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4,4'-Dimethoxytrityl and 4-Monomethoxytrityl Tetrafluoroborate: Convenient Reagents for the Protection of Primary Alcohols Including Sugars

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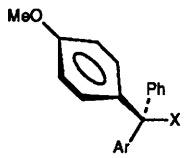
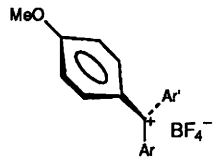
In a non-donor solvent (*e.g.* acetonitrile) and in the presence of 2,6-di-t-butyl-4-methylpyridine, the readily prepared 4-methoxytrityl tetrafluoroborate (**3**) and 4,4'-dimethoxytrityl tetrafluoroborate (**2**) are highly effective reagents for the methoxytritylation and dimethoxytritylation, respectively, of primary alcohols including sugars.

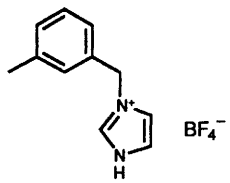
For the preparation of oligonucleotides specifically labelled with ^{15}N we required[1] a highly efficient method for the protection of the 5'-hydroxy group of nucleosides with 4,4'-dimethoxytrityl. The classical method for the introduction of trityl and methoxy-substituted trityl groups employs the appropriate chlorotriarylmethane in pyridine.[2] It has been reported that the rate of dimethoxytritylation is enhanced by the addition of silver nitrate to dimethoxytrityl chloride (**1**) in pyridine–tetrahydrofuran.[3] Others have reported improvements in the rate and selectivity of tritylation by the use of tritylpyridinium tetrafluoroborate in acetonitrile[4] and trityl chloride/4-(dimethylamino)pyridine triethylamine in dimethylformamide.[5]



(**1**) X = Cl, Ar = 4 - $MeOC_6H_4$
(**4**) X = OH, Ar = 4 - $MeOC_6H_4$
(**5**) X = OH, Ar = Ph



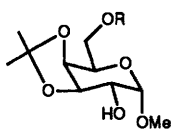
(**2**) Ar = 4 - $MeOC_6H_4$, Ar' = Ph
(**3**) Ar = Ar' = Ph
(**6**) Ar =



Ar' = 4 - $MeOC_6H_4$

We assumed that the rate limiting factor in all tritylations [and (di)methoxytritylations] is the concentration of the triarylmethyl cation, and we therefore investigated the preparation and properties of 4,4'-dimethoxytrityl tetrafluoroborate ($DMTBF_4$) (**2**) and 4-methoxytrityl tetrafluoroborate ($MMTBF_4$) (**3**). We have found that tetrafluoroborate (**2**) can be easily prepared as an analytically pure, air-stable, orange–red crystalline solid by treating 4,4'-dimethoxytrityl alcohol (**4**) with tetrafluoroboric acid in acetic anhydride (*cf.* analogous method for preparing trityl tetrafluoroborate from trityl alcohol[6]). Similarly, the tetrafluoroborate (**3**) has been obtained as a pure, yellow–brown solid from 4-methoxytrityl alcohol (**5**).[7] In a suitable solvent (see below) and in the presence of 2,6-di-t-butyl-4-methylpyridine (DBMP) both tetrafluoroborate (**2**) and (**3**) are excellent reagents for the rapid protection of a wide variety of primary alcohols (NB secondary alcohols react much more slowly and tertiary alcohols do not react at all), including nucleosides and pyranose sugars (see below).

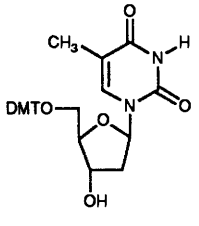
The tetrafluoroborate (**2**) exhibits λ_{max} 411 (log ε 4.46) and 497 nm (log ε 4.87) in acetonitrile. These absorptions are *ca.* 100-fold greater than those observed for 4,4'-dimethoxytrityl chloride (**1**) and suggest that a corresponding rate enhancement for dimethoxytritylation of alcohols will be achieved for (**2**) *versus* (**1**) in acetonitrile. Other non-donor solvents containing the tetrafluoroborate (**2**) which show similar extinction coefficients to (**2**) in acetonitrile are dichloromethane, nitromethane, and 1,1,1,3,3,3-hexafluoropropan-2-ol, whereas the donor solvents dimethylformamide, dimethyl sulphoxide and 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one all co-ordinate strongly to (**2**) and quench its colour.[8] Both triethylamine and Hunig's base (di-isopropylethylamine) co-ordinate to the tetrafluoroborate (**2**) as shown by the progressive loss of the visible absorptions of (**2**) in acetonitrile on titration with these bases. However, the visible spectrum of (**2**) is hardly affected by titration with 1.5 mol equiv. 2,6-di-t-butyl-4-methylpyridine and this base therefore serves as a useful acid scavenger for dimethoxytritylations performed with tetrafluoroborate (**2**). Thus, full exploitation of the electrophilic properties of tetrafluoroborate (**2**) requires both a non-donor solvent and base. The poorly characterised tetrafluoroborate (**6**) has been recently reported[9] to effect blocking of the 5'-hydroxy group of nucleosides under conditions where the corresponding chloride was ineffective. This difference seems surprising because the strong donor solvent dimethylformamide was used for both the tetrafluoroborate and chloride.



