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New Applications of the Protecting Group Di-(4-methoxyphenyl)methyl: *N*-Protection of Urethanes and Uridines, and Efficient Removal by either Ceric Ammonium Nitrate/Silica or 2,3-Dichloro-5,6-Dicyanoquinone

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Abstract: *The protecting group di-(4-methoxyphenyl)methyl, removable by ceric ammonium nitrate on silica or 2,3-dichloro-5,6-dicyanoquinone, is shown to facilitate syntheses of urethanes (eg vinyl urethane, 1a) and uridine derivatives (eg 2-O-allyluridine, 8).*

There have been sporadic reports of di-(4-methoxyphenyl)methyl ('dimethoxybenzhydryl', DMB) as an *N*-protecting group for amino acids,[1,2] allylic amines[3] and a β-lactam.[4] The DMB group was removed under rather harsh acidic conditions (trifluoroacetic acid/anisole;[2] 88% formic acid at 80 °C,[3] ceric ammonium nitrate in aqueous acetonitrile[4]). For the synthesis of vinyl urethane **1a**, eventually isotopically labelled (*eg* with deuterium) and for preparing 2- and 3-*O*-substututed derivatives of uridine, we required an *N*-protecting group (N^3 in uridine derivatives) that could be removed under conditions that would not affect the double bond of **1a** and the base-sugar bond of uridine derivatives. We have found that DMB is suitable for these applications because it can be removed chemoselectively either by ceric ammonium nitrate/silica [Ce(IV)/silica (see ref 5 for the preparation of the reagent) stirred in dichloromethane for *N*-dimethoxydiphenylmethyl urethanes or uridines] or 2,3-dichloro-5,6-dicyanoquinone (DDQ) in wet dichloromethane (for some urethane derivatives). The oxidative method for removal of DMB is analogous to the uses of Ce(IV) and DDQ for cleavage of 4-methoxybenzyl ethers

$ROCONH_2$	**(1a)**	$R = CH_2{=}CH$	**(1b)**	$R = PhCH_2$
	(1c)	$R = n\text{-}C_8H_{17}$	**(1d)**	$R = PhSeCH_2CH_2$
ROCONHDMB	**(2a)-(2d)**	R as in **(1a)-(1d)**		

[DMB = di-(4-Methoxyphenyl)methyl]

N-PROTECTION OF URETHANES

Vinyl urethane **1a** is believed to be an intermediate in the metabolism of ethyl carbamate.[7,8] To explore mechanistic aspects of this metabolic pathway we required a convenient laboratory synthesis of **1a**, both free and in masked form. The possible use of DMB for achieving this aim was demonstrated with benzyl and octyl carbamate (**1b** and **1c**, respectively), which were converted into their *N*-DMB derivatives (**2b** and **2c**, respectively) in over 80% yield by treatment with 4,4′-dimethoxydiphenylmethanol in glacial acetic acid containing sulphuric acid as catalyst.[2] Reaction of **2b** in wet dichloromethane with DDQ[6] gave benzyl carbamate **1c** (71%), whilst stirring **2c** in dichloromethane with Ce(IV)/silica[5] gave octyl carbamate **1b** (74%).

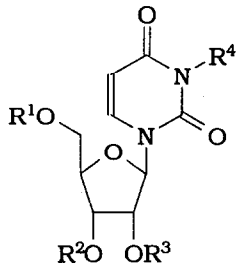
Reaction of the phenylselenyl anion[9] with ethylene oxide[10] gave 2-phenylselenoethanol, which was converted (method of ref 11) into its carbamate **1d** and hence, by the procedure of ref 2, into DMB derivative **2d**. A 0.04 M solution of **2d** in acetonitrile-water (3:1, v/v) was reacted with 4 equiv sodium periodate[10] to give a selenoxide that underwent fragmentation to **1d** on refluxing (1 h) in benzene containing 5 equiv di-isopropylamine (overall yield of **1d**: 68%). Finally, stirring a 0.5 M solution of **1d** in dichloromethane at -10 °C for 4.5 h with 2.1 equiv 20% (w/w) ceric ammonium nitrate on silica gave **1a** [45%, separated from 4,4′-dimethoxyphenylmethanone and unreacted **1d** by a solvent extraction procedure[12]].

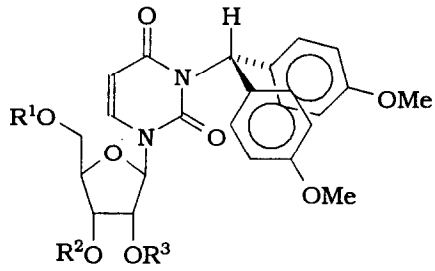
N^3-PROTECTION OF URIDINE

Several protecting groups for uridine NH have been recommended in the context of RNA synthesis, including *p*-anisoyl,[13] *O*-phenyl,[14] 2,2,2-trichloro-*t*-butyloxycarbonyl[15] and methoxyethoxymethyl (MEM).[16] In connection with studies of potential inhibitors of ribonucleotide reductase, we required 2- and 3-*O*-substituted uridines. It is well-known that direct alkylation of uridine gives mixtures of *O*- and *N*-alkyl products (*eg* methylation,[15] benzylation[17]) and we therefore sought a suitable *N*-protecting group to enable subsequent *O*-alkylation to be better controlled. We initially explored allyl, benzyl and 4-methoxybenzyl as *N*/*O*-protecting groups for uridine, but were unable to achieve the selective removal of *N*-protecting groups when required. Thus, calcium/ammonia failed to remove *N*- and *O*-benzyl in **3** in preference to allyl; treatment of **4** with DDQ removed only the *O*-4-methoxybenzyl group; only the *O*-allyl group of **5** was isomerised (by Wilkinson's catalyst [$(PhP)_3RhCl$]: for details of procedure see below).

