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The Selective Protection and Deprotection of Ambident Nucleophiles with Parent and Substituted Triarylmethyls

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N-triphenylmethyl and N-4,4'-dimethoxytriphenylmethyl of *o*-aminophenol, *m*-aminophenol, and *p*-aminophenol compounds were easily prepared from triphenylmethyl chloride and 4,4'-dimethoxytriphenylmethyl chloride. S-triphenylmethyl-2-mercapto ethanol was also selectively synthesized using the triphenylmethyl chloride and 2-mercapto ethanol. The reactivity of nitrogen and sulfur versus oxygen in the protection reactions was compared. In principle, the protection of aminophenols and 2-mercapto ethanol with triarylmethyls (trityls) may take place on the oxygen. However, in this framework, we discuss the different reactivities of oxygen, nitrogen and sulfur towards triphenylmethyl chloride (TrCl) and 4,4'-dimethoxytriphenylmethyl chloride (DMTrCl) and find that nitrogen and sulfur are more reactive than oxygen.

Key Words: Aminophenols, triphenylmethyl chloride, 4,4'-dimethoxytriphenylmethyl chloride and selective protection.

Introduction

The last few years have seen a tremendous improvement in the methods used to protect hydroxy groups with trityls. However, there is limited work on the selective protection and deprotection of ambident nucleophiles (e.g. amines, alcohols and sulfurs) with trityls and *p*-methoxy substituted trityls[1]. Methoxy-substituted trityl functions have been used as N-protecting groups in pro-drugs, designed to release the amino function selectively in tumor cells because of the purported lower pH of these cells relative to normal cells[2]. The application of 4,4'-dimethoxytrityl to the protection of the 5'-hydroxy groups in nucleotides was a breakthrough that led to the rational synthesis of oligonucleotides[3]. The di- and trinucleotides bearing the N-trityl-*p*-aminophenyl group were isolated by solvent extraction, and the protecting group was removed by mild oxidative hydrolysis. The resulting tetranucleotide (pTpTpTpT) was finally purified by ion-exchange chromatography[4].

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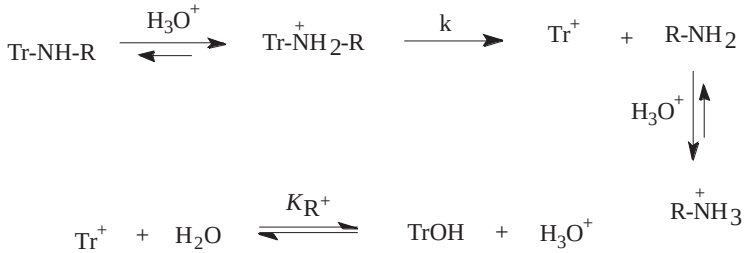
One of the contributions to the developments of synthetic organic chemistry was the protection and deprotection of amines with trityl and *p*-methoxysubstituted trityls that an otherwise reactive functional group could be temporarly rendered inert by appending a suitable protecting group[5], which could then be later removed[6]. Despite an intervening century of fabulous progress in the synthetic methodology, the proliferation of protecting groups is a tacit acknowledgment that selectivity in functional group transformations remains a central and unsolved problem in organic synthesis[7].

It is interesting that, in contrast, the database contains 32 structures of N,N-dialkylhydroxylamines, so the N,N-isomers represent a large majority of known dialkylhydroxylamines. Presumably, the steric bulk of the first N-trityl group prevents further N-alkylation even though the nitrogen remains more basic than the oxygen[7]. This property of the trityl group can be exploited in its use as a protecting group for nitrogen in the ambident aminophenols and related compounds as over-alkylation on nitrogen can be a problem with less bulky alkyl groups[8]. Our ongoing work also showed that the N-trityl, O-trityl and S-trityl groups prevent the formation of complexes with Cd^{+2} [9].

S_{N^1} is one of the most commonly studied of all organic reaction mechanisms, yet there are still unresolved questions of detail. Our kinetics study of the deprotection of substituted N-tritylamines was initiated to provide a basis in synthesis to allow improved control in the selective removal of one substituted trityl group is in the presence of others that are differently substituted. The extention of the study is that one trityl group is in the presence of an identical one but on a different type of amino group in a multi-protected polyamine. The kinetics results for the deprotection of several substituted N-trityl-N-alkylamines[6], and a detailed mechanistic investigation of the deamination of 4,4'-dimethoxytritylamine under controlled acidic conditions have been reported[10]. Our early work indicated that cleavage of substituted trityl amines under acidic conditions occurs by preequilibrium protonation followed by a simple S_{N^1} cleavage (Scheme 1)[6].



