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A SIMPLE, ONE-STEP SYNTHESIS OF FUSED PYRIMIDINETHIONES[1]

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Abstract—Conversion of *o*-aminonitriles to their ethoxymethyleneamino derivatives with ethyl orthoformate, followed by treatment with alcoholic sodium hydrosulfide, constitutes a simple, one-step synthesis of fused pyrimidinethiones. This reaction sequence is equally applicable to aromatic, heterocyclic and alicyclic *o*-aminonitriles and represents the synthetic method of choice.

FUSED pyrimidinethiones[3] are of considerable chemical and pharmacological importance.[4] With the exception of the pyrimidinethiones prepared by a recently described "one-step" conversion of *o*-aminonitriles with thioformanilide and dimethylformamide saturated with dry hydrogen chloride,[4a] almost all known compounds of this type have been prepared by laborious and inefficient multi-stage syntheses, often from difficultly available starting materials. We wish to describe a simple, one-step synthesis of fused pyrimidinethiones from *o*-aminonitriles employing much milder conditions than our previously described one-step synthesis and which is consequently of wider applicability.

This new procedure consists of treatment of an *o*-aminonitrile (I) either with a 1:1 mixture of ethyl orthoformate and acetic anhydride,[5] or with ethyl orthoformate alone,[6] to give an intermediate ethoxymethyleneamino derivative (II) which, without isolation, is treated with an ethanolic solution of sodium hydrosulfide. The reaction mixture is evaporated to dryness, taken up in water, treated with charcoal, and acidified. The fused pyrimidinethione (III) is obtained in an extremely high state of purity and in yields generally considerably in excess of 90%.

The preparation of cyclopenteno(*d*)pyrimidine-7(6*H*)-thione may be cited as an illustration of the effectiveness of this new pyrimidine synthesis. The latter compound has previously been prepared in 9·7% crude overall yield in a 4-step reaction sequence

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[3] We prefer to utilize the structurally significant "thione" nomenclature for these compounds despite the widespread designation of related compounds (e.g., 6-mercaptopurine) as "mercapto" derivatives.

[4] For discussions and leading refs, see (a) E. C. Taylor and J. A. Zoltewicz, *J. Amer. Chem. Soc.* **83**, 248 (1961); R. K. Robins, *J. Med. Chem.* **7**, 186 (1964).

[5] L. Goldman, J. W. Marsico and A. L. Gazzola, *J. Org. Chem.* **21**, 599 (1956).

[6] A mixture of equal volumes of ethyl orthoformate and acetic anhydride is the reagent of choice for the formation of ethoxymethyleneamino derivatives. However, in some cases acetylation of the amino group takes precedence over formation of the latter derivative and resort must be made to the use of ethyl orthoformate alone.

starting with 2-carboethoxycyclopentanone.[7] We have prepared the desired purine analog in 70% yield in a single step from the readily accessible 1-amino-2-cyanocyclopent-1-ene. Similarly, pyrazolo (3,4-*d*)pyrimidine-4(5*H*)-thione was prepared by Cheng and Robins[8] from 3-amino-4-cyanopyrazole in a 4-step sequence involving initial hydrolysis of the nitrile with concentrated sulphuric acid to the amide, cyclization with formamide to pyrazolo(3,4-*d*)pyrimidine-4(5*H*)-one, then to the 4-chloro derivative with phosphorus oxychloride, and finally conversion to the desired pyrazolo(3,4-*d*)pyrimidinethione with thiourea. Direct conversion of the above pyrimidone derivative with phosphorus pentasulfide in tetralin as solvent proved even less satisfactory. From the same starting material (3-amino-4-cyanopyrazole) we have prepared pyrazolo(3,4-*d*)pyrimidine-4(5*H*)-thione in a single step in 97% yield. It should be noted that the latter compound prepared independently by the method of Cheng and Robins was impure (TLC) even after repeated recrystallizations; by contrast, the product prepared by our procedure was analytically pure (1 spot on TLC, colorless) as isolated directly from the reaction mixture.

