture was cooled to room temperature and filtered to remove insolubles, and the filtrate was concentrated, leaving a viscous oil. This oil was chromatographed over 100 g of silica gel with 19:1 ethyl acetate/MeOH as eluant to afford 0.57 g (41%) of 2 as a white solid: mp 224–225 °C; NMR (Me_2SO-d_6) 8.63 (s, 1 H), 8.48 (d, 1 H), 7.86 (d, 1 H), 5.90 (br, 2 H).

Anal. Calcd for $C_7H_6N_5Cl$: C, 42.78; H, 3.09; H, 35.80. Found: C, 43.05; H, 3.39; N, 35.83.

3-Methoxyisonicotinonitrile (4). A mixture of 4.05 g (75.0 mmol) of sodium methoxide in 25 mL of DMF was stirred at 5 °C, and 10.0 g (72.5 mmol) of 1 was added. The mixture was then allowed to warm to room temperature and stirred for 2 h. The mixture was concentrated thoroughly to remove all traces of DMF, leaving a solid which was triturated with isopropyl ether. The solid, which was collected by filtration, amounted to 6.2 g, mp 66–68 °C. Addition of low-boiling petroleum ether to the filtrate resulted in precipitation of another 2.0 g of material, identical in all respects with the first batch. The total yield of 4 was thus 8.2 g (84%). An analytical sample of 4 was prepared by recrystallization from isopropyl ether/petroleum ether to give white plates: mp 71–72 °C; IR (KBr) 2220 cm^{-1} (CN). NMR ($CDCl_3$)

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8.46 (s, 1 H), 8.38 (d, 1 H), 7.41 (d, 1 H), 4.06 (s, 3 H).

Anal. Calcd for $C_7H_6N_2O$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.83; H, 4.51; N, 20.93.

3-Amino-5-(3-methoxy-4-pyridyl)triazole (5). A solution of 1.0 g (7.24 mmol) of 1 in 10 mL of DMF was cooled to 10 °C, and 0.43 g (7.9 mmol) of sodium methoxide was added. The mixture was then stirred at room temperature for 0.5 h. To this were added 0.86 g (15.9 mmol) of sodium methoxide followed by 3.9 g (15.9 mmol) of aminoguanidine sulfate and another 5 mL of DMF, and the mixture was heated at 120 °C for 19 h. The mixture was cooled to room temperature and filtered to remove insoluble inorganics, and the filtrate was concentrated, leaving an oil. This was taken up into 40 mL of 1:1 ethyl acetate–EtOH, and ethanolic HCl was slowly added to pH 5.0. The mixture was allowed to sit in a refrigerator for 20 h. The resulting precipitate was filtered, washed with ethyl acetate, and dried in vacuo to afford 0.58 g (36%) of 5 as its monohydrochloride salt: mp 232–234 °C; NMR (Me_2SO-d_6) 8.50 (s, 1 H), 8.26 (d, 1 H), 7.80 (d, 1 H), 7.1 (b, 3 H), 4.02 (s, 3 H); mass spectrum, m/e 191 (M^+, free base).

Anal. Calcd for $C_8H_9N_5O$·HCl: C, 42.20; H, 4.42; N, 30.76. Found: C, 41.44; H, 4.16; N, 31.22.

3-Phenoxyisonicotinonitrile (6). Potassium (0.31 g, 8.0 mmol) was dissolved at room temperature under nitrogen in 5 mL of isopropyl alcohol, and to this was added 0.71 g (7.5 mmol) of phenol, followed by 15 mL of dry DMF. To this solution was added 1.0 g (7.2 mmol) of 1, the mixture becoming dark red. Gradually, the color changed to light brown. After 2 h, the mixture was concentrated, and the residue was diluted with 25 mL of H_2O and then extracted three times with a total of 60 mL of $CHCl_3$. The combined $CHCl_3$ extracts were washed with 2 N NaOH, dried over Na_2SO_4, filtered, and then evaporated, leaving 1.04 g (74%) of 6 as a colorless liquid: IR (neat) 2220 cm^{-1} (CN); NMR ($CDCl_3$) 8.40 (d, 1 H), 8.32 (s, 1 H), 7.52 (d, 1 H), 7.4–7.0 (m, 5 H).

