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REMOVAL OF N-BENZYL-AND N-BENZYLOXYMETHYL SUBSTITUENTS FROM SUBSTITUTED URACILS WITH BORON TRIBROMIDE

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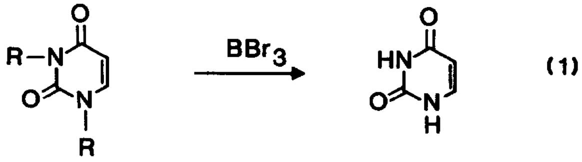
Summary: N_1, N_3-Dibenzyl uracil derivatives have been successfully deblocked by using boron tribromide in refluxing xylene. Also, N_1, N_3-dibenzyloxy methyl uracil derivatives can be easily converted to uracils by treatment with boron tribromide in benzene in the cold and subsequent boiling of the intermediate with water.

In the previous communication[1], we have described a very convenient method for the reduction of the 5,6-double bond of uracil and orotic acid derivatives using L-Selectride. We found, however, that such reduction can only be carried out if the uracil and orotic acid derivatives are protected on the nitrogen atom with methyl, benzyl or, benzyloxy methyl groups. An obvious necessity, then, for the synthesis of 5-substituted 5,6-dihydrouracils or orotic acids or the corresponding 5-substituted uracils and orotic acids derived from them, is the removal of the protecting groups on nitrogen. A survey of literature on the removal of protecting groups revealed that although there are excellent methods [2-12] available for the deprotection of 0-alkyl and 0-benzyl groups, methods for the de-protection of N-alkyl and N-benzyl groups are of limited number.

Catalytic hydrogenation has been used to remove[13] N-benzyl groups but is of limited success[14] with N-benzylated purines and pyrimidines. Particularly, catalytic hydrogenation cannot be used when other reducible groups are present in the molecule[15]. Sodium in liquid ammonia[14,16] and sodium naphthalene[17] have also been used for deblocking N-benzyl derivatives, but suffer from the limitation of being basic reagents that will lead to undesirable elimination reactions in cases of 5-halogen-substituted-5,6-dihydrouracil derivatives[18].

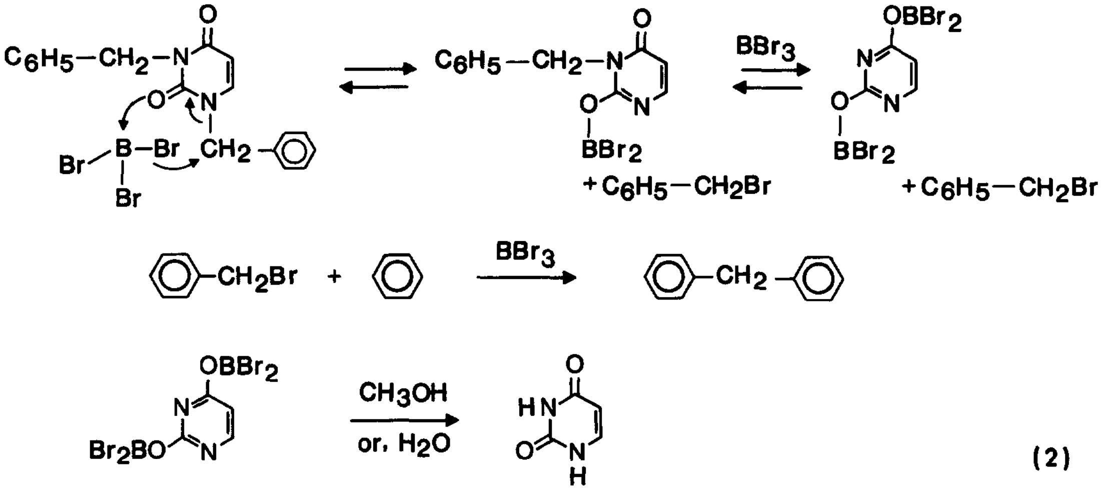
We have, thus, been forced to study other reagents for the debenzylation of N-benzyl derivatives, and have found boron tribromide to be an effective reagent for the removal of N-benzyl derivatives under certain conditions. Boron tribromide[19,20] has been used with success for dealkylation of O-alkyl derivatives. Table I lists the type of N-benzyl compounds that we so far have been able to debenzylate according to reaction scheme (1)



