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Synthesis and reactivity of novel trityl-type protecting groups

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Abstract: Trityl-type new protecting groups were easily prepared from the reaction of 1-bromonaphthalene or 2-bromonaphthalene and 4-methoxy substituted benzophenones following the Grignard reaction. Aryl-methyl alcohols were transferred to tetrafluoroborate salts using tetrafluoroboric acid. The alcohols also reacted with acetyl chloride to give halides of the protecting groups. The selective protection of amine, sulfur, and hydroxyl groups was obtained by the reaction of the newly synthesized protecting groups (halides and tetrafluoroborate salts). Slightly aqueous acidic conditions were used for deprotection reactions to give alcohols. It can be said that the new protective groups synthesized in this study can be a good alternative to other protecting groups in terms of low solvent use, simple procedures, economic advantages, and environmental protection.

Keywords: Protecting groups; selective protection; kinetic; deprotection.

1. Introduction

In organic synthesis, many of the molecules targeted for synthesis have more than one functional group and these groups can interact with reagents during their synthesis. The most practical method to solve this problem is to protect the relevant functional group by converting it to another group.[1] In the literature, the most protected groups are ketones, aldehydes, amines,[2] alcohols,[3] carboxylic acids, and sulfides.[4] In protective group studies, not only the synthesis of protective groups but also studies on the determination of their kinetics and pKa values have gained importance.[4] These include a limited number of studies on alkylamines and ambident nucleophiles (Scheme 1).[4,5] Methoxy-linked triphenylmethyl protecting groups are used in the selective protection and deprotection for amines and alcohols.[5]

Both hydrogen atoms of the primary amine can be protected with appropriate bis trityl cation created under acidic conditions.[6,7] It is also known that bis trityl cation and di tetrafluoroborate are used together to protect primary anions.[8]

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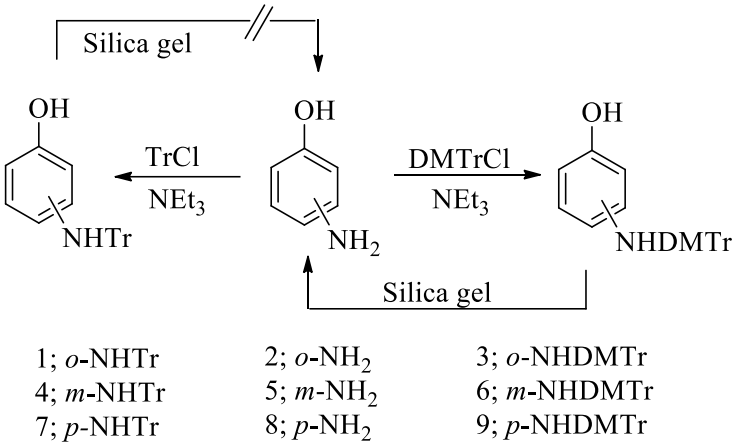


Scheme 1. Selective preservation of aminophenols

In the protection process of N-triethylamines, important results have been obtained in kinetic studies for selective protection when one of the substituted trityl groups contains different structures. Kinetic studies for the protection of substituted N-trityl-N-alkylamines[6] and a detailed mechanistic study for the deamination of 4,4'dimethoxytriethylamines under acidic conditions have been reported.[9] These studies have shown that the substitutes are separated more efficiently and without any problems. S_N1 reactions are common and simple in organic reaction mechanisms. Our previous studies have demonstrated that the separation of trityl amines under acidic conditions occurs by a simple S_N1 reaction (Scheme 1).[6]

In this work, we report the synthesis of novel bulky protecting groups for selective protection and deprotection of amino, hydroxyl and sulfur groups in different nucleophiles. Both the NH-protecting and S-protecting groups were removed for 1-naphthyl-4,4'-dimethoxytrityl alcohol (1-NDMTr) even in silica gel under acidic conditions, however, a mechanical subtlety in the H-induced detritylation pathway made it much easier to remove group 4,4'-dimethoxytrityl (DMTr) from nitrogen compared to the Tr group.

2. Experimental

2.1. Chemical Material and Apparatus

Bromonaphthalene, tetrafluoroboric acid (HBF_4), and 4,4'-dimethoxybenzophenone were purchased from Merck. All solvents (Sigma Aldrich) were dried and distilled by standard procedures. ^{1}H– and ^{13}C– NMR spectra were recorded on a Brucker Advance III instrument (400 MHz). FT–IR spectra were obtained by Jasco FT/IR–430 spectrometer. As internal standards served TMS (δ = 0.00) for ^{1}H NMR and (δ = 0.00) for ^{13}C NMR spectroscopy *J* values are given in Hz.