TABLE

Starting material	Reaction conditions	Time hr	Final product	Yield
N-Benzyl-3-cyano-4-amino-Δ^3-piperidine	EOF/Ac_2O^a	1	6-Benzyl-5,6,7,8-tetrahydropyridino-(4,3-*d*)pyrimidine-4(3*H*)-thione	81^b 62^c
3-Amino-4-cyanopyrazole	EOF	3	Pyrazolo(3,4-*d*)pyrimidine-4(5*H*)-thione	97^b
1-Methyl-4-cyano-5-amino-pyrazole	EOF/Ac_2O	2	1-Methylpyrazolo(3,4-*d*)pyrimidine-4(5*H*)-thione	91^b 59^c
1-Phenyl-4-cyano-5-amino-pyrazole	EOF/Ac_2O	2	1-Phenylpyrazolo(3,4-*d*)pyrimidine-4(5*H*)-thione	94^b
1-Phenyl-3-methyl-4-cyano-5-aminopyrazole	EOF/Ac_2O	2	1-Phenyl-3-methylpyrazolo(3,4-*d*)-pyrimidine-7(5*H*)-thione	92^b 68^c
4-Amino-5-cyanopyrimidine	EOF/Ac_2O	2	Pyrimido(4,5-*d*)pyrimidine-4(3*H*)-thione	69^b 60^d
Anthranilonitrile	EOF	2	Quinazoline-4(3*H*)-thione	63^b 73^d
1-Amino-2-cyanocyclopent-1-ene	EOF	1	Cyclopenteno(*d*)pyrimidine-7(6*H*)-thione	70^b
1-Amino-2-cyanocylohex-1-ene	EOF/Ac_2O	½	5,6,7,8-Tetrahydroquinazoline-4(3*H*)-thione	68^b

In a few instances, conversion of the *o*-aminonitrile to an *o*-aminothioamide followed by cyclization with ethyl orthoformate competes favorably with our new procedure. For example, the conversion of anthranilonitrile to quinazoline-4(3*H*)-thione can be carried out in slightly better yield (73% vs. 63%) by this procedure than by the one-step reaction as described here. On the other hand, alicyclic *o*-aminonitriles such as 1-amino-2-cyanocyclopent-1-ene and the corresponding cyclohexene derivative cannot be converted to the thioamides by reaction either with hydrogen sulfide alone or with hydrosulfide anion; they are, however, converted in high yield (see Table) to fused pyrimidinethiones by the new procedure.

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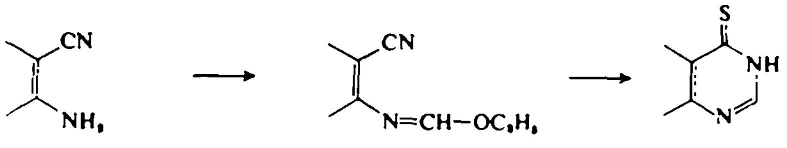
[7] L. O. Ross, L. Goodman and B. R. Baker, *J. Amer. Chem. Soc.* **81**, 3108 (1959).

[8] C. C. Cheng and R. K. Robins, *J. Org. Chem.* **21**, 1240 (1956).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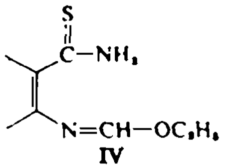
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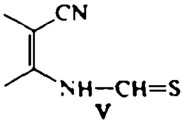
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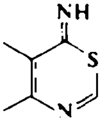
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TABLE

m.p., °C	Formula	Calcd. C,	Calcd. H,	Calcd. N,	Found C,	Found H,	Found N
220–225 dec.	$C_{14}H_{15}N_3S$	65·33	5·87	16·33	65·35	5·75	16·38
354–356 dec.[e]							
309–311 dec.[f]							
280–282 dec.[g]							
256–258 dec.	$C_{12}H_{10}N_4S$	59·48	4·16	23·12	59·39	4·38	23·08
>360[h]							
326–330 dec.[i]							
275–277 dec.[j]							
268–274 dec.	$C_8H_{10}N_2S$	57·79	6·06	16·86	57·56	6·02	17·04

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[a] In general, a ratio of 1 g aminonitrile, 10 ml ethyl orthoformate and 10 ml acetic anhydride was used.