(1)

R=CH_2Ph or, CH_2-O-CH_2Ph

It was observed that complete debenzylation does not take place in dichloromethane or ethylenedichloride as solvents. The use of aromatic solvents, particularly xylenes, gives a much better yield of deblocked compounds. We postulate that debenzylation takes place through the following mechanism (Scheme 2) -



(2)

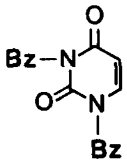
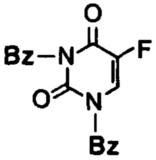
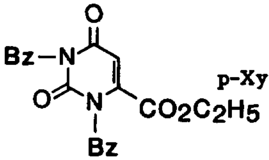
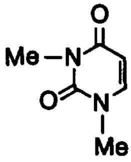
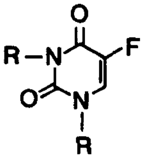
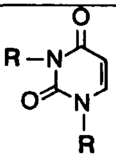
Benzyl bromide formed during the reaction can undergo a Friedel-Crafts reaction with the aromatic solvent used. This was substantiated with the isolation of diphenylmethane[25] in the reaction shown in Scheme 2, where benzene was used as solvent. This furthermore assures irreversibility of the deprotecting step. When N_1,N_3-dimethyluracil was used as starting material, demethylation was found to be much more sluggish than debenzylation, which supports our reaction mechanism. When the benzyloxy methyl group[22,23] is used as a blocking group instead of benzyl, it can be deblocked under much milder conditions. Typical experimental procedures for deblocking are as follows:

Boron tribromide (5 mmole) was added to N_1,N_3 dibenzyluracil (1 mmole) in xylenes (20 ml). The mixture was refluxed for 19 hr, cooled, methanol (5 ml) was added, and the mixture stirred at room temperature for 30 min. Solvents were distilled at 60-65°, and the mixture on cooling yielded a white precipitate, which was filtered, washed with ether and dried. The product was crystallized from H_2O to give pure uracil, identical with an authentic sample by TLC, NMR and mmp comparisons.

A mixture of N_1,N_3-dibenzyloxymethyl-5-fluorouracil (1 mmole) in benzene (10 ml) and boron tribromide (0.4 ml, 4 mmole) was stirred at room temperature for 1 hr. MeOH (1 ml) was added, stirred for 1/2 hr and the MeOH and low boiling fractions were removed under vacuum. The residue was boiled with H_2O (40 ml) for 30 min. Water was removed under vacuum and the product was crystallized from H_2O to give pure 5-fluorouracil identical with an authentic sample.

The above methods of deblocking N-benzyl or, N-benzyloxy methyl derivatives will prove valuable in cases where catalytic hydrogenation or alkaline methods cannot be used.

TABLE I: DEBLOCKING WITH BORON TRIBROMIDE

Starting Materials[21,23]	Solvents	Temp., °C	Reaction Time	Products[24] and Yield
	CH_2Cl_2	40	3 days	Uracil, 20% Monobenzyl uracils, 40%
	$ClCH_2CH_2Cl$	80	3 days	Uracil, 30% Monobenzyl uracils, 40%
	Mixed Xylenes	138	19 hr	Uracil, 80%
	Benzene	80	1 day	Uracil,50% Monobenzyl uracils, 20%
	Mixed Xylenes	138	1 day	5-Fluorouracil, 80%
	p-Xylene	138	6 hr	Orotic acid, 50%
	Mixed Xylenes	138	1 day	No uracil Mixture of starting material and monomethyl uracils
	Benzene	Room Temp. and subsequent boiling with H_2O	1 hr	5-Fluorouracil, 60%
 R = CH_2—O—$CH_2C_6H_5$	Benzene	Room Temp. and subsequent boiling with H_2O	1 hr	Uracil, 55%

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23. 1,3-Dibenzyloxymethyl uracil and the corresponding 5-fluoro derivative have been first synthesized by Drs. Walter Wolf and A. Ghanbarpour, School of Pharmacy, University of Southern California, Los Angeles, California (Manuscript in press). We are grateful to them for suggesting the use of this blocking group and informing us of their methodology.
24. Products were identified by comparing with authentic samples by mp, mmp, NMR and TLC studies.
25. Formation of diphenyl methane was proved by NMR and mass spectral data.

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