2.2. Procedure for the Synthesis of Naphthlane-methoxy–phenylmethyl alcohol

To a suspension of Mg (72 mg, 3 mmol) in dry THF (10 mL), a solution of bromonaphthalene (414 mg, 2 mmol) in dry THF (25 mL) was added under Ar, followed by the addition of a small amount of I_2. The solution was heated at reflux (65 °C) for 3 h (dark-brown suspension); then, it was cooled to room temperature. For this suspension, a solution of 4,4'-dimethoxybenzophenone (500 mg, 2 mmol) in dry THF (25 mL) was added over 25 min at room temperature, and the mixture was then refluxed for 3 h at 65 °C. After 15 min, the solution was added slowly to ice water (50 mL), followed by the addition of 30 mL of 1M NH_4Cl. The resulting mixture was extracted with $CHCl_3$ (3x150 mL). The combined organic extracts were washed with water (3x100 mL), and dried over $MgSO_4$ and subsequent evaporation of the solvent (30 °C, 20 mmHg) gave alcohol. After removal of the solvent, the crude product was chromatographed on TLC eluted with hexane/$CHCl_3$ (3:1).

2.3. Procedure for Synthesis of Naphthalene-methoxydiphenylmethyl tetrafluoroborate

A mixture of naphthalene-methoxy–phenylmethyl alcohol (500 mg, 1.4 mmol) in acetic anhydride was added slowly to a solution of tetrafluoroboric acid (HBF_4) (122 mg, 1.4 mmol) in ether (25 ml) at room temperature. The mixture was stirred vigorously at 25 °C for 48 h. To the residue, 50 mL of water was added, and the solution was extracted with $CHCl_3$ (3x100 mL). The organic layer was separated, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated to give - Naphthalene-methoxydiphenylmethyl tetrafluoroborate.

2.4. Syntheses of 5'-O-2-Naphthalene-4-monomethoxydiphenylmethylthymidine

To a stirred solution of 2-naphthalene-4-monomethoxydiphenylmethyl tetrafluoroborate **(6)** (0.50 g, 1.22 mmol) in 25 ml $CHCl_3$ the solution of thymidine (0.30 g, 1.22 mmol) in 5 ml of $CHCl_3$ was added at 25 °C. To this suspension, a solution of pyridine (2 ml) in dry $CHCl_3$ was then added. The mixture was stirred for 72 h at room temperature. Crude product was purified by column chromatography on silica gel or preparative thin-layer chromatography (TLC) (20x20 cm plates, 2 mm thick) using *n*-hexane / $CHCl_3$ (1:1) as eluent.

*2-naphthlane-4,4'-dimethoxy diphenylmethyl alcohol (**1**)*: Yield: 70%; white crystals; Mp 130-131 °C; ν_{max} (KBr): 3477, 3056, 3001, 2932, 2835, 1608, 1508, 1298, 1250, 1177, 1034, 815, 732 cm^{-1}; δ_H (300 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.7 Hz, 1H), 7.81 (dd, *J* = 15, 8.2 Hz, 2H), 7.40-7.35 (m, 1H), 7.29-7.23 (m, 2H), 7.19-7.16 (m, 4H), 6.90-6.65 (m, 5H), 3.78 (s, 6H, 2xOCH_3), 3.27 (s, 1H, OH); δ_C (75 MHz, $CDCl_3$): δ = 158.70, 144.68, 139.27, 132.79, 132.45, 129.27, 128.44, 127.60, 127.49, 126.37, 126.27, 126.11, 113.69, 81.61, 55.29. Anal. Cald for $C_{25}H_{22}O_3$: C, 81.16; H, 5.89; Found: C, 80.81; H, 5.91.

*2-naphthalene-4,4'-dimethoxydiphenylmethyl tetrafluoroborate (**2**)*: Yield: 90%; red crystals; Mp 158-160 °C. ν_{max} (KBr): 3103, 3060, 2951, 2850, 1579, 1502, 1463, 1377, 1277, 1164, 1056, 920, 851, 764 cm^{-1}; δ_H (300 MHz, $CDCl_3$): δ = 8.06-7.96 (m, 4H), 7.81-7.76 (m, 1H), 7.61-7.62 (m, 5H), 7.47-7.44 (m, 1H), 7.34-7.32 (m, 4H), 4.12 (s, 6H, 2xOCH_3); δ_C (75 MHz, $CDCl_3$): δ = 193.92, 172.09, 144.35, 142.58, 137.30, 136.65, 132.63, 132.42, 132.11, 131.32, 131.04, 129.24, 128.45, 128.09, 117.40, 57.70. Anal. Cald for $C_{25}H_{21}BF_4O_2$: C, 68.23; H, 4.81; Found: C, 68.13; H, 4.81.

*1-naphthlane-4,4'-dimethoxy diphenylmethyl alcohol (**3**)*: Yield: 68%; white crystals; Mp 150-152 °C. ν_{max} (KBr): 3496, 3047, 3001, 2954, 2835, 1607, 1506, 1463, 1296, 1244, 1174, 1030, 905, 829, 802, 773, 726 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ = 8.13 (d, *J* = 9 Hz, 1H), 7.84 (dd, *J* = 15, 8.2 Hz, 2H), 7.40-7.35 (m, 1H), 7.29-7.23 (m, 2H), 7.20-7.18 (m, 4H), 6.90-6.88 (m, 1H), 6.84-6.81 (m, 4H), 3.77 (s, 6H, 2xOCH_3), 3.34 (s, 1H, OH); δ_C (75 MHz, $CDCl_3$): δ = 158.49, 142.50, 139.55, 134.89, 131.35, 129.15, 128.91, 128.72, 128.16, 127.94, 125.42, 125.20, 124.20, 113.22, 82.76, 55.16. Anal. Cald for $C_{25}H_{22}O_3$: C, 81.10; H, 5.92; Found: C, 81.18; H, 6.03.