Scheme 1. Deprotection of a generic N-tritylamine under acidic conditions.

In the present work, we show the value of Tr and DMTr for selective protection of sulfur and amine functions against the hydroxy group in ambident nucleophiles. Both NH-protecting and S-protecting groups were removed under acidic conditions even in silica gel for DMTr, although a mechanistic subtlety in the H^+-induced pathway for detritylation made the DMTr group much easier to remove from nitrogen compared to the Tr group.

Experimental Section

General. All solvents were dried and distilled by standard procedures. All column chromatography was performed on silica (60-230 mesh, Merck) or activated basic alumina (Brockmann grade 1, 150 mesh). Fluka TLC-Card alumina (0.2 mm) and Merck silica gel 60 F_{254} plates were used for TLC analysis and

visualized under UV light. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WP-200 instrument (200 MHz or 400 MHz for ^{1}H and 50 MHz or 100 MHz for ^{13}C) with tetramethylsilane and $CDCl_3$ as standards. IR was recorded on a FT/IR-430 Jasko Fourier Transform IR spectrophotometer. Absorbances were recorded using a Jasco V-530 UV/VIS Spectrophotometer linked to a Calibra Pentium PC. The elemental analysis carried out with a CHNS-932 (LECO) analyzer and mass spectra using a micromass VG Platform-II spectrometer in electron impact (EI) mode.

N-trityl-*o*-aminophenol (1): *o*-Aminophenol (1.09 g, 0.01 mol) was treated with triphenylmethyl chloride (2.78 g, 0.01 mol) in triethylamine (1.01 g, 0.01 mol). The mixture was stirred for two days at room temperature. The reaction was monitored by TLC and completed to give dark residue. After purification on a silica gel column chromatography, the title compound was obtained (2.20 g, 63%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.80 (s, OH, 1H), 7.10-7.42 (m, ArH, 15H), 6.80 (t, J = 8.0 Hz, ArH, 1H), 6.0 (m, ArH, 2H), 5.9 (d, J = 8.0 Hz, ArH, 1H), 3.2 (s, NH, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.50, 150.01, 145.68, 129.64, 128.88, 128.27, 128.14, 105.64, 103.57, 101.21, 71.57.

N-(4,4'-dimethoxytrityl)-*o*-aminophenol (3): *o*-Aminophenol (1.09 g, 0.01 mol) and 4,4'-dimethoxytrityl chloride (3.55 g, 0.01 mol) were dissolved in triethylamine (10 mL) and stirred at room temperature. The reaction was completed in two days, as judged by TLC (eluent ethyl acetate:hexane; 1:4). Trietylamine was removed by evaporation. The crude product was recrystallized from ethanol to give 2.50 g (61%) of title compound. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.78 (s, OH, 1H), 7.20-7.40 (m, ArH, 9H), 7.10 (d, J = 8.0 Hz, ArH, 2H), 6.90 (d, J = 8.0 Hz, ArH, 2H), 6.80 (t, J = 8.0 Hz, ArH, 1H), 6.0 (m, ArH, 2H), 5.9 (d, J = 8, ArH, 1H), 3.80 (s, 2xOMe, 6H), 3.2 (s, NH, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.50, 150.01, 148.74, 145.68, 140.59, 129.64, 128.88, 127.90, 127.62, 126.64, 112.93, 105.64, 103.57, 101.21, 71.57, 54.81.

N-trityl-*m*-aminophenol (4): A solution of *m*-aminophenol (1.09 g, 0.01 mol), triphenylmethyl chloride (2.79 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) in 5 mL of $CHCl_3$ was stirred at room temperature for two days. The solvent was removed under reduced pressure. Chromatography on silica gel (10 g) eluting with dichloromethane/hexane (200 mL, 1:1) gave the title compound as dark-brown crystals (1.80 g, 51%); mp 139-140°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.18-7.42 (m, ArH, 15H), 6.78 (t, J = 7.0 Hz, 1H), 6.08 (d, J = 7.0 Hz, 1H), 5.95 (m, 2H), ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.81, 147.94, 145.68, 129.48, 128.88, 128.27, 128.14, 128.00, 127.00, 108.68, 71.57; IR (KBr, cm^{-1}) 3519, 3397, 3058, 2360, 1600, 1492, 1446, 1415, 1330, 1282, 1151.