A sample of this material was converted to its hydrochloride salt for analytical purposes by dissolving it in absolute ether and then adding ethereal HCl. The resulting precipitate was filtered and dried in vacuo, thereby affording analytically pure hydrochloride, mp 157–159 °C.

Anal. Calcd for $C_{12}H_8N_2O$·HCl: C, 61.95; H, 3.90; N, 12.04. Found: C, 61.53; H, 4.10; N, 12.01.

3-(Benzyloxy)isonicotinonitrile (7). Sodium hydride (0.38 g, 8.0 mmol as a 50% oil dispersion) was dissolved in 6 mL of benzyl alcohol at room temperature under nitrogen. To this solution was added directly a solution of 1.0 g (7.2 mmol) of 1 in 15 mL of DMF. A deep red color formed initially but gradually dispersed. After being stirred at room temperature for 1 h, the mixture was concentrated to remove the solvent and excess alcohol. The residue was diluted with 25 mL of H_2O and then extracted three times with a total of 45 mL of toluene. The combined toluene extracts were dried (Na_2SO_4), filtered, and evaporated, leaving a white solid. Recrystallization from cyclohexane afforded 1.12 g (74%) of 7 as a white crystalline solid: mp 123–124 °C; NMR ($CDCl_3$) 8.50 (s, 1 H), 8.32 (d, 1 H), 7.2–7.5 (m, 6 H), 5.29 (s, 2 H); IR (KBr) 2225 cm^{-1} (CN).

Anal. Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32. Found: C, 74.10; H, 5.03; N, 13.13.

3-(*n*-Butylthio)isonicotinonitrile (8). A solution of 2.4 mL (22 mmol) of *n*-butylmercaptan in 25 mL of DMF was stirred at room temperature under nitrogen, 1.08 g (20 mmol) of sodium methoxide was added, and the mixture was stirred at room temperature for 2 h. The mixture was concentrated, and the residue was diluted with 30 mL of H_2O and then extracted three times with a total of 60 mL of ether. The combined ether extracts were dried (Na_2SO_4), filtered, and evaporated, leaving a liquid. Distillation under reduced pressure afforded 2.6 g (68%) of 8 as a colorless liquid: bp 111 °C (0.4 torr); IR (neat) 2230 cm^{-1} (CN); NMR ($CDCl_3$) 8.65 (s, 1 H), 8.47 (d, 1 H), 7.40 (d, 1 H), 3.08 (t, 2 H), 2.0–1.3 (m, 4 H), 0.96 (t, 3 H).

A sample of this material was converted to its hydrochloride salt for analytical purposes (mp 147–150 °C).

Anal. Calcd for $C_{10}H_{12}N_2S$·HCl: C, 52.50; H, 5.75; N, 12.25. Found: C, 52.17; H, 5.59; N, 12.40.

3-Azidoisonicotinonitrile (10). A mixture of 6.9 g (50 mmol) of 1, 3.9 g (60 mmol) of sodium azide, and 60 mL of DMF was heated at 95 °C for 8 h. The mixture was concentrated, and the residue was diluted with 50 mL of water and then extracted three times with 25-mL portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4), filtered, and evaporated, leaving 5.3 g of a crude solid. Recrystallization from cyclohexane afforded 4.6 g (64%) of 10 as a white crystalline solid: mp 82–83 °C; NMR ($CDCl_3$) 8.73 (s, 1 H), 8.51 (d, 1 H), 7.52 (d, 1 H); IR (KBr) 2230 (CN), 2120 cm^{-1} (N_3).

Anal. Calcd for $C_6H_3N_5$: C, 49.66; H, 2.08; N, 48.26. Found: C, 49.29; H, 2.00; N, 47.99.