*1-naphthalene-4,4'-dimethoxydiphenylmethyl tetrafluoroborate (**4**)*: Yield: 94%; red crystals; Mp 178-180 °C. ν_{max} (KBr): 3103, 2951, 2852, 1606, 1578, 1458, 1372, 1278, 1161, 1059, 913, 852, 782 cm^{-1}; δ_H (300 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 8.2 Hz, 2H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.54-7.49 (m, 6H), 7.42-7.32 (m, 2H), 7.25-7.22 (m, 4H), 4.08 (s, 6H, 2xOCH_3); δ_C (75 MHz, $CDCl_3$): δ = 192.56, 172.71, 143.78, 137.83, 137.33, 137.24, 134.05, 133.61, 133.48, 129.04, 128.88, 127.51, 125.63, 125.03, 117.57, 57.50. Anal. Cald for $C_{25}H_{21}BF_4O_2$: C, 68.23; H, 4.84; Found: C, 68.14; H, 4.71.

*2-naphthlane-4-monomethoxy diphenylmethyl alcohol (**5**)*: Yield: 72%; white crystals; Mp 163-165 °C. ν_{max} (KBr): 3475, 3057, 2958, 2933, 2835, 1607, 1508, 1251, 1179, 1034, 819, 749, 702 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ = 7.86-7.76 (m, 4H, H-4″, 5″, 6″, 7″), 7.52-7.48 (m, 3H, H-8″ 2″ , 3″), 7.39-7.26 (m, 7H, H-2, 3, 4, 5, 6, 2′, 6′), 6.89-6.86 (m, 2H, H-3', 5'), 3.81 (s, 3H, OCH_3), 3.06 (s, 1H, OH); δ_C (75 MHz, $CDCl_3$): δ = 159.28 (C4′), 147.59 (C1′), 145.153 (C1), 139.71 (C1″), 133.39 (C9″), 133.08 (C10″), 130.00 (C3, 5), 129.05 (C2, C6), 128.62, 128.56, 128.22, 128.09, 127.84, 127.09, 127.06, 126.75, 126.71, 113.90, 82.51, 55.77. $C_{24}H_{20}O_2$: C, 84.61; H, 5.98; Found: C, 84.71; H, 5.85.

*2-naphthalene-4-monomethoxydiphenylmethyl tetrafluoroborate (**6**)*: Yield: 92%; red crystals; Mp 185-186 ºC. ν_{max} (KBr): 3060, 2978, 1601, 1584, 1462, 1381, 1300, 1178, 1063, 852, 756, 702 cm^{-1}; δ_H (300 MHz, $CDCl_3$): δ = 8.09-8.021 (m, 3H), 7.98-7.93 (m, 2H), 7.81-7.62 (m, 6H), 7.47-7.41 (m, 5H), 4.19 (s, 3H, OCH_3); δ_C (75 MHz, $CDCl_3$): δ = 197.42, 175.67, 144.74, 141.41, 139.17, 138.66 138.38, 137.81, 136.70, 133.39, 133.05, 132.32, 131.63, 131.47, 129.60, 129.53, 128.51, 128.05, 118.69, 58.33. Anal. Cald for $C_{24}H_{19}BF_4O$: C, 70.25; H, 4.697; Found: C, 70.21; H, 4.59.

*1-naphthlane-4-monomethoxy diphenylmethyl alcohol (**7**)*: Yield: 65%; white crystals; Mp 149-151 ºC. ν_{max} (KBr): 3473, 3055, 2956, 2933, 2835, 1607, 1509, 1249, 1178, 1033, 801, 779, 748 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ = 8.07 (d, *J* = 8.7 Hz, 1H, H-8″), 7.82-7.74 (m, 2H, H-4″, 5″), 7.39-7.34 (m, 2H, H- 6″, 7″), 7.29-7.14 (m, 9H, H-2, 3, 4, 5, 6, 2′, 6′, 2′, 3″), 6.86-6.78 (m, 2H, H- 3′, 5′), 3.78 (s, 3H, OCH_3), 3.20 (s, 1H, OH); δ_C (75 MHz, $CDCl_3$): δ = 158.97 (C4′), 147.73 (C1′), 142.86 (C1), 139.72 (C1″), 135.38 (C9″), 132.91 (C10″), 129.644, 129.41, 129.18, 128.59, 128.44, 128.34, 128.13, 127.44, 125.88, 125.64, 124.57, 113.67 (C3′, C5′), 83.36 (C-OH), 55.40. $C_{24}H_{20}O_2$: C, 84.61; H, 5.95; Found: C, 84.69; H, 5.94.

