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Tetrabutylammonium bromide: an efficient media for dimethoxytritylation of the 5′-hydroxyl function of nucleosides

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Abstract—An efficient procedure for selective dimethoxytritylation of the 5′-hydroxyl function of nucleosides in the presence of DABCO in molten tetrabutylammonium bromide is described. The methodology is very practical, environmentally benign and produced the desired product in less than 5 min by grinding in a hot mortar. In addition, the effects of the room temperature ionic liquid (1-butyl-3-methylimidazolium chloride) and microwave irradiation on this system were also studied and the results showed that depurination of the nucleosides occurred under microwave irradiation.

Nucleoside derivatives are interesting classes of compounds because they possess important biological activity and have found widespread application in anticancer and antiviral drugs. These applications increase the demand for synthetic oligonucleotides and stimulate organic chemists to introduce efficient and practical methods towards protected ribonucleosides.[1]

Among the various hydroxyl protecting groups, triphenyl (Tr), monomethoxytriphenyl (MMTr) and dimethoxytriphenyl (DMTr) methyl ethers have been widely used for protection of hydroxyl moieties in saccharide and nucleoside chemistry for about 50 years. Their utility is attributed to the high selectivity for protecting primary hydroxyl groups of polyols as well as the ease and mildness in preparing and removing the trityl group. Other less common derivatives of trityl have been used for this purpose.[2]

The classical methods for introducing trityl and their methoxy derivatives to the 5′-hydroxyl function of nucleosides include reaction of the appropriate chlorotriarylmethane with nucleosides in pyridine,[2] which can be speeded up by using a catalytic amount of silver nitrate.[4] Other methods use *N*-tritylpyridinium tetrafluoroborate in acetonitrile,[5] or trityl chloride/dimethylaminopyridine and triethylamine in *N*,*N*-dimethylformamide (DMF),[6] and dimethoxytrityl or monomethoxytrityl tetrafluoroborate in nitromethane.[7] Solid phase tritylation of nucleosides and nucleotides has also been reported.[8]

The major challenging problem in protection and other reactions of nucleosides is the insolubility of these compounds in many organic solvents. Pyridine, DMF and *N*-methylpyrrolidine (NMP) are usually used in nucleoside transformations, however, they are not environmentally friendly solvents.

The use of environmentally benign reaction media is very important in view of today's environmentally conscious attitude. In connection with this, molten salts[9] and room temperature ionic liquids[10] have received a great deal of attention over the past decade as novel solvent systems for organic transformations. More recently the solubility of some deoxynucleosides and their acylation in various ionic liquids has been studied.[11]

Herein, and as an extension of our previous studies on the application of green chemistry principles in organic synthesis,[12] especially for the protection of nucleosides,[13] we wish to report a simple, remarkable fast and selective procedure for dimethoxytritylation of the 5′-hydroxyl function of various nucleosides in molten tetrabutylammonium bromide as homogenizer in the presence of an appropriate acid scavenger. The reaction proceeded very quickly with high yields and gave the desired dimethoxytrityl ethers at >140 °C in less than

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Table 1. The results for dimethoxytritylation of uridine in the presence of different solid bases at 140 °C

Base	Yield (%)
DABCO	84
DMAP[a]	72
Basic alumina	15
K_2CO_3	20
Cs_2CO_3	27

5 min by grinding in a hot mortar. The results are summarized in Table 2.

In order to choose the appropriate base, the reaction of uridine with dimethoxytrityl chloride was carried out in the presence of several solid bases. As shown in Table 1, 1,4-diazabicyclo[2,2,2]octane (DABCO) gave the highest yield and was therefore selected as the base for subsequent reactions. Liquid bases cannot be used, because of evaporation at the high temperature employed.

The effect of temperature in the range of 100–150 °C was investigated. The results showed that a temperature range between 140 and 150 °C gave the best yields. Subsequent studies showed that the presence of tetrabutylammonium bromide was essential for achieving an efficient and fast reaction.

