A CONVENIENT SYNTHESIS OF FUSED 4-MERCAPTOPYRIMIDINES FROM *o*-AMINONITRILES

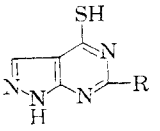
Sir:

Fused 4-mercaptopyrimidine heterocycles have received considerable recent attention, both because of the antimitotic activity of such purine derivatives as 6-mercaptopurine,[1] 6-mercapto-9-β-D-ribofuranosylpurine,[2-4] 2-amino-6-mercaptopurine (thioguanine),[4] and 2-amino-6-mercapto-9-β-D-ribofuranosylpurine (thioguanosine),[5] and because of the facility with which the mercapto group of such compounds may be exchanged for hydrogen,[6] hydroxyl,[6] amino[6] or halogen[7,8] substituents. Previously available methods for the preparation of 4-mercaptopyrimidine derivatives have involved either direct replacement of oxygen by sulfur through the agency of phosphorus pentasulfide,[6] or of a halogen atom by the action of thiourea or an alkali hydrosulfide,[6] or occasionally by suitable ring-closure procedures such as the cyclization of *o*-aminothioamides with orthoesters,[9-11] acetic anhydride–formic acid,[12] acid anhydrides,[13] and the closely related cyclization of *o*-aminonitriles with sodium sulfide and acid anhydrides.[13]

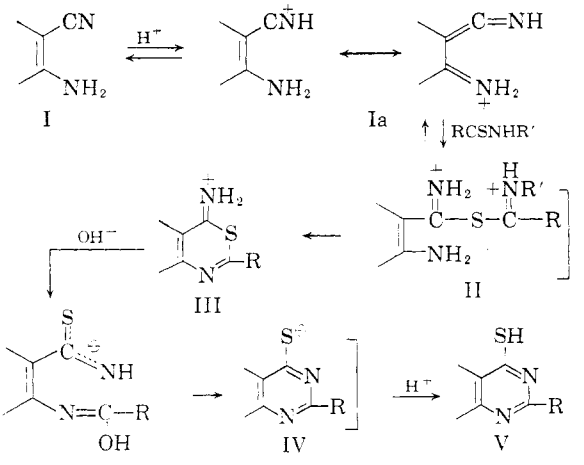
We wish to report a convenient, one-step synthesis of fused 4-mercaptopyrimidine heterocycles which involves the condensation of *o*-aminonitriles with thioamides in ethanol saturated with dry hydrogen chloride, then evaporation and treatment with alkali. Variation of the thioamide allows the introduction of hydrogen, alkyl or aryl groups into the 2-position. The method is illustrated by the condensation of 3-amino-4-cyanopyrazole with various thioamides to give the 4-mercapto-6-substituted pyrazolo[3,4-d]pyrimidines listed in Table I.

We believe that the reaction is initiated by the addition of the sulfur atom of the thioamide to the protonated nitrile Ia to give intermediate II, which then cyclizes by loss of ammonia (or amine) to the *m*-thiazine III. Addition of alkali to III, which need not be isolated, initiates a facile skeletal rearrangement *via* the ring-opening, ring-closure sequence pictured to give the stable, aromatic anion of the fused 4-mercaptopyrimidine (IV). Final acidification of the reaction mixture results in precipitation of the product V. The *m*-thiazine (III) was isolated (as its hydrochloride) in several instances but proved to be too unstable for complete characterization; all attempts at recrystallization, for example, resulted in at least partial conversion to V. The rearrangement of *m*-thiazines to mercaptopyrimidines has been described previously.[16,17]

TABLE I



Thioamide employed	R	M.p. °C.	Yield, %	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
HCSNHPh	H[14]	>300 dec.	62	39.5	2.65		39.85	2.9	
CH_3CSNH_2	CH_3[15]	>300 dec.	72	43.4	3.6		43.2	3.8	
$C_6H_5CSNH_2$	C_6H_5	308–310 dec.	69	57.9	3.5	24.55	58.15	3.7	24.4
p-$H_2NC_6H_4CSNH_2$	p-$H_2NC_6H_4$	>300 dec.	74	54.3	3.7	28.8	54.05	3.9	28.55
p-$CH_3OC_6H_4CSNH_2$	p-$CH_3OC_6H_4$	299–300	59	55.8	3.9	21.7	55.9	3.9	21.9
p-$O_2NC_6H_4CSNH_2$	p-$O_2NC_6H_4$	>300 dec.	40	48.35	2.6	25.6	48.6	2.9	25.7



(1) J. H. Burchenal, R. R. Ellison, M. L. Murphy, D. A. Karnofsky, M. P. Sykes, T. C. Tan, A. C. Mermann, M. Yuceoglu, W. P. L. Myers, I. Krakoff and N. Alberstadt, *Ann. N. Y. Acad. Sci.*, **60**, 359 (1954).