*1-naphthalene-4-monomethoxydiphenylmethyl tetrafluoroborate (**8**)*: Yield: 96%; red crystals; Mp 173-175 ºC. ν_{max} (KBr): 3059, 2975, 1601, 1582, 1508, 1450, 1303, 1253, 1066, 1029, 803, 781, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 7.8 Hz, 1H), 7.99-7.97 (m, 2H), 7.89 (m, 1H), 7.73-7.68 (m, 1H), 7.65-7.61 (m, 3H), 7.54-7.45 (m, 5H), 7.36-7.31 (m, 1H), 7.24-7.20 (m, 2H), 4.22 (s, 3H, OCH_3); δ_C (75 MHz, $CDCl_3$): δ = 196.34, 177.27, 147.76, 146.83, 140.20, 140.11, 138.93, 138.74, 137.82, 134.66, 134.09, 133.76, 130.05, 129.29, 127.77, 125.93, 125.30, 119.26, 119.12, 58.78. Anal. Cald for $C_{24}H_{19}BF_4O$: C, 70.27; H, 4.67; Found: C, 70.24; H, 4.78.

*1-(chlorobis(4-methoxyphenyl)methyl)naphthalene (**9**)*: Yield: 82%; white crstall; Mp 163-164 ºC, ν_{max} (KBr): 3048, 3001, 2952, 1607, 1579, 1508, 1462, 1297, 1251, 1178, 1033, 835, 804, 783, 737 cm^{-1}; δ_H (300 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.7 Hz, 1H), 7.85-7.77 (m, 2H), 7.43-7.38 (m, 1H), 7.26-7.17 (m, 6H), 6.85-6.74 (m, 5H), 3.81 (s, 6H, 2xOCH_3); δ_C (75 MHz, $CDCl_3$): δ = 160.46, 143.93, 140.34, 137.02, 134.69, 132.46, 130.81, 129.71, 128.79, 128.72, 128.64, 125.57, 125.05, 113.57, 77.42, 55.52. Anal. Cald for $C_{25}H_{21}ClO_2$: C, 77.21; H, 5.44; Found: C, 77.30; H, 5.39.

*1-(chloro(4-methoxyphenyl)(phenyl)methyl)naphthalene (**10**)*: Yield: 85%; white cryslall; Mp 136-139 ºC, ν_{max} (KBr): 3054, 2945, 2833, 1617, 1509, 1444, 1293, 1256, 1184, 1035, 814, 735 cm^{-1}; δ_H (300 MHz, $CDCl_3$): δ = 8.16-8.13 (d, *J* = 8.7 Hz, 1H), 7.85-7.80 (t, *J* = 6.0 Hz, 2H), 7.43-7.38 (m, 1H), 7.34-7.25 (m, 6H), 7.22-7.20 (m, 3H), 6.84-6.81 (m, 2H), 6.77-6.75 (m, 1H), 3.81 (s, 3H, OCH_3); δ_C (75 MHz, $CDCl_3$): δ = 160.00, 143.97, 137.20, 134.77, 132.03, 131.12, 130.59, 130.92, 129.43, 128.95, 128.75, 128.72, 128.66, 127.99, 125.52, 123.99, 113.43, 80.88, 55.44. Anal. Cald for $C_{24}H_{19}ClO$: C, 80.33; H, 5.34; Found: C, 80.43; H, 5.24.

*O-5'-(2-naphthalene-4-monomethoxydiphenylmethyl)thymidine (**11**)*: Yield 45%; pale yellow crystall; Mp 192-195 ºC, ν_{max} (KBr): 3251, 3051, 2948, 2833, 2716, 1740, 1705, 1502, 1453, 1323, 1223, 1105, 821, 734 cm^{-1}; δ_H (400 MHz, $CDCl_3$): δ = 9.25 (s, CO–NH–CO, 1H), δ = 7.92 (s, 1H), δ = 7.77-7.71 (m, 3H), 7.61-7.59 (m, 1H), 7.46-7.40 (m, 5H), 7.34-7.20 (m, 7H), 6.85-6.82 (m, 2H), 6.45-6.40 (m, 1H), 4.59-4.58 (m, 1H), 4.09-4.07 (m, 1H), 3.76 (s, 3H, OCH_3), 3.50-3.38 (m, 2H), 2.97 (s, 1H), 2.47-2.27 (m, 2H), 1.39 (s, 3H, -CH_3); δ_C (75 MHz, $CDCl_3$): δ = 164.09, 159.32, 150.69, 144.18, 141.51, 137.07, 135.99, 135.23, 133.18, 132.79, 128.79, 128.64, 128.51, 128.16, 127.86, 127.48, 126.99, 126.84, 126.74, 113.80, 111.64, 87.77, 86.46, 85.14, 76.99, 72.84, 64.26, 55.68, 41.40, 12.19. Anal. Cald for $C_{34}H_{34}N_2O_6$: C, 72.07; H, 6.04; Found: C, 71.92; H, 6.12.

