A Synthesis of Isothiazoles and Pyrimidines *via* a Vilsmeier-Haack Reaction

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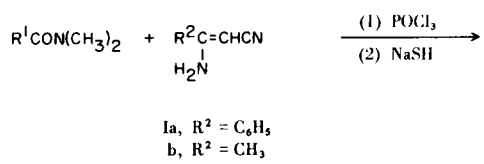
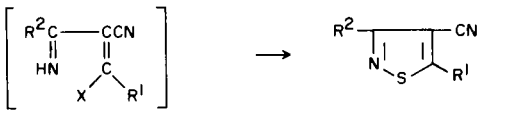
A new synthesis of isothiazoles is reported which involves the reaction of Vilsmeier salts of *N,N*-dimethylamides with enamino nitriles, and treatment of the intermediates successively with sodium hydrosulfide and iodine. 4-Isothiazolecarbonitriles prepared were: 3-phenyl; 3,5-dimethyl; 3,5-diphenyl; 3-methyl-5-phenyl; and 3-phenyl-5-methyl. The 5-phenylisothiazoles were obtained in low yields due to a side reaction involving the formation of pyrimidines. Pyrimidines encountered were 6-chloro-2,4-diphenyl and 6-chloro-4-methyl-2-phenylpyrimidines.

Earlier work from these laboratories demonstrated that condensation of enamines of type I with dithioesters yielded intermediates, postulated to have structure IIc, which could be oxidized to isothiazoles (1,2). A report by McKenzie and Reid (3) that Vilsmeier adducts of cyclic enamines yielded thioaldehydes upon treatment with sodium hydrosulfide suggested to us that an analogous Vilsmeier reaction with enamines of type I might provide an improved synthesis for IIc (Scheme I). Accordingly, we condensed a Vilsmeier salt prepared from

SCHEME I



Ia, $R^2 = C_6H_5$
b, $R^2 = CH_3$



IIa, X = $N(CH_3)_2$
b, X = Cl
c, X = SH

IIIa, $R^2 = C_6H_5$; $R^1 = H$
b, $R^2 = C_6H_5$; $R^1 = CH_3$
c, R^2, $R^1 = CH_3$
d, R^2, $R^1 = C_6H_5$
e, $R^2 = CH_3$; $R^1 = C_6H_5$

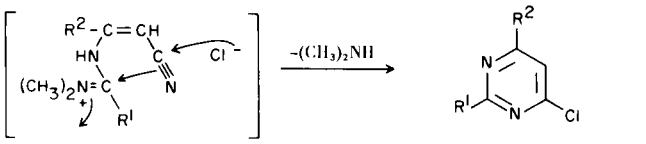
phosphorus oxychloride and dimethylformamide with 3-aminocinnamonitrile (Ia) and treated the resultant product, thought to be a dichlorophosphoric acid salt of IIa, successively with sodium hydrosulfide and iodine. The isothiazole IIIa was obtained in 14% yield. When phosphorus oxychloride was added directly to a mixture of the enamine and dimethylformamide, the yield of IIIa was increased to 60%. The synthesis then was extended successfully to the reaction of dimethylacetamide with the aryl and alkyl enamines Ia and Ib to yield the isothiazoles IIIb and IIIc, respectively.

Attempts were not made to characterize the intermediate assumed to be IIc. Assays on tlc of the intermediate typically showed four or five spots which disappeared after iodine oxidation. These spots possibly represent tautomeric forms of the enethiol structure IIc. The disappearance of these spots after oxidation is associated with a considerable increase in intensity of the spot due to isothiazole which is present in trace amounts in the intermediate before oxidation.

To demonstrate further the generality of the reaction, *N,N*-dimethylbenzamide and the enamine Ia were subjected to the same reaction sequence (Scheme 1). Surprisingly, the expected diphenyl isothiazole IIId was only a minor product of the reaction. The major product obtained was a compound fitting the analysis $C_{16}H_{11}ClN_2$. The analysis corresponds to IIb (R^1, R^2 = C_6H_5), a possible intermediate in the reaction, but spectral and chemical properties were inconsistent with this structure. The infrared spectrum showed neither NH nor nitrile absorptions, and hydrolysis with 30% sulfuric acid gave a compound $C_{16}H_{12}N_2O$, rather than smaller degradation products which would be expected from structure IIb. A more likely possibility for the structure appeared to be pyrimidine Va, which would, upon acid hydrolysis, yield the corresponding hydroxy pyrimidine of the required formula. The pyrimidine structure could arise from the reaction if the aryl Vilsmeier reagent resulted in preferential acylation of the enamine on nitrogen, rather than carbon, to produce a salt such as IV which could cyclize as shown to the pyrimidine structure (Scheme 2). Authentic samples of 6-chloro-2,4-diphenylpyrimidine and 6-hydroxy-

2,4-diphenylpyrimidine (4) proved identical with our products.