(**7**) R = H
(**9**) R = DMT

MeCHOHCH$_2$ODMT

(**8**)



(**10**)

Simple primary alcohols, and diols containing primary and secondary hydroxy groups are readily dimethoxytritylated by the tetrafluoroborate (**2**) in acetonitrile in the presence of 2,6-di-t-butyl-4-methylpyridine. With propane-1,2-diol and α-methoxy-3,4-di-*O*-isopropylidenegalactopyranoside (**7**),[10] selective protection of the primary hydroxy group occurs to

Table.[a] Reactions of the fluoroborates (2) and (3) with alcohols (DMT = 4,4′-dimethoxytrityl, MMT = 4-methoxytrityl).

Alcohol	Fluoroborate	Reaction time	Product	Yield (%)
Butan-1-ol	(2)	20 min	$MeCH_2CH_2CH_2ODMT$	82
Butan-1-ol	(3)	15 min	$MeCH_2CH_2CH_2OMMT$	80
Butan-2-ol	(2)	17 h	$MeCH_2CH(ODMT)Me$	32
Butan-2-ol	(3)	17 h	$MeCH_2CH(OMMT)Me$	27
Propane-1,2-diol	(2)	30 min	(8)	80
Propane-1,2-diol	(3)	3 h	$MeCHOHCH_2OMMT$	82
(7)	(2)	2 h	(9)	98
Thymidine	(2)	75 min	(10)	84

[a] All reactions were performed in acetonitrile with 1.1 mol equiv. fluoroborate (2) or (3) for the butanols, 1 mol equiv. (2) or (3) for propane-1,2-diol, 3 mol equiv. (2) for thymidine. Reactions of thymidine were also performed in nitromethane [→ 93% (10)], 1,1,1,3,3,3-hexafluoropropan-2-ol [→ 53% (10)] and pyridine [→ 51%(10)]. With the exception of the reaction with thymidine in acetonitrile, which was refluxed, all reactions were done at 20 °C. All reactions, except thymidine in pyridine contained 2,6-di-t-butyl-4-methylpyridine (1.1 mol equiv. for the butanols and propane-1,2-diol, 2 mol equiv. for thymidine in hexafluoropropanol, 3 mol equiv. for thymidine in acetonitrile, and 4 mol equiv. for thymidine in nitromethane).

give products (8) and (9), respectively. Dimethoxytritylation of thymidine with the tetrafluoroborate (2) is efficiently accomplished under homogeneous conditions in acetonitrile, 1,1,1,3,3,3-hexafluoropropan-2-ol (HFP), or nitromethane. Similar results to those described with tetrafluoroborate (2) have been obtained with the tetrafluoroborate (3). Both reagents are, therefore, recommended for protecting a variety of primary hydroxy functions, owing to their ease of use and rapidity of action (see Table and illustrative procedures). These protecting groups are readily removed under mild acidic conditions.[2,11]

Experimental: Selected Data

4,4′-Dimethoxytrityl Alcohol.—4,4′-Dimethoxytrityl chloride (3.38 g, 10 mmol) in tetrahydrofuran–0.5M aqueous sodium hydroxide (1:1, v/v; 40 ml) was stirred at room temperature (0.5 h). The mixture was extracted with dichloromethane (80 ml) and the extract dried (Na_2SO_4). The concentrated extract was chromatographed on silica in methanol–dichloromethane (0:10 to 1:9) to yield a clear oil which crystallised and was recrystallised from ether–light petroleum to give 4,4′-dimethoxytrityl alcohol as a white solid (3.18 g, 99%), m.p. 75–77 °C; (lit.,[12] m.p. 76–77 °C); $\delta_H(CCl_4)$ 2.90 (1 H, s, OH), 3.60 (6 H, s, 2 × OCH_3), and 6.45–7.15 (13 H, m, ArH).