3. Results and Discussion

There are studies on the synthesis of various trityl derivatives in the literature.[10] In this study, we focused on the synthesis of new protecting groups with higher reactivity towards alcohols, amines, and thiols as selective protection. The newly synthesized protecting groups were characterized by spectroscopic methods (^{1}H–, ^{13}C– NMR, FT–IR and Elemental analysis). In addition, 1-NDMTrOH was

obtained with a crystalline compound and characterized by crystallography (Figure 1). The new protecting groups have been used for the selective protection of alcohols, amines, and thiols.

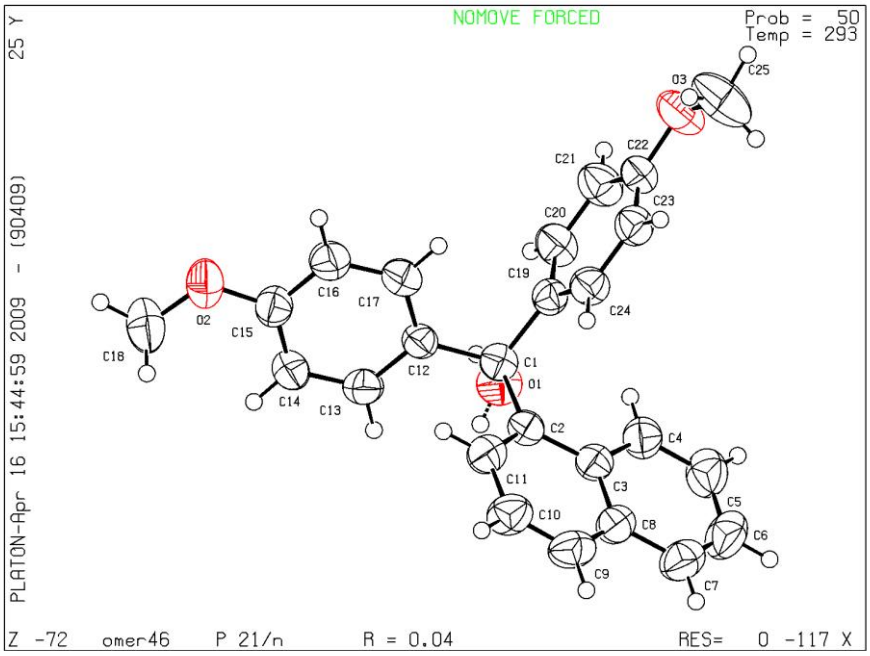
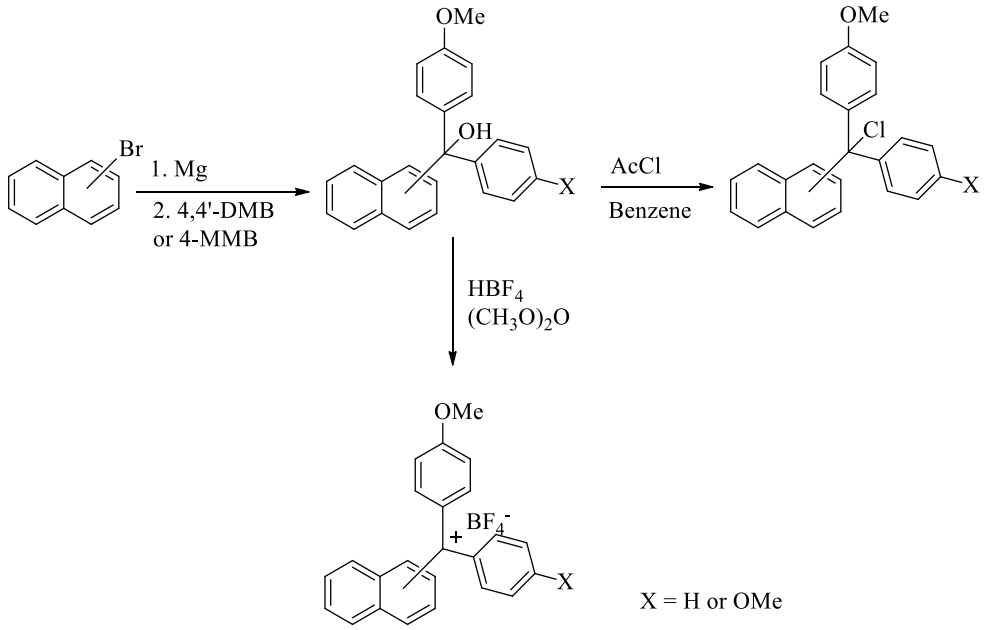


Figure 1. Molecular structure of 1-NDMTrOH showing the atom numbering scheme (40% thermal ellipsoids).

Paramethoxytriphenylmethyl was used as the protecting group. To make the reaction selective, naphthalene, a bulkier group, was replaced with one of the phenyl rings of triphenylmethyl chloride. The selective protection methods were investigated in compounds with –OH, –S and $–NH_2$ groups of the new protective group obtained. In amphoteric compounds containing hydroxyl and amine groups, it has been observed that the $–NH_2$ group is primarily protected because it is more effective than the –OH group in terms of nucleophilic properties. The $–NH_2$ group is protected before one mole of protector and one mole of amphoteric reactant react as in this selective protection method. The $–NH_2$ group is protected by the newly synthesized group to selectively protect and easily remove it. Then, the molecule was purified on silica gel by protecting it with triphenylmethyl chloride, which is difficult to remove, with the –OH group. The molecule, which was easily removed during purification, was separated, and thus the –OH group with lower nucleophilic strength was preserved.