As shown in Table 2, uridine, thymidine and adenosine (entries 1, 4 and 5, respectively), were easily protected using dimethoxytrityl chloride (DMTrCl) in high yields. Trityl chloride (TrCl) and monomethoxytrityl chloride (MMTrCl) have also been used as protecting groups in this reaction (entries 2 and 3, respectively). We found that there were no significant differences on the rate and yields of reaction between these protective groups and dimethoxytrityl chloride. We also tried to protect the 5′-hydroxyl function of guanosine and cytidine using this method but all efforts failed and a mixture of several unidentified products was obtained.

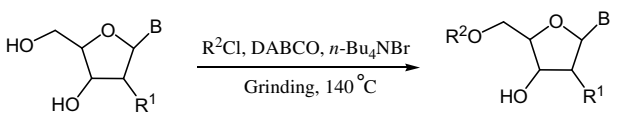
To gain a comparison between the effect of conventional heating and microwave irradiation on this reaction, dimethoxytritylation of uridine in the presence of DABCO and tetrabutylammonium bromide under microwave irradiation was carried out. The corresponding dimethoxytrityl ether was formed after 3 min at 900 W (microwave power) in moderately low yield. Efforts to obtain a higher yield by increasing the irradiation time failed resulting in depurination. To the best of our knowledge, there is no previous report of the depurination of nucleosides under microwave irradiation.

Because of the high relative solubility of the nucleosides in 1-butyl-3-methyl imidazolium chloride (bmimCl),[11] this ionic solvent was applied for the dimethoxytritylation of uridine. On this occasion the reaction took a long time and did not give complete conversion of uridine to 5′-dimethoxytrityluridine even after 6 h at 120 °C. The isolated yield of 5′-dimethoxytrityluridine in this case was less than 35%.

In conclusion, the use of this environmentally friendly reaction system was found to be a very suitable procedure for the preparation of some protected nucleosides. Moreover, this methodology offers significant improvements with regard to yield of the products and simplicity of operation especially purification. We believe that this procedure could be applied as a practical alternative to previously reported methods.

General procedure: Protection of the nucleoside was carried out by grinding the mixture of nucleoside (1.1 mmol), dimethoxytrityl chloride (1 mmol), DABCO (1.3 mmol) and tetrabutylammonium bromide (0.5 g) in a hot mortar for 5 min (the mortar was placed in an oven for 2 h at 140 °C). The reaction mixture was then allowed to cool, dissolved in EtOAc (50 mL) and extracted with 5% $NaHCO_3$. The organic layer was separated and washed with water (2×30 mL), dried over anhydrous Na_2SO_4 and after evaporation of the solvent the product was further purified by column chromatography using ethyl acetate/*n*-hexane (9/1) as the eluent.

Table 2. Selective tritylation of the 5′-hydroxyl group of nucleosides in the presence of DABCO and tetrabutylammonium bromide



Entry	B	R^1	R^2	Yield[a] (%)	Mp (°C)
1	Uracil	OH	DMTr	84	111–112[4]
2	Uracil	OH	Tr	82	105–107[14]
3	Thymine	H	MMTr	85	102–104[3]
4	Thymine	H	DMTr	86	121–123[3]
5	Adenine	OH	DMTr	79	142–144[4]

[a] Isolated pure product.

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14. Spectral data for 5′-trityluridine (Table 1, entry 2), ^{1}H NMR (250 MHz, DMSO-d^6) 10.53 (s, 1H, N3-H, exch. with D_2O), 7.72 (d, J = 8.1 Hz, 1H, H-6), 7.25–7.35 (m, 15H, arom), 5.94 (m, 1H, H-1′), 5.34 (d, J = 8.1 Hz, 1H, H-5), 4.39–4.46 (m, 3H, H-2′, H-3′, H-4′), 4.13 (m, 1H, OH), 4.07 (m, 1H, OH), 3.54 (m, 2H, H-5′); ^{13}C NMR (62.5 MHz, DMSO-d^6) 164.7, 151.2, 143.3, 140.0, 129.1, 128.5, 127.8, 102.1, 90.5, 87.2, 83.6, 75.3, 69.9, 62.8.