We have found that chloro-4,4′-dimethoxyphenylmethane[19] (1.1 equiv) alkylates 0.4 M tri-*O*-acetyluridine **6** in tetrahydrofuran containing a suspension of NaH (1 equiv) [reflux 45 h, chromatograph crude product on silica, elution with ether, followed by ether-ethyl acetate (95:5)] to give **7a** (80%, white foam). The derivative **7a** can be cleaved in high yield to **6** either using DDQ in wet CH_2Cl_2 or Ce(IV)/silica/CH_2Cl_2. Exposure of **7a** [0.16 M] to methanol-conc ammonia (4:1, v/v) [room temp, overnight] gave after removal of solvents a quantitative yield of **7b** (colourless syrup), which was converted into its 4,4′-dimethoxytrityl (DMT) derivative **7c** (54%, yellow foam) by the method described.[20] Allylation[21] of **7c** using 1.1 equiv allyl bromide gave a mixture of **7d** (33%) and **7e** (44%, white foam)[separated by chromatography on silica, elution with ether-petrol-triethylamine (70:30:1)], indicating that reaction occurs selectively at the 2-*O* position, presumably because of shielding of the 3-*O* position by the DMT group.[22]

The structure of **7e** was confirmed by a COSY experiment (^1H NMR in d^6-DMSO) that showed that the OH proton (δ 5.34, d, exchanges on addition of D_2O) is coupled to a proton that is *not* coupled to H-1. Compound **7e** is a versatile intermediate, further reactions of which lead to 2- and 3-*O*-substituted uridines. Thus, **7e** could be *t*-butyldimethylsilylated (*t*-butyldimethylsilyl chloride/imidazole/dimethylformamide) to **7f**





(3) $R^1 = R^4 = PhCH_2$ $R^2 = R^3 = CH_2{=}CHCH_2$

(4) $R^1 = R^4 = 4\text{-}MeOC_6H_4CH_2$ $R^2R^3 = Me_2C$

(5) $R^1 = R^4 = CH_2{=}CHCH_2$ $R^2 = R^3 = H$

(6) $R^1 = R^2 = R^3 = MeCO$ $R^4 = H$

(8) $R^1 = R^2 = R^4 = H$ $R^3 = CH_2{=}CHCH_2$

(9) $R^1 = R^3 = R^4 = H$ $R^2 = CH_2{=}CHCH_2$

(7a) $R^1 = R^2 = R^3 = MeCO$

(7b) $R^1 = R^2 = R^3 = H$

(7c) $R^1 = DMT$ $R^2 = R^3 = H$

(7d) $R^1 = DMT$ $R^2 = R^3 = CH_2{=}CHCH_2$

(7e) $R^1 = DMT$ $R^2 = H$ $R^3 = CH_2{=}CHCH_2$

(7f) $R^1 = DMT$ $R^2 = t\text{-}BuMe_2Si$ $R^3 = CH_2{=}CHCH_2$

(7g) $R^1 = H$ $R^2 = t\text{-}BuMe_2Si$ $R^3 = CH_2{=}CHCH_2$

(7h) $R^1 = DMT$ $R^2 = H$ $R^3 = MeCH{=}CH$

(7i) $R^1 = DMT$ $R^2 = CH_2{=}CHCH_2$ $R^3 = MeCH{=}CH$

(7j) $R^1 = H$ $R^2 = CH_2{=}CHCH_2$ $R^3 = MeCH{=}CH$

(82%, white foam), which was selectively deprotected (catalytic 2,6-di-*t*-butyl-4-methylpyridinium borofluorate in methanol[23]) at the 5-*O* to give **7g** (92%, white foam). This was cleaved [0.15 M solution in dichloromethane treated with Ce(IV)/silica (2 equiv, stir 5 h at room temp)] to 2-*O*-allyluridine **8** (92%, white fibrous crystals, mp 165-168 °C). Alternatively, **7e** was isomerised[24] [catalytic 1,4-diazabicyclo[2,2,2]octane and tris(triphenylphosphine)rhodium chloride in ethanol-water (9:1, v/v)] to **7h** (75%, white foam, mixture of *E*- and *Z*-isomers), which was allylated[21] to **7i** (95%, white foam). Removal of the DMT group from **7i** by catalytic 2,6-di-*t*-butyl-4-methylpyridinium borofluorate in methanol[23] afforded **7j** (73%, white foam), which on treatment with Ce(IV)/silica/CH_2Cl_2 gave 3-*O*-allyluridine **9** (76%, white foam).

The intermediates described (with protection at uridine NH and at 2- and 3-OH) should enable phosphorylation reactions to be performed at the 5-OH, without competing side-reactions.

NB All new compounds in this paper were chromatographically homogeneous (TLC) and gave analytical/spectroscopic data (NMR, IR and MS; combustion analyses for crystalline compounds) in accord with their assigned structures.

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