We investigated an alternative procedure for selective protection using 4,4'-dimethoxy-trityl and unsubstituted trityl groups (Scheme 1). This method was considered superior to the previously used method in that it could be carried out under trityl or methoxy-substituted trityl groups. The procedure was first investigated using 4,4',4"-trimethoxytrityl alcohol (TMTrOH) and trityl alcohol (TrOH), which gave 99% and 60% yields of tetrafluoroborates of (substituted) trityl cations, respectively. Naphthyldiphenylmethyl alcohol was also subjected to the same procedure.

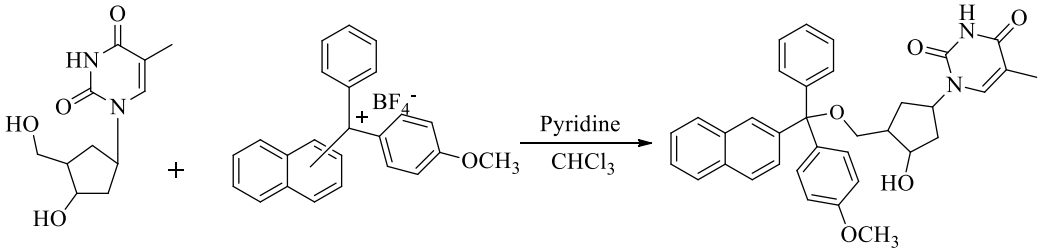
A dark brown color was observed upon the addition of HBF_4, which was identified as tetrafluoroborate salts as stable cations by ^1H– and ^{13}C– NMR spectra with careful spectroscopic identification. The halides were obtained by the reaction of alcohols and acetyl chloride. The total yield of tetrafluoroborate salts and halides were about 95% and 85%, respectively. The protecting groups were synthesized as halides (chloride) and salts (tetrafluoroborate) in relatively high yields as shown in Scheme 2.



Scheme 2. Synthesis of protecting groups

3.1. Protection of Thymidine with 2-Naphthalene-4-monomethoxydiphenylmethyl tetrafluoroborate (2-NMMTrBF4)

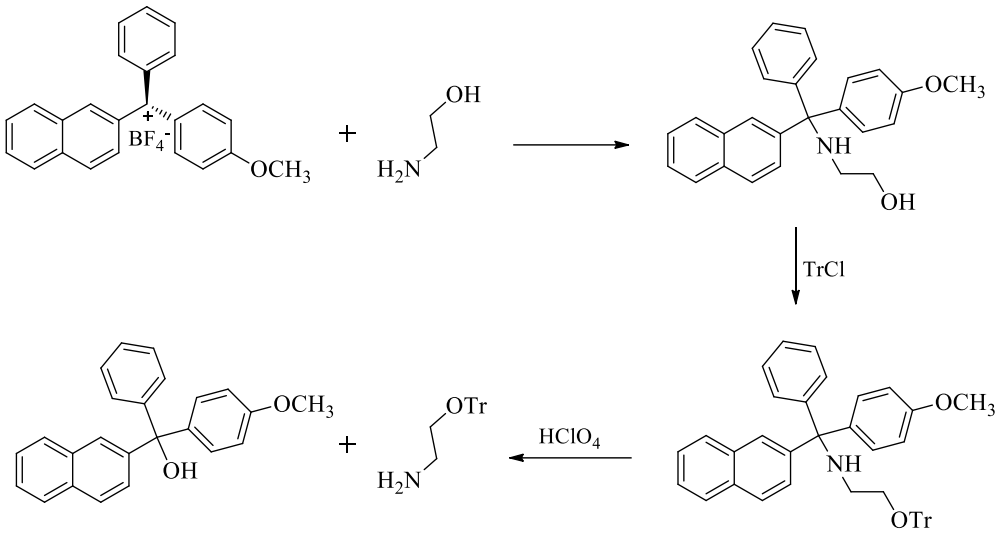
Protection of 5'-hydroxyl thymidine was achieved by reacting newly synthesized 2-NMMTrBF$_4$ with thymidine as shown in Scheme 3. The yield of the title compound is 45%. The identity of the product was confirmed by comparing the ^{1}H– and ^{13}C– NMR spectra with the spectra of the reactants (thymidine and 2-NMMTr).