3-Aminoisonicotinonitrile (9). A mixture of 3.6 g (25 mmol) of 10, 350 mg of 10% Pd/C, and 100 mL of absolute EtOH was hydrogenated at room temperature and 3 atm for 1 h. The mixture was filtered to remove the catalyst and the filtrate concentrated to leave 2.8 g of a solid. Recrystallization from toluene afforded 2.4 g (81%) of 9 as a yellow crystalline solid: mp 137–138 °C; NMR (Me_2SO-d_6) 8.04 (s, 1 H), 7.57 (d, 1 H), 7.10 (d, 1 H), 6.18 (br, 2 H); IR (KBr) 2200 cm^{-1} (CN).

Anal. Calcd for $C_6H_5N_3$: C, 60.50; H, 4.23; N, 35.27. Found: C, 60.62; H, 4.40; N, 35.02.

3-(Benzylamino)isonicotinonitrile (11). A mixture of 0.50 g (3.6 mmol) of 1 and 3 mL of benzylamine was heated at 120 °C under nitrogen for 60 h. The mixture was concentrated, and the residue was chromatographed over 30 g of silica gel with 1:1 hexane/ethyl acetate as eluant. The amount of 11 isolated as a yellow solid was 0.12 g (16%): mp 117–118.5 °C; IR (KBr) 2220 cm^{-1} (CN); NMR ($CDCl_3$) 8.17 (s, 1 H), 7.96 (d, 1 H), 7.5–7.1 (m, 6 H), 5.1 (br, 1 H), 4.49 (d, 2 H).

Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.61; H, 5.29; N, 20.08. Found: C, 74.59; H, 5.62; N, 19.60.

4-Acetyl-3-chloropyridine (12). A solution of 6.92 g (50 mmol) of 1 in 150 mL of absolute ether was added dropwise at room temperature under nitrogen to a stirred solution of 33 mL (100 mmol) of 3.0 M methylmagnesium bromide in ether (Aldrich). After the addition was complete (10 min), the mixture was stirred at room temperature for 5 min and then made basic with solid Na_2CO_3. The aqueous solution was extracted, and the extract was dried (Na_2SO_4), filtered, and evaporated, leaving a brown liquid. Distillation under reduced pressure afforded 6.3 g (81%) of 12 as a colorless liquid: bp 55 °C (0.1 torr); IR (neat) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) 8.61 (s, 1 H), 8.57 (d, 1 H), 7.36 (d, 1 H), 2.66 (s, 3 H).

Anal. Calcd for C_7H_6ClNO: C, 54.04; H, 3.59; N, 9.00. Found: C, 54.34; H, 3.91; H, 9.42.

2-(Carboethoxy)-3-aminothieno[2,3-*c*]pyridine (13). A mixture of 4.8 mL (5.2 g, 43 mmol) of ethyl thioglycolate, 4.7 g (86 mmol) of sodium methoxide, and 60 mL of DMF was stirred at room temperature under nitrogen for 20 min. To this mixture was added 6.0 g (43 mmol) of 1 in portions. After the addition was complete, the mixture was stirred at room temperature for 1.5 h and then diluted with 60 mL of H_2O. The resulting precipitate was filtered, washed with H_2O, ether, and petroleum ether, and dried in vacuo to afford 6.5 g of 13 as pale yellow needles, mp 166–168 °C. Another 0.5 g of 13 could be obtained by concentration of the filtrate, triturating the residue with 100 mL of H_2O, and collecting the product by filtration; thus, the total yield was 7.0 g (75%): IR (KBr) 1700 cm^{-1} (CO_2Et); NMR ($CDCl_3$) 9.10 (s, 1 H), 8.51 (d, 1 H), 7.48 (d, 1 H), 5.85 (br, 2 H), 4.40 (q, 2 H), 1.38 (t, 3 H).

Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.03; H, 4.53; N, 12.60. Found: C, 53.79; H, 4.60; N, 12.94.