N-(4,4'-dimethoxytrityl)-*m*-aminophenol (6): To a solution of 4,4'-dimethoxytrityl chloride (1 g, 2.95 mmol) in 5 mL of triethylamine was added *m*-aminophenol (0.32 g, 2.95 mmol). The mixture was stirred at room temperature for 2 days. The reaction was monitored by TLC during the reaction. Triethylamine was removed under reduced pressure. Chromatography on alumina (10 g) eluting with ethyl acetate/hexane (150 mL, 1:9) gave white crystals (900 mg, 75%). M.p. 99-100°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.10-7.40 (m, ArH, 10H), 6.80 (d, J = 9.0 Hz, 2H), 6.70 (d, J = 9.0 Hz, 2H), 6.05 (dd, J = 2.0 Hz, ArH, 1H), 5.90 (dd, J = 2.0 Hz, ArH, 1H), 5.80 (t, J = 2.0 Hz, ArH, 1H), 3.80 (s, 2xOMe, 6H), 3.75 (s, NH, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.64, 156.06, 147.30, 139.40, 137.66, 131.75, 128.96, 127.60, 126.84, 126.41, 112.91, 108.51, 104.16, 102.99, 69.87, 54.51; IR (KBr, cm^{-1}) 3397, 2998, 2931, 2832, 2048, 1901, 1606, 1508, 1461, 1444, 1415, 1299, 1249, 1176.

N-trityl-*p*-aminophenol (7): *p*-Aminophenol (1.09 g, 0.01 mol) and triphenylmethyl chloride (2.79

g, 0.01 mol) were dissolved in $CHCl_3$ (15 mL) and triethylamine (1.01 g, 0.01 mol) was added to the solution. The solution was stirred at room temperature for a day. The solvent was evaporated and the residue purified by crystallization from $CHCl_3$:hexane (1:1, 10 mL) giving compound **7** (3 g, 85%): white crystals, mp 152-154°C (lit.[14] 153-154°C); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.80 (br, OH, 1H), 7.10-7.40 (m, ArH, 15H), 6.20 (d, J = 9.0 Hz, 2H), 6.00 (d, J = 9.0 Hz, 2H), 4.50 (br, NH, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.64, 147.30, 139.41, 137.66, 128.83, 126.85, 126.43, 112.93, 68.00; Anal. Calcd for ($C_{25}H_{21}ON$) (351.45): C, 85.47; H, 5.98; N, 3.99. Found C, 85.44; H, 5.61; N, 3.84).

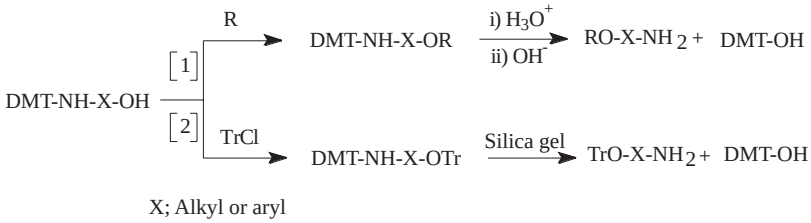
N-(4,4'-dimethoxytrityl)-*p*-aminophenol (9): *p*-Aminophenol (0.225 g, 2.06 mmol) and 4,4'-dimethoxytrityl chloride (700 mg, 2.06 mmol) were dissolved in triethylamine (10 mL) at room temperature. The mixture was stirred for four days at room temperature Then the mixture was washed with water (25 mL) and chloroform (25 mL). The crude product was chromatographed on a small alumina column (5 g) to give pale yellow crystals (0.6 g, 71%); mp 112-114°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.20-7.30 (m, ArH, 9H), 7.15 (d, J = 10.0 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 10.0 Hz, 2H), 6.65 (d, J = 9.0 Hz, 2H), 3.80 (s, 2xOMe, 6H), 3.75 (br, NH, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.62, 147.33, 139.39, 135.31, 130.08, 130.01, 128.39, 127.57, 127.54, 113.20, 112.26, 95.74, 68.00, 54.41.

S-Trityl-2-mercapto ethanol (12): Trityl chloride (1.0 g, 3.6 mmol) was dissolved in 2-mercaptoethanol (3 mL). The mixture was stirred magnetically for 24 h at room temperature. It was then washed with water (20 mL) and chloroform (20 mL). The organic phase was separated, dried ($CaCl_2$), filtered and evaporated. The crude product was chromatographed on silica gel using chloroform:hexane (ratