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San H. Thang [a b], Keith G. Watson [a b], Wayne M. Best [a c], Marie-Anne M. Fam [a d] & Philip L. C. Keep [a e]

[a] ICI Australia, Research Group, Ascot Vale, Vic., 3032, Australia

[b] CSIRO, Division of Chemicals & Polymers, Private Bag 10, Clayton, Vic., 3168, Australia

[c] University of Western Australia, Chemistry Department, Nedlands, WA, 6009, Australia

[d] University of Melbourne, Department of Chemistry, Parkville, Vic., 3052, Australia

[e] David Bull Laboratories Pty. Ltd., 7-23 Lexia Place, Mulgrave North, Vic., 3170, Australia

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A CONVENIENT SYNTHESIS OF 4,6-DICHLORO-5-BENZYLTHIOPYRIMIDINE

San H. Thang,*[1a] Keith G. Watson,*[1a] Wayne M. Best,[1b]
Marie-Anne M. Fam[1c] and Philip L.C. Keep[1d]

ICI Australia, Research Group,
Ascot Vale, Vic. 3032, Australia

ABSTRACT: A practical and convenient two-step synthesis of the title compound 4,6-dichloro-5-benzylthiopyrimidine (3) from 4,6-dihydroxypyrimidine (1) is described.

As part of our research program in the area of crop protection agents, we required a simple procedure for the preparation of the title compound, 4,6-dichloro-5-benzylthiopyrimidine (3), in multigram quantities. This material (3) is a key precursor in the synthesis of various types of 4,6-di-substituted pyrimidine-5-sulfonamides, derivatives of which possess interesting biological activities.[2,3] In our experience, these pyrimidine-5-sulfonamides cannot be prepared by the traditional chlorosulfonation / aminolysis approach from the

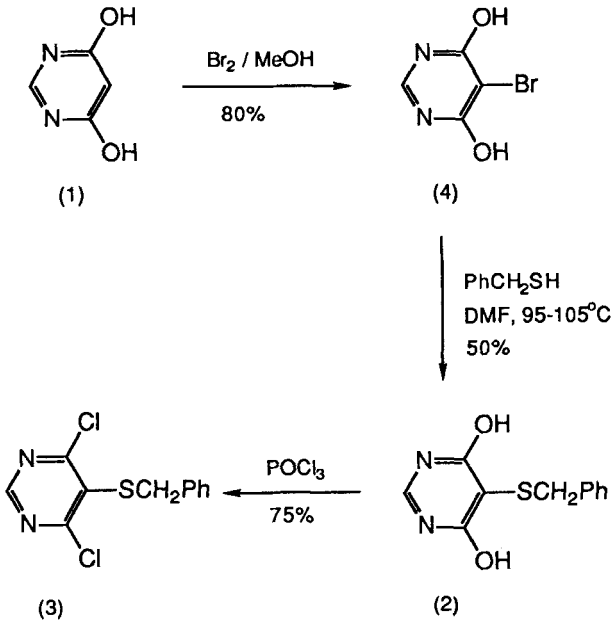
* To whom correspondence should be addressed.

corresponding pyrimidines. The conversion of the title compound into these novel pyrimidine-5-sulfonamides will be described in a future paper.[4]

The literature contains only a few examples of pyrimidine compounds with alkylthio- substituents at the 5-position.[5,6] Furthermore, there have not been any reports on the synthesis of 4,6-dihydroxy-5-alkylthiopyrimidines nor the 4,6-dichloro-5-alkylthiopyrimidines. In this *communication,* we wish to report the successful synthesis of 4,6-dihydroxy-5-benzylthiopyrimidine (2), and subsequently the title compound (3).

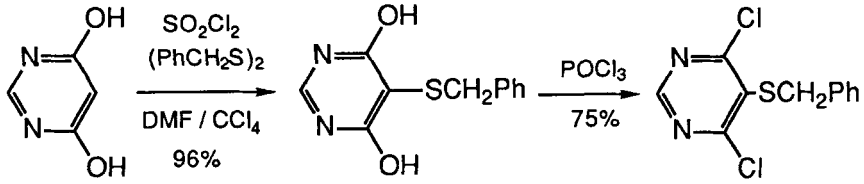
Initially, a three-step synthesis for the title compound (3) was adopted (Scheme 1). 4,6-Dihydroxypyrimidine (1) was simply converted to 4,6-dihydroxy-5-bromopyrimidine (4) in 80% yield according to the literature procedure.[7] In the second step, compound (4) was heated and stirred vigorously under nitrogen with benzylmercaptan and anhydrous potassium carbonate in N,N-dimethylformamide. This substitution reaction gave very variable results, and in our hands the best yield for compound (2) was 50% (see method B in Experimental section). The reason for the capricious nature of this reaction step is not apparent at this point in time. The final step was simple and straightforward in that the 4,6-dihydroxy-5-benzylthiopyrimidine (2) was heated at reflux in phosphorus oxychloride for 3 hours, and after a quick purification by column chromatography, the title compound (3) was obtained in 75% yield.

Scheme 1



In view of the difficulty in displacing the bromo- with the benzylthio- group in the second step of Scheme 1, an improved synthetic method was sought. The use of sulfenyl chloride chemistry[5] afforded a superior result, thus compound (2) was obtained in quantitative yield by reacting benzyl sulfenyl chloride with 4,6-dihydroxypyrimidine (1) in N,N-dimethylformamide (Scheme 2, method A in Experimental section). The benzyl sulfenyl chloride was prepared from the dibenzyl disulfide by the treatment with sulfuryl chloride.[8] This sulfenyl chloride methodology was also applied to other 2-substituted-4,6-dihydroxypyrimidine derivatives such as 2-methyl-4,6-dihydroxypyrimidine.[9]

Scheme 2



(1) (2) (3)

In conclusion, the title compound 4,6-dichloro-5-benzylthiopyrimidine (3) can be prepared in a practical two-step synthesis in ~72% overall yield starting from commercially available 4,6-dihydroxypyrimidine.

EXPERIMENTAL

The reagents 4,6-dihydroxypyrimidine (1), sulfuryl chloride, dibenzyl disulfide and phosphorus oxychloride are commercially available and were used as received. ^{1}H-NMR spectra were recorded on a Bruker AC-250 MHz spectrometer. Melting points were recorded in capillary tubes using an Electrothermal melting point apparatus and are uncorrected.

4,6-Dihydroxy-5-benzylthiopyrimidine (2)

Method A:

Sulfuryl chloride (3.5ml, 0.043 mole) was added to a stirred suspension of dibenzyl disulfide (10.35g, 0.042 mole) in carbon tetrachloride (55ml)

containing three drops of triethylamine. The orange solution was stirred for 30 minutes at room temperature before being added dropwise to a stirred suspension of 4,6-dihydroxypyrimidine (1) (8.6g, 0.077 mole) in N,N-dimethylformamide (120ml). The resulting mixture was stirred at room temperature for 3.5 hours, after which time the precipitate was collected by filtration, washed several times with water followed by diethyl ether and then air dried to give the title compound (2) as a pale yellow powder (17.35g, 96%). The product (2) can be crystallized by precipitation from dimethyl sulfoxide into water, m.p. 320°C (dec.). ^{1}H-NMR (DMSO-d_6) 3.96 (s, 2H); 7.20 (broad m, 5H); 8.11 (s, 1H); 12.20 (broad s, 2H). ^{13}C-NMR (DMSO-d_6) 35.4; 126.6; 128.1; 128.7; 128.8; 138.7; 148.3; 164.3.

Method B:

Benzylmercaptan (6ml, 0.050 mole) was added to a stirred and heated (90°C) suspension of 5-bromo-4,6-dihydroxypyrimidine (4) (9.5g, 0.050 mole) and anhydrous potassium carbonate (7.5g, 0.055 mole) in N,N-dimethylformamide (25ml). The reaction mixture was stirred and heated at 95-105°C under an atmosphere of dry nitrogen for 3.5 hours. The mixture was poured into ice cold water (400ml) with vigorous stirring and then acidified to pH 1 with hydrochloric acid. After stirring for 30 minutes, the suspension was filtered and the solid was rinsed several times with n-hexane and diethyl ether to remove traces of dibenzyl disulfide. The resulting pale brown solid was air dried to give 4,6-dihydroxy-5-benzylthiopyrimidine (2) (5.5g, 50%).

4,6-Dichloro-5-benzylthiopyrimidine (3)

A mixture of phosphorus oxychloride (50ml) and 4,6-dihydroxy-5-benzylthiopyrimidine (8.20g) was stirred and heated at reflux for 3 hours. Excess phosphorus oxychloride was removed by distillation under reduced pressure. The residue was then diluted with chloroform (200ml), and washed with water (3X200ml). The chloroform layer was dried over $MgSO_4$ and then concentrated to give the crude product as a brown oil (8.80g, 92%). Purification of the crude product (3.30g) by column chromatography (silica-gel 60, 70-230 mesh, n-hexane:chloroform 1:1) gave 4,6-dichloro-5-benzylthiopyrimidine (3) as a nearly colourless low-melting solid (2.65g, 72%), m.p. 40-41°C. ^{1}H-NMR ($CDCl_3$) 4.18 (s, 2H); 7.20 (m, 5H); 8.60 (s, 1H).

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1. Current addresses:

   a. CSIRO, Division of Chemicals & Polymers, Private Bag 10, Clayton, Vic. 3168, Australia

   b. University of Western Australia, Chemistry Department, Nedlands, WA 6009, Australia

c. University of Melbourne, Department of Chemistry, Parkville, Vic. 3052, Australia

d. David Bull Laboratories Pty. Ltd., 7-23 Lexia Place, Mulgrave North, Vic. 3170, Australia

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