(2) J. A. Johnson and H. J. Thomas, THIS JOURNAL, **78**, 3863 (1956).

(3) H. E. Skipper, J. R. Thomson, D. J. Hutchison, F. M. Schabel and J. J. Johnson, *Proc. Soc. Exper. Biol. Med.*, **95**, 135 (1957).

(4) H. E. Skipper, J. A. Montgomery, J. R. Thomson and F. M. Schabel, *Cancer Research*, **19**, 425 (1959).

(5) J. J. Fox, I. Wempen, A. Hampton and I. L. Doerr, THIS JOURNAL, **80**, 1669 (1958).

(6) The literature on such transformations is extensive; for recent reviews see (a) A. Bendich in "The Nucleic Acids: Chemistry and Biology," ed. by E. Chargaff and J. N. Davidson, Academic Press, Inc., New York, N. Y., Vol. 1, 1955, p. 81, (b) G. W. Kenner and A. Todd in "Heterocyclic Compounds," ed. by R. C. Elderfield, John Wiley and Sons, Inc., New York, N. Y., Vol. 6, 1957, p. 234.

(7) C. W. Noell and R. K. Robins, THIS JOURNAL, **81**, 5997 (1959).

(8) R. K. Robins, *ibid.*, **82**, 2654 (1960).

(9) A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

(10) E. C. Taylor, J. A. Carbon and D. R. Hoff, THIS JOURNAL, **75**, 1904 (1953).

(11) H. G. Mautner, *J. Org. Chem.*, **23**, 1450 (1958).

(12) G. Shaw and D. N. Butler, *J. Chem. Soc.*, 4040 (1959).

(13) M. T. Bogert, H. C. Breneman and W. F. Hand, THIS JOURNAL, **25**, 372 (1903).

(14) R. K. Robins, *ibid.*, **78**, 784 (1956).

(15) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **23**, 191 (1958).

A minor side-reaction observed is dissociation of the intermediate II to the thioamide derived from I and the nitrile (or presumably iminochloride when $R^1 \neq H$) derived from the initially-added thioamide.[18] This side-reaction can be utilized to advantage in the synthesis of 2-unsubstituted 4-mercaptopyrimidines from *o*-aminonitriles and thioformanilide by employing dimethylformamide-hydrogen chloride as the reaction medium. The thioamide derived from I by the exchange reaction is formylated by the dimethylformamide–hydrogen chloride mixture (a variant of the Vilsmeier–Haack procedure) and the resulting *o*-formylaminothioamide then cyclizes under the reaction conditions to the same 4-mercaptopyrimidine obtained *via* the *m*-thiazine pathway pictured above. Improved yields are thus generally obtained.

(16) C. J. Cavallito, C. M. Martini and F. C. Nachod, THIS JOURNAL, **73**, 2544 (1951).

(17) M. R. Atkinson, G. Shaw, K. Schaffner and R. N. Warrener, *J. Chem. Soc.*, 3847 (1956).

(18) E. C. Taylor and J. A. Zoltewicz, THIS JOURNAL, **82**, 2656 (1960).

(19) N.S.F. Coöperative Fellow, 1959–1960.

FRICK CHEMICAL LABORATORY
PRINCETON UNIVERSITY — EDWARD C. TAYLOR
PRINCETON, N. J. — JOHN A. ZOLTEWICZ[19]

RECEIVED OCTOBER 10, 1960

CATALYSIS OF THE DIELS-ALDER REACTION

Sir:

The recent report[1] that certain Diels–Alder reactions are accelerated by aluminum chloride prompts us to outline the results of our own investigations, which are the subject of a patent.[2] We found that in the presence of catalysts of the Friedel Crafts type, for example aluminum chloride, stannic chloride, boron trifluoride, ferric chloride, titanium tetrachloride, *etc.*, a number of Diels–Alder additions could be effected under much milder conditions than those required in the absence of such catalyst.

A good example of this catalytic effect was shown in the reaction of butadiene with methyl vinyl ketone to afford 4-acetylcyclohexene. This reaction was originally investigated by Petrov,[3] who reported yields of 75–80% on heating the reactants at 140° in a sealed tube for 8–10 hours. We found that similar yields of the adduct could be obtained by adding methyl vinyl ketone at room temperature to an excess of butadiene in benzene (or similar solvent) in the presence of the above-mentioned catalysts. Less than one molar proportion of catalyst could be used; thus with 0.18 mol. equiv. of stannic chloride, a 73% yield of the adduct was obtained after reaction during 1 hour. In the absence of catalyst no adduct was formed under otherwise similar conditions.