[b] Represents the yield of fused pyrimidinethione from the aminonitrile, without isolation of the intermediate ethoxymethyleneamino derivative.

[c] Represents the yield of fused pyrimidinethione from the aminonitrile in a two-step reaction sequence in which the intermediate ethoxymethyleneamino derivative was isolated and subsequently treated with an ethanolic solution of sodium hydrosulfide.

[d] Represents the yield of fused pyrimidinethione from the aminonitrile in a two-step reaction sequence in which the intermediate aminothioamide was prepared (by addition of hydrogen sulfide to the nitrile), isolated and subsequently treated with ethyl orthoformate.

[e] This compound has been reported to melt "above 360°" (see Ref. 8).

[f] This compound has been reported to melt at >300° (Ref. 8).

[g] This compound has been reported to melt variously at 264–265° (J. Druey and P. Schmidt, U.S. Pat. 2,965, 643, Dec. 20, 1920; *Chem. Abstr.* **57**, 11211e (1962)); at 265–267° (P. Schmidt and J. Druey, *Helv. Chim. Acta* **39**, 986 (1956)); and at 280–281° (see Ref. 8).

[h] H. G. Mautner, *J. Org. Chem.* **23**, 1450 (1958). W. A. Ehrhart, Ph.D. Thesis, Princeton University, 1960.

[i] N. J. Leonard and D. Y. Curtin, *J. Org. Chem.* **11**, 349 (1946).

[j] See Ref. 7.

The major limiting factor in the one-step synthesis of fused pyrimidinethiones as described here appears to be the effectiveness of the initial reaction leading to the formation of the ethoxymethyleneamino derivative. With anthranilonitrile, for example, even 30 hr of refluxing with ethyl orthoformate failed to effect complete conversion to the ethoxymethyleneamino derivative; the depressed overall yield (63%) in the one-step conversion of anthranilonitrile to quinazoline-4(3*H*)-thione is thus directly attributable to the incompleteness of the initial reaction.[9] When the ethoxymethyleneamino derivatives were actually isolated and purified and then treated subsequently with an ethanolic solution of sodium hydrosulfide, cyclization to the fused pyrimidinethiones proceeded uniformly in extremely high yield. However, since isolation and purification of the intermediate ethoxymethyleneamino derivatives resulted in some lowering of the overall yield, the one-step procedure is to be preferred for preparative purposes.

The mechanism of the conversion of the ethoxymethyleneamino derivatives to fused pyrimidinethiones with sodium hydrosulfide is not yet clear. It may proceed by addition of hydrosulfide anion to the *o*-situated nitrile to give an intermediate *o*-ethoxymethyleneamino thioamide (IV), which subsequently cyclizes with loss of ethanol. Alternately, initial displacement of ethanol from the ethoxymethyleneamino derivative would give an intermediate *o*-cyanothioformamide (V) which cyclizes under the basic reaction conditions to a 4-amino-*m*-thiazine (VI). We have previously shown[4a] that such compounds are unstable in alkaline medium and undergo a facile ring-opening, ring-closure rearrangement to give fused pyrimidinethiones. However, attempts to isolate intermediates in the conversion of II to III were vitiated by the alkaline reaction medium. The use of more weakly basic reaction media such as pyridine and hydrogen sulfide also effected the conversion of II to III, but in a more complex reaction and in substantially lower yield. Attempts to convert II to III with hydrogen sulfide in the absence of added base (i.e., in ethanol solution) resulted in recovery of unchanged II, with no detectable conversion to the fused pyrimidinethiones.

We consider this new one-step synthesis to be the method of choice for the preparation of fused pyrimidinethiones where *o*-aminonitriles are available as intermediates.

EXPERIMENTAL[10]

1-*Benzyl-3-cyano-4-amino-*Δ^3*-piperidine*. K (26·4 g) was added in small portions to a vigorously stirred mixture of 140 ml freshly distilled t-butanol and 375 ml anhydrous toluene. When the K had dissolved the mixture was stirred, heated to reflux, and 132 g bis-(2-cyanoethyl)benzylamine[11] added slowly. After addition was completed, refluxing and stirring were continued for a further 3 hr,

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[9] Attempts to raise the overall yield in the one-step reaction by prolonging the reaction time for the initial conversion led to secondary reactions which depressed rather than raised the yield of the final product.

[10] M.ps were determined on a Thomas-Hoover silicon bath apparatus and are uncorrected. Microanalyses were performed by the Robertson Microanalytical Laboratory, Florham Park, New Jersey, and by the Spang Microanalytical Laboratory, Ann Arbor, Michigan. Where appropriate, identity of compds was confirmed by comparison of IR spectra determined by the normal Nujol mull technique on a Perkin-Elmer Model 237B Grating Infracord.

[11] N. A. Preobrazhenskii, K. M. Malkov, M. E. Maurit, M. A. Vorob'ev and A. S. Vlasov, *Zhur. Obschei Khim.* **27**, 3162 (1957).

after which the mixture was cooled and allowed to stand overnight at room temp. The mixture was filtered to remove the crude product which had precipitated, the filtrate treated with 250 ml water and the mixture shaken vigorously. The precipitate which formed was filtered off and the organic layer treated with successive portions of water, as described above, until no more precipitation was observed. The combined aqueous layers were then extracted with $CHCl_3$ (3 × 250 ml), the $CHCl_3$ and toluene layers combined, dried (Na_2SO_4) and evaporated to leave a yellow solid. This was combined with the solid which had been obtained by shaking the organic layer with water and the whole triturated with cold ether. The solid was then filtered off and crystallized from EtOH to give 96 g pale yellow product, m.p. 152–153°.

The crude product which had precipitated from the reaction mixture on standing overnight was purified as follows. The solid was dispersed in cold water, and after standing for 24 hr was filtered off and crystallized 3 times from EtOH giving a further 35 g of pure material. The yield of pure product was thus 131 g (99%) m.p. 152–153°.

An analytical sample was obtained as a colourless solid, m.p. 152–153°, by repeated recrystallization from EtOH. (Found: C, 73·02; H, 7·31; N, 19·48. Calc. for $C_{13}H_{15}N_3$: C, 73·21; H, 7·09; N, 19·70%.)

N-*Benzyl-3-cyano-4-ethoxymethyleneamino-*Δ^3*-piperidine*. A mixture of 15 g N-benzyl-3-cyano-4-amino-Δ^3-piperidine, 75 ml ethyl orthoformate and 75 ml Ac_2O was heated under reflux for 1 hr, evaporated under red. press. and the residue dissolved in hot EtOH. The product which separated on cooling was recrystallized from EtOH to give 11·3 g (65%) of yellow needles, m.p. 73–74°. (Found: C, 71·42; H, 7·16; N, 15·57. Calc. for $C_{16}H_{19}N_3O$: C, 71·34; H, 7·11; N, (15·60%.)