4,4′-Dimethoxytrityl Tetrafluoroborate.—4,4′-Dimethoxytrityl alcohol (1.0 g, 3.12 mmol) was dissolved in warm acetic anhydride (6.1 ml, 64 mmol). The solution was allowed to cool and 40% aqueous tetrafluoroboric acid (1.1 ml, 14.6 mmol) added at such a rate that the temperature of the reaction mixture did not rise above 25 °C (over 2 h for this scale of reaction). A dark red solution was formed. Addition of dry ether caused the product to precipitate as deep orange crystals. These were dried *in vacuo* (10 mmHg, 1 h, then 0.02 mmHg, 2 h) to give the title compound (1.16 g, 95%), m.p. 193–196 °C (Found: C, 64.35; H, 5.0. $C_{21}H_{19}BF_4O_2$ requires C, 64.61; H, 4.87%); $\lambda_{max}(CH_3CN)$ 209 (log ε 4.75), 266 (4.07), 411 (4.46), and 497 nm (4.87); $\delta_H(CDCl_3)$ 3.95 (6 H, s, 2 × OCH_3) and 7.05–7.6 (13 H, m, ArH); *m/z* (FAB) 303 ($M^+ - BF_4$, 100%).

(±)-1-O-(4,4′-Dimethoxytrityl)propane-1,2-diol.—Propane-1,2-diol (24.6 μl, 0.34 mmol) was added to a solution of $DMTBF_4$ (131 mg, 0.34 mmol) and DBMP (74 mg, 0.36 mmol) in dry acetonitrile (1 ml). The reaction mixture was stirred under nitrogen at 20 °C (30 min). Evaporation of the acetonitrile left a white solid ($DBMPBF_4$) which was washed with ether (10 ml in 2 ml portions) and filtered off. The combined ether washings were evaporated, and the residue chromatographed on silica in light petroleum–ether–triethylamine (74:25:1) to give the title compound as a colourless oil (101 mg, 80%); δ_H(200 MHz, [$^2H_6$]-DMSO) 1.33 (3 H, d, *J* 7 Hz, CH_3), 2.95 (1 H, dd, *J* 5 and 10 Hz, 1′-H), 3.15 (1 H, dd, *J* 5 and 10 Hz, 1″-H), 3.95 (6 H, s, 2 × OCH_3), 4.05–3.95 (1 H, m, 2-H), 4.90 (1 H, d, *J* 5 Hz, OH exch. D_2O), and 7.15–7.65 (13 H, m, ArH); *m/z* (EI) 378.1852 (M^+, calc. for $C_{24}H_{26}O_4$: 378.1831).

5′-O-(4,4′-Dimethoxytrityl)thymidine.—$DMTBF_4$ (0.9 g, 2.33 mmol), and DBMP (0.485 g, 2.37 mmol) was added to a stirred suspension of thymidine (143 mg, 0.59 mmol) in dry nitromethane (5 ml). The mixture was stirred at 20 °C (17 h), after which dissolution was complete and the orange–red colour of the tetrafluoroborate salt had disappeared. The solvent was evaporated under reduced pressure and the residue chromatographed on silica in dichloromethane–methanol–triethylamine (99:0:1 to 94:5:1) to give the title compound as a white solid (299 mg, 93%), m.p. 119–122 °C (from ethyl acetate–light petroleum, lit.,[13] m.p. 123–124 °C); δ_H([$^2H_6$]-DMSO) 1.53 (3 H, s, CH_3), 3.26 (2 H, m, 2′-H, 2″-H), 3.46 (2 H, m, 5′-H, 5″-H), 3.82 (6 H, s, 2 × OCH_3), 3.97 (1 H, m, 3′-H), 5.47 (1 H, d, *J* 6 Hz, OH exch. D_2O), 6.30 (1 H, t, *J* 5 Hz, 1′-H), 6.96–7.50 (13 H, m, ArH), 7.60 (1 H, s, 6-H), 11.45 (1 H, s, NH exch. D_2O); *m/z* (FAB) 544 (M^+, 24%) and 303 (DMT^+, 100%).

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