Scheme 3. Protection of Thymidine with 2-naphthalene-4-monomethoxydiphenylmethyl tetrafluoroborate (2-NMMTrBF$_4$) (**6**)

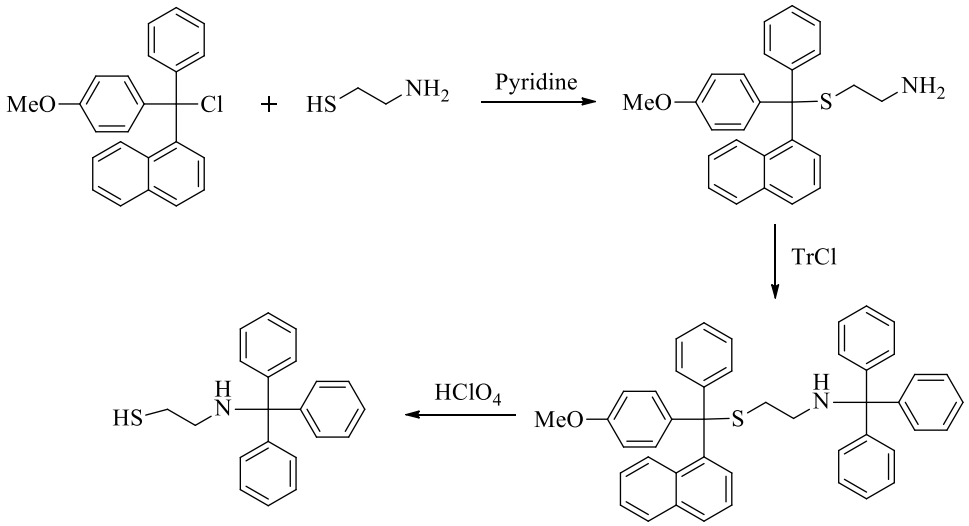
3.2. Selective Protection of Hydroxyl with 2-NMMTrBF4

The tetrafluoroborate salt of 2-NMMTr was reacted with ethanolamine according to the procedure in the literature to give N-2-NMMTr-ethanolamine.[6] The 2-ethanolamine was treated with TrCl and, to protect hydroxyl group and 2-NMMTr, it was decomposed with aqueous perchloric acid to give O-Tr-2-ethanolamine (Scheme 4).



Scheme 4. Selective protection of hydroxyl with 2-NMMTrBF$_4$

The N-protected thioethanolamine was synthesized by the reaction of 1-NMMTrCl with thioethanolamine (Scheme 5). The FT–IR, elemental analysis, ^{1}H– and ^{13}C– NMR of N-Tr-thioethanolamine were in complete agreement with the proposed structure.



Scheme 5. The reaction of 1-NMMTrCl with thioethanolamine

According to our literature search, it was determined that the main compounds synthesized and other compounds in which *p*-methoxy-substituted trityl protecting groups were first synthesized were also known. It seems possible to make many applications related to the compounds synthesized in this study. Simple trityl chlorides, NMMTrCl, NDMTrCl, and tetrafluoroborate salts were synthesized with higher efficiency by adding a single trityl group to nitrogen and sulfide which are the most commonly used ambident nucleophile. The fact that the obtained compounds have extremely high protective properties, that they show specific properties to many compounds, and are obtained at temperatures lower than room temperature makes this study important. It is possible to obtain trityl groups to be used as protectors simply and easily. However, they cannot be easily removed from the medium after the reaction is over. For this, stronger acidic conditions are required. Since they are prepared with appropriate tetrafluoroborates, the p-methoxy-linked groups used in this study may be easily removed in very moderate conditions. Furthermore, in this study, it was seen that the removal of trityl groups containing nitrogen groups requires stronger acidic conditions compared to trityl groups containing sulfide. It can be stated that protective groups reported in this study can be a good alternative to other protective groups in terms of lower solvent use, simple procedures, economic advantages, and

environmental protection properties. The chemical shift values in ^{1}H– NMR spectrums of the protons in the phenyl ring of the synthesized compounds are in concordance with the similar structures in the literature. The peak numbers in the ^{13}C– NMR spectra of the structures coincide with the carbon numbers in the compounds.

3.3. Kinetics

The preliminary kinetic investigation showed that the decomposition of sulfur with 1-NMMTr is not very fast to follow at room temperature. The deprotection reaction with aqueous perchloric acid was obtained in a different time period (Figure 2). The reaction is time-dependent and acid-catalyzed. However, the second substituted methoxy group would be much faster to follow in UV/Vis spectrophotometer. The kinetics of the reaction between tetrafluoroborate salts of protecting groups and methanol was studied using NMR spectroscopy. However, the low-temperature reaction in NMR resulted in equilibrium and was not completed under our conditions.