SCHEME 2



IV

Va, R^1, $R^2 = C_6H_5$
b, $R^2 = CH_3$; $R^1 = C_6H_5$

Similarly, reaction of *N,N*-dimethylbenzamide and the aliphatic enamine Ib according to Scheme I gave 6-chloro-4-methyl-2-phenylpyrimidine (Vb) as the major product with relatively minor amounts of the isothiazole IIIc.

Several modifications of conditions in the reaction of *N,N*-dimethylbenzamide and the enamine Ia according to Scheme I did not appreciably improve the yield of isothiazole (*cf.* Experimental). It may be significant that in reactions employing dimethylformamide and dimethylacetamide, the amides were used in excess to serve as a solvent. It seemed more practical to use *N,N*-dimethylbenzamide in theoretical quantities because of its relatively high melting point. Since reaction with the aliphatic amides resulted in no detectable *N*-acylation, while reactions with the aromatic amide employing the same enamines gave preferential *N*-acylation, it is possible that the polarity of the medium determines the course of the reaction. To obtain an indication if a more polar medium would enhance *C*-acylation, and hence isothiazole formation, with the aromatic Vilsmeier salt, the reaction of *N,N*-dimethylbenzamide and the enamine Ia according to Scheme I was effected in hexamethylphosphoramide. The product contained about equal amounts of the isothiazole IIId and pyrimidine Va, but the yields were low.

Treatment of a solution of *N,N*-dimethylbenzamide and the enamine Ia in methylene chloride with hydrogen chloride over 24 hours produced no pyrimidine Va. This result discounts the likelihood that the pyrimidine arises simply from an acid-catalyzed reaction between the benzamide and enamine.

EXPERIMENTAL (5)

3-Phenyl-4-isothiazolecarbonitrile (IIIa).

Phosphorus oxychloride (4.4 ml., 0.047 mole) was added dropwise to a mixture of 3-aminocinnamonitrile (5.00 g., 0.035 mole) and dimethylformamide (10 ml.) at -60°. After the addition, the temperature was slowly increased until at -40°, an exothermic reaction occurred. The temperature rapidly reached about 60° before subsiding, despite dry ice cooling.

The mixture was stirred at room temperature for 10 minutes. Additional dimethylformamide (10 ml.) was added and the mixture was poured onto a solution of sodium hydrosulfide (14 g.) in water (150 ml.) at 5°. The mixture was extracted into chloroform which, after washing with water and drying, was evaporated. The residue was dissolved in benzene (60 ml.) and the solution was treated with a solution of iodine (10.60 g., 0.042 mole) in benzene (170 ml.) followed by potassium carbonate (5.78 g., 0.042 mole).

The mixture was stirred at 28° for 16 hours and then was washed with aqueous sodium thiosulfate solution. Drying and removal of the solvent left 5.82 g. of solid. Tlc indicated one major component plus a small amount of sulfur and a minor impurity which remained at the origin; no component attributable to a pyrimidine was observed. Chromatography (alumina; elution with toluene) gave IIIa (3.85 g., 60%), m.p. 54.5-56°; reported, 54-55° (6).

Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.49; H, 3.25; N, 15.04; S, 17.22. Found: C, 64.30; H, 3.49; N, 15.24; S, 17.15.

5-Methyl-3-phenyl-4-isothiazolecarbonitrile (IIIb).

Phosphorus oxychloride (4.4 ml., 0.047 mole) was added slowly to a mixture of 3-aminocinnamonitrile (5.00 g., 0.035 mole) and dimethylacetamide (11.2 ml.) at -15°. After a brief period, the temperature increased rapidly to 73°, despite dry ice cooling, and then subsided. The mixture was heated at 115° for 35 minutes and then was treated with sodium hydrosulfide and iodine as described above, yield 3.57 g.; tlc indicated one major component plus minor impurities at origin; no spot attributable to a pyrimidine was detected. Chromatography on alumina (elution with toluene) gave IIIb (2.67 g., 38%), m.p. 74-75.5°, identical (ir, mmp) with IIIb from an alternative synthesis (1).

3,5-Dimethyl-4-isothiazolecarbonitrile (IIIc).

Phosphorus oxychloride (4.4 ml., 0.047 mole) was added slowly to a mixture of 3-aminocrotononitrile (2.86 g., 0.035 mole) and dimethylacetamide (11.2 ml.) at -15°. After 4 minutes an exothermic reaction (to 65°) occurred as described above. When the temperature subsided, the mixture was stirred at 28° for 11 minutes and was treated with sodium hydrosulfide and iodine as described previously; yield 3.34 g. gum; tlc and glpc gave no indication of the presence of a pyrimidine. Sublimation (82°/33 mm) gave IIIc (2.68 g., 56%), m.p. 50-52°; reported, 51-54° (1), identical (ir) with IIIc from an alternative synthesis (1). Recrystallization (Skellysolve B) gave white needles, m.p. 54-55.5°.