Reaction of 1 with Sodium Benzylmercaptide. A mixture of 3.5 mL (30 mmol) of benzylmercaptan and 40 mL of DMF was stirred at room temperature under nitrogen, and 3.2 g (60 mmol) of sodium methoxide was added. This was stirred for 5 min, and then 4.1 g (30 mmol) of 1 was added directly. After 2 h, TLC showed that all of 1 was consumed and that two new materials had formed. The mixture was allowed to stir at room temperature for another 16 h, but no further changes were detected by TLC. The mixture was concentrated, and the residue was diluted with 30 mL of H_2O and extracted twice with 20-mL portions of ether. The combined ether extracts were dried (Na_2SO_4), filtered, and evaporated, leaving 6.4 g of an oil. This was chromatographed over 150 g of silica gel with ether as eluant. When all of the less polar material had eluted, the column was eluted with 19:1 chloroform/methanol, and this resulted in the elution of the more polar material. The less polar material amounted for 4.6 g (69%)

of 3-(benzylmercapto)isonicotinonitrile (14): mp 53–54 °C (cyclohexane); IR (KBr) 2220 cm^{-1} (CN); NMR ($CDCl_3$) 8.58 (s, 1 H), 8.42 (d, 1 H), 7.37 (d, 1 H), 7.22 (s, 5 H), 4.22 (s, 2 H).

Anal. Calcd for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38. Found: C, 68.84; H, 4.67; N, 12.34.

The more polar material amounted to 0.79 g (12%) of a crystalline solid [mp 170–171 °C (toluene)] which was identified as 3-amino-2-phenylthieno[2,3-c]pyridine (15): NMR ($CDCl_3$) 8.78 (s, 1 H), 8.30 (d, 1 H), 7.76–7.18 (m, 6 H), 4.06 (br, 2 H).

Anal. Calcd for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38. Found: C, 68.71; H, 4.70; N, 12.55.

Compound 15 could also be prepared from 3-(benzylmercapto)isonicotinonitrile (14) in the following way. Sodium (50 mg, 2.2 mmol) was dissolved in 25 mL of absolute EtOH under nitrogen at room temperature. To this was added 0.45 g (2.0 mmol) of 14, and the mixture was heated at reflux for 16 h. The mixture was concentrated, and the residue was dissolved in 20 mL of water. The aqueous mixture was extracted three times with a total of 45 mL of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4), filtered, and evaporated, leaving a pale yellow solid. Recrystallization from toluene afforded 0.32 g (71%) of 15, identical in all respects with the material isolated previously.

3-Ethoxyisonicotinonitrile (16). By use of the exact procedure used for the synthesis of 4, 16 was prepared in 83% yield: mp 49–51 °C; IR (KBr) 2225 cm^{-1} (CN); NMR ($CDCl_3$) 8.45 (s, 1 H), 8.34 (d, 1 H), 7.40 (d, 1 H), 4.32 (q, 2 H), 1.48 (t, 3 H).

A sample of this material was converted to its hydrochloride salt (as was done for 6) for analytical purposes; mp 184–186 °C.

Anal. Calcd for $C_8H_8N_2O$·HCl: C, 52.04; H, 4.91; H, 15.18. Found: C, 51.83; H, 4.75; N, 15.03.

3-Ethoxyisonicotinic Acid (17). A mixture of 12.0 g (81 mmol) of 16, 6.48 g (162 mmol) of sodium hydroxide, and 120 mL of absolute EtOH was heated at reflux for 20 h. The mixture was cooled to room temperature and then concentrated, leaving a pale yellow solid. This was dissolved in a minimum amount of water, and the pH was adjusted to 3.0 with 1 N HCl. The mixture was concentrated, and the residue was digested with 500 mL of boiling absolute EtOH, filtered while hot to remove inorganic material, and then concentrated, leaving 13.3 g (98%) of 17 as a white solid: mp 141–144 °C; IR (KBr) 1715 cm^{-1} (carbonyl); NMR (Me_2SO-d_6/D_2O) 8.50 (s, 1 H), 8.30 (d, 1 H), 7.55 (d, 1 H), 4.32 (q, 2 H), 1.21 (t, 3 H). An analytical sample was prepared by recrystallization from ethanol; mp 154–155 °C.

Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.42; N, 8.38. Found: C, 56.91; H, 5.15; N, 8.48.

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Registry No. 1, 68325-15-5; 2, 78790-72-4; 4, 26414-90-4; 5·HCl, 78790-73-5; 6, 78790-74-6; 6·HCl, 78790-75-7; 7, 78790-76-8; 8, 78790-77-9; 8·HCl, 78790-78-0; 9, 78790-79-1; 10, 78790-80-4; 11, 78790-81-5; 12, 78790-82-6; 13, 78790-83-7; 14, 78790-84-8; 15, 78790-85-9; 16, 78790-86-0; 16·HCl, 78790-87-1; 17, 78790-88-2.

Sulfinic Acids and Related Compounds. 13. Unsymmetrical Disulfides Based on Methyl 4-Mercaptobutanesulfinate and 4(*S*)- or 4(*R*)-Mercaptoprolines[1,2]

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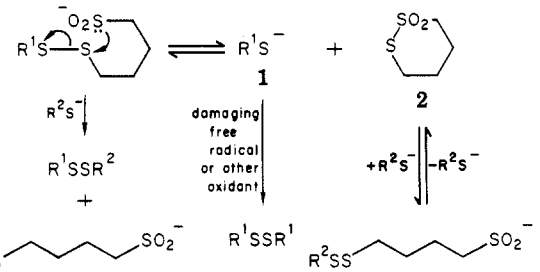
In a study of disulfide–sulfinates containing prolylthio moieties epimeric at C-4, the OH group of N-acetylated 4(*R*)-hydroxy-2(*S*)-pyrrolidinecarboxylic acid ("*trans*-4-hydroxy-L-proline", 3) was converted to an epimeric SH group (11) by replacing a 4-*O*-tosyl group with $PhCH_2S$ (to give 5) and debenzylating. Reaction of 11 as the disodium salt with 1,2-dithiane 1,1-dioxide (2) replaced the H of the SH with $S(CH_2)_4SO_2Na$ to give a disulfide–sulfinate salt (9). Since 9 was unstable in solution, with conversion of disodium 4,4′-trithiobis(butanesulfinate) (22) to the diester 23 as a model, 9 was converted to the disulfide–sulfinic ester 10. Subsidiary peaks in the ^{13}C NMR spectra of *N*-acetyl derivatives were shown to originate from rotamers. Similarly, the epimeric 4(*S*)-hydroxyproline (16) was converted to the 4(*R*)-mercaptoproline epimer (19) of 11, which was converted in turn to the disulfide–sulfinate epimer (21) of the sulfinic ester 10. The two disulfide–sulfinate esters 10 and 21 were stable under ambient conditions and began to disproportionate to the two symmetrical disulfides in refluxing ethyl acetate in 1.5 (21) to ca. 7 h (10). The sulfinic esters 10, 21, and 23 seem likely to serve as biological precursors of sulfinate and thiolate salts, which may be useful for several purposes.

A variety of sulfinate salts containing di- or trisulfide linkages are promising antiradiation drugs.[3] To learn whether chirality might be important in the future design of congeners, study of chiral representatives became desirable; with drugs of the (*S*)-(2-aminoethyl)isothiouronium type, a D enantiomer was twice as protective as the L.[4] If protection against ionizing radiation by di- or trisulfide sulfinates depends upon interactions with enzymes or nucleic acids, chirality might play a key role. Alternatively, protection may involve cyclization of the sulfinate–disulfide (Scheme I),[1] with chirality being unimportant; thus

Scheme I



(1) For paper 12, see: Field, L.; Eswarakrishnan, V. *J. Org. Chem.* **1981**, *46*, 2025.

(2) Abstracted from part of the Ph.D. dissertation of V.E., Vanderbilt University, May 1981, which can be consulted for further details.

(3) Srivastava, P. K.; Field, L.; Grenan, M. M. *J. Med. Chem.* **1975**, *18*, 798.

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