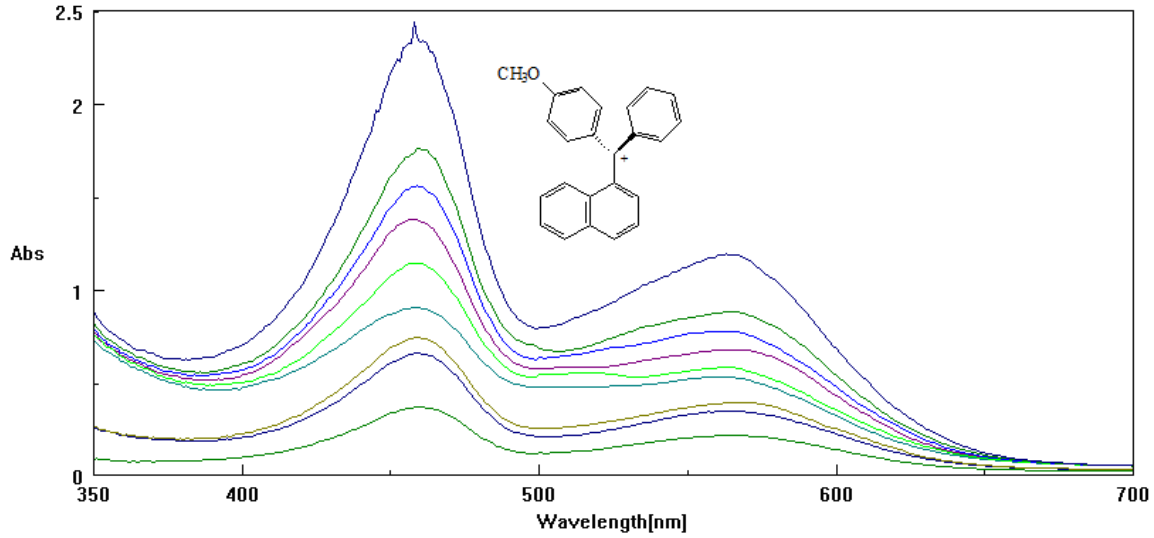


Figure 2. Spectra of the reaction mixture of S-1-NMMTr-2-mercaptoethanol in acid concentrations, ($HClO_4$, 1M) at a different time to give 1-NMMTr^{+}

4. Conclusion

In this study, selective protection of functional groups such as nitrogen, oxygen and sulfur with a bulky and stable protecting group was investigated. The results described in this paper lead us to recommend the wider use of NMMTrCl and NDMTrCl (preferably, NMMTrBF$_4$ and NDMTrBF$_4$) protecting groups for primary and secondary amino and sulfur groups in ambident nucleophiles in the presence of hydroxyl groups. The trityl reacted only with -NH_2 of ethanolamine and -HS of thioethanolamine, and also tetrafluoroborate forms react with ethanolamine and thioethanolamine, then hydrolyze with $HClO_4$, and pyridine easily, thus the study is a useful and stereoselective method. As a result, the new protecting groups can be used for good protection and easy deprotection. These groups are not only easily removable from protected atoms but are also selective.

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References

[1] Kocienski, P. J. Protecting Groups. Ed. Georg Thieme Verlag: Stuttgart-New York, **2004**.
[2] Canle, M.L.; Clegg, W.; Demirtaş, I.; Elsegood, M.R.J.; Maskill, H. Preparations, X-ray crystal structure determinations, and base strength measurements of substituted tritylamines. *J. Chem. Soc. Perkin Trans.* **2000**, *1*, 85-92.
[3] Agarwal, K.L.; Yamazaki, A.; Cashion, P.J.; Khorana, H.G. Chemical synthesis of polynucleotides. *Angew. Chem., Int. Ed. Engl.*, **1972**, *11*, 451-459.
[4] Demirtaş, I.; Buyukkidan, B.; Elmastas, M. The selective protection and deprotection of ambident nucleophiles with parent and substituted triarylmethyls. *Turk. J. Chem.* **2002,** *26*, 889-896.
[5] Canle, M.L.; Clegg, W.; Demirtaş, I.; Elsegood, M.R.J.; Haider, J.; Maskill, H.; Miatt, P.C. N-Tritylhydroxylamines: preparations, structures, base strength and reactions with nitrous acid and perchloric acid. *J. Chem. Soc., Perkin Trans.* **2001**, *2*, 1742-1747. 2001
[6] Canle, M.L.; Martinez, J.C.; Demirtaş, I.; Maskill, H.; Stix, E. Substituent effect in deamination reactions of triarylmethylamines. *Organic React.* **1997**, *31*, 71-77.
[7] Henderson, A.P.; Riseborough, J.; Bleasdale, C.; Clegg, W.; Elsegood, M.R.J.; Golding, B.T. 4',4'-dimethoxytrityl and 4,4',4''-trimethoxytrityl as protecting groups for amino functions; selectivity for primary amino groups and application in 15N-labelling. *J. Chem. Soc., Perkin Trans.* **1997**, *1*, 3407-3413.
[8] Carey, K.A.; Clegg, W.; Elsegood, M.R.J.; Golding, B.T.; Stuart, M.N.; Maskill, H. Synthesis of highly hindered oxepins and an azepine from bis-trityl carbenium ions: structural characterization by NMR and X-ray crystallography. *J. Chem. Soc., Perkin Trans.* **2002**, *1*, 2673-2679.
[9] Lopez, M.C.; Demirtas, I.; Maskill, H.; Mishima, M. Acid-catalysed hydrolysis of methoxy-substituted trityl trifluoroethyl ethers: a kinetic and computational investigation of leaving group effects. *J. Phys. Org. Chem*. **2008**, *21*, 614-621.
[10] Verkade, P.E.; Nijon, H.; Tollenaar, F.D.; van Rij, J.H.; van Leeuwen, M. Trityl derivatives of amines: I. N-trityl derivatives of aromatic primary amines. *Recl. Trav. Chim. Pays-Bas.* **1952**, *71*, 1007-1011.