Anal. Calcd. for $C_6H_6N_2S$: C, 52.17; H, 4.38; N, 20.28; S, 23.17. Found: C, 52.12; H, 4.45; N, 20.22; S, 22.89.

6-Chloro-2,4-diphenylpyrimidine (Va) and 3,5-Diphenyl-4-isothiazolecarbonitrile (IIId).

Phosphorus oxychloride (4.4 ml., 0.047 mole) was added over 5 minutes to a mixture of 3-aminocinnamonitrile (5.00 g., 0.035 mole) and *N,N*-dimethylbenzamide (5.20 g., 0.035 mole) at 25°. After a brief induction period the temperature increased slowly to 90° and then subsided spontaneously. The mixture was heated at 100-120° for 50 minutes and then was treated with sodium hydrosulfide and iodine as described previously, yield, 6.50 g., m.p. 86-96°. Recrystallization (acetonitrile) gave 4.50 g. of Va; m.p. 104-105°, unchanged upon further recrystallization.

Anal. Calcd. for $C_{16}H_{11}ClN_2$: C, 72.05; H, 4.16; Cl, 13.29; N, 10.50; mol. wt., 266.74. Found: C, 71.87; H, 4.21; Cl, 13.33; N, 10.68; mol. wt., 266 (mass spect).

The mother liquor was evaporated and the residual 2.00 g. was chromatographed on alumina (elution with 80:20 Skellysolve B:toluene) to give an additional 1.26 g. of Va, m.p. 104-105°; total yield of Va was thus 5.76 g. (62%). The product was identi-

cal (ir, nmr, mmp) with a sample of 6-chloro-2,4-diphenylpyrimidine (m.p. 102-104°) made according to Anker and Cook (4).

Further elution of the alumina (toluene-ethanol) gave 0.67 g. isothiazole IIId (7% yield), m.p. 149-150°, unchanged upon recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{10}N_2S$: C, 73.25; H, 3.84; N, 10.68; S, 12.22. Found: C, 73.01; H, 4.06; N, 10.67; S, 12.12.

The reaction was repeated using the same quantities of reactants as above with the following modifications: (a) The phosphorus oxychloride and *N,N*-dimethylbenzamide were heated at 120° for 15 minutes. The product was dissolved in methylene chloride and the solution was added to a solution of the enamine in methylene chloride at -40°. The mixture was stirred at -30° for 5 minutes, and then was treated with sodium hydrosulfide and iodine as described above. The product obtained contained no Va or IIId; it was chromatographed to yield 2.14 g. (37% theory) *N,N*-dimethylthiobenzamide, m.p. 68-69°. (b) The reaction was repeated as in (a) but the methylene chloride solution was stirred at 0° for 1 hour before treatment with sodium hydrosulfide and iodine. The product (8.00 g.) contained 92% Va and 8% IIId (determined by glpc); this corresponds to a yield of 73% and 6% of pyrimidine Va and isothiazole IIId, respectively. (c) Phosphorus oxychloride was added dropwise to a solution of the enamine and *N,N*-dimethylbenzamide in hexamethylphosphoramide (10 ml.). The mixture was heated at 110-120° for 1 hour, and then was treated as described previously. The product was chromatographed to yield 1.27 g. (14%) of pyrimidine Va and 1.35 g. (15%) of isothiazole IIId.

6-Chloro-4-methyl-2-phenylpyrimidine (Vb) and 3-methyl-5-phenyl-4-isothiazolecarbonitrile (IIIe).

Phosphorus oxychloride (4.4 ml., 0.047 mole) was added slowly to a mixture of 3-aminocrotononitrile (2.86 g., 0.035 mole) and *N,N*-dimethylbenzamide (5.20 g., 0.035 mole). After a brief period at 25°, the temperature increased spontaneously to 75° (with ice cooling), and then subsided. The mixture was heated at 100 ± 5° for 20 minutes, and then was treated with sodium hydrosulfide and iodine as described previously; yield 5.50 g. oil. Chromatography on alumina (elution with 80:20 Skellysolve B:toluene) gave 1.89 g. (27%) pure (tlc) Vb; recrystallization (Skellysolve B) gave m.p. 73-74°.

Anal. Calcd. for $C_{11}H_9ClN_2$: C, 64.55; H, 4.43; Cl, 17.32; mol. wt., 204.67. Found: C, 64.62; H, 4.35; Cl, 17.38; mol. wt., 204 (mass spect).

The product was identical (ir, nmr, mmp) with a sample of 6-chloro-4-methyl-2-phenylpyrimidine (m.p. 72-74°) prepared according to Pinner (7).

Further elution yielded 0.75 g. (11%) pure isothiazole IIIe. Recrystallization (pentane) gave m.p. 73.5-76°; reported (8), 69-70°.

Anal. Calcd. for $C_{11}H_8N_2S$: C, 65.99; H, 4.03; N, 13.99; S, 15.99. Found: C, 66.01; H, 4.23; N, 14.07; S, 15.83.

Further elution yielded other components which were not identified.

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