The results of our investigations with a range of dienes and dienophiles may be summarized: Of the dienophiles which were studied in conjunction with butadiene, only acrolein, methyl vinyl ketone, and acrylic acid gave useful yields of the Diels–Alder adducts under the above conditions. The general utility of the catalysts was obviously subjected to a further limitation by the readiness with which many dienes polymerize. In comparative experiments with methyl vinyl ketone and titanium tetrachloride, 2,3-dimethylbutadiene and cyclopentadiene yielded only polymer and dimer, respectively,[4] whereas butadiene afforded 4-acetylcyclohexene in 63% yield, and anthracene[5] gave a 46% yield of 9,10-(acetylethano)-9,10-dihydroanthracene,[6] m.p. 151° (2,4-dinitrophenylhydrazone,[6] m.p. 194–195°).

(1) P. Yates and P. Eaton, THIS JOURNAL, **82**, 4436 (1960).

(2) Sir Robert Robinson and G. I. Fray, British Patent 835,840 (1960).

(3) A. A. Petrov, *J. Gen. Chem. U.S.S.R.*, **11**, 309 (1941).

(4) With 2,3-dimethylbutadiene, the use of a milder catalyst, *viz.*, zinc chloride, enabled the adduct to be obtained in 16% yield.

(5) At 40–45°.

(6) Satisfactory analyses were obtained.

RESEARCH LABORATORY — G. I. FRAY
SHELL CHEMICAL COMPANY LIMITED
EGHAM, SURREY, ENGLAND — R. ROBINSON

RECEIVED NOVEMBER 9, 1960

CHEMISTRY OF THE METAL CARBONYLS. VII. PERFLUOROALKYL IRON COMPOUNDS[1]

Sir:

A new class of transition metal compound is represented by perfluoroalkyl derivatives of iron. These perfluoroalkyl transition metal compounds have properties significantly different from those of perfluoroalkyl derivatives of main group metals, or alkyl compounds of transition metals.

Iron pentacarbonyl (29 g., 150 mmoles) and *n*-perfluoropropyl iodide (25 g., 85 mmoles) were heated under nitrogen at 45° for 21 hr. in benzene (50 ml.). The mixture then was cooled and evaporated to dryness. Sublimation (25° at 10^{-1} mm.) of the solid residue onto a probe cooled to 0° gave 11.0 g. (28% yield) of red crystalline *n*-$C_3F_7Fe(CO)_4I$ (m.p. 69–70° (dec.)), soluble in organic solvents. *Anal.* Calcd. for $C_7F_7O_4IFe$: C, 18.1; F, 28.7; I, 27.4; Fe, 12.1; mol. wt., 464. Found: C, 18.2; F, 28.5; I, 27.3; Fe, 12.5; mol. wt. (isopiestic), 480.

The perfluoropropyliron compound reacts with iodine at 150° with quantitative release of four moles of carbon monoxide per mole of complex. Perfluoropropyliron tetracarbonyl iodide, however, is not attacked by water or concentrated hydrochloric acid, and is much more stable than alkyl iron compounds such as $C_5H_5Fe(CO)_2CH_3$.[2]

Whereas perfluoroalkyl derivatives of main group metals react rapidly with base at moderate temperatures with quantitative release of their perfluoroalkyl groups as $C_nF_{2n+1}H$,[3] perfluoroalkyl derivatives of transition metals studied are much less affected by base. A sample (0.722 g., 1.56 mmoles) of perfluoropropyliron tetracarbonyl iodide heated (100° for 65 hr.) with concentrated sodium hydroxide solution (2 ml.) gave carbon monoxide and only 14.7 cc. (S.T.P.) of heptafluoropropane (42% of theor.), identified by its infrared spectrum. Moreover, certain perfluoroalkyl transition metal compounds do not give the

(1) Previous article in this series, T. A. Manuel and F. G. A. Stone, THIS JOURNAL, **82**, 6240 (1960).

(2) T. S. Piper and G. Wilkinson, *J. Inorg. & Nuclear Chem.*, **3**, 104 (1956).

(3) H. C. Clark and C. J. Willis, THIS JOURNAL, **82**, 1888 (1960); H. D. Kaesz, J. R. Phillips, and F. G. A. Stone, *ibid.*, **82**, 6228 (1960).