1-*Methyl-4-cyano-5-ethoxymethyleneaminopyrazole* was prepared as described in the literature.[12]

1-*Phenyl-3-methyl-4-cyano-5-ethoxymethyleneaminopyrazole*. 1-Phenyl-3-methyl-4-cyano-5-aminopyrazole[9] (3·0 g) was refluxed for 2 hr in a mixture of 30 ml ethyl orthoformate and 30 ml Ac_2O. Removal of the solvents by distillation under red. press. left a light brown-coloured liquid which rapidly solidified on cooling. Distillation gave 3·06 g (80%) of a colourless oil, b.p. 160–165°/0·1 mm, which rapidly solidified; m.p. 73–75°. (Found: C, 65·88; H, 5·63; N, 21·96. Calc. for $C_{14}H_{14}N_4O$: C, 66·12; H, 5·55; N, 22·04%.)

4-*Amino-5-thiocarboxamidopyrimidine* was prepared and converted to pyrimido(4,5-*d*)pyrimidine-4(3*H*)-thione with ethyl orthoformate as described in the literature (for refs see Table, footnote *h*).

Thioanthranilamide. Anthranilonitrile (5·0 g, 0·042 mole) was dissolved in 7·5 ml of anhydrous pyridine, 4·3 g (0·042 mole) of triethylamine added and dry H_2S bubbled through the soln for 4 hr. The mixture was then stirred into 50 ml of cold water, the yellow solid filtered off, washed with 50 ml of cold water and dried. This gave 5·07 g of thioanthranilamide, m.p. 114–118° (lit.[13] m.p. 121·5°).

Quinazoline-4(3H)-thione. Thioanthranilamide (3·0 g) was refluxed for 2 hr in 50 ml ethyl orthoformate, the soln chilled, and the bright yellow solid filtered off, washed with cold EtOH and dried. This gave 2·95 g (92%) of quinazoline-4(3*H*)-thione, m.p. 326–330°.

General procedure for the preparation of fused pyrimidinethiones. The various ethoxymethylene derivatives required as intermediates were prepared by refluxing 3·0 g of the *o*-aminonitrile with a mixture of 30 ml ethyl orthoformate and 30 ml Ac_2O, or with 30 ml of ethyl orthoformate alone, the reaction times being indicated in the Table. The solvents were then removed by distillation under red. press. and the crude product added to 100 ml 1·5N soln of sodium hydrosulfide in anhydrous EtOH.[14] This mixture was then refluxed for 10–12 hr, the EtOH removed by distillation under red. press. and the residual solid dissolved in hot water. The aqueous soln was heated to reflux, treated with C, filtered, and the filtrate acidified while hot with glacial AcOH. The precipitated product was filtered off, washed with water, EtOH and dried.

[12] E. C. Taylor and P. K. Loeffler, *J. Amer. Chem. Soc.* **82**, 3147 (1960).

[13] A. Reissert and F. Grube, *Ber. Dtsch. Chem. Ges.* **42**, 3710 (1909). The yield reported by these authors (70%) is the highest reported in the literature for the preparation of thioanthranilamide.

[14] W. P. Hall and E. E. Reid, *J. Amer. Chem. Soc.* **65**, 1466 (1943). It is essential to use an anhydrous soln of ethanolic sodium hydrosulfide, since the intermediate ethoxymethyleneamino derivatives are rapidly hydrolysed to the *o*-aminonitriles by water.

The same procedure was used in those cases where the intermediate ethoxymethyleneamino derivatives were isolated and purified. Thus, N-benzyl-3-cyano-4-amino-Δ^3-piperidine was converted in 65% yield to its ethoxymethyleneamino derivative, which in turn was converted in 95% yield to 6-benzyl-5,6,7,8-tetrahydropyridino(4,3-*d*)pyrimidine-4(3*H*)-thione; 1-methyl-4-cyano-5-aminopyrazole was converted in 69% yield to the ethoxymethyleneamino derivative and this in 85% yield to 1-methylpyrazolo(3,4-*d*)pyrimidine-4(5*H*)-thione. The ethoxymethyleneamino derivative of 1-phenyl-4-cyano-5-aminopyrazole was obtained in 80% yield; treatment with sodium hydrosulfide gave 1-phenylpyrazolo(3,4-*d*)pyrimidine-4(5*H*)-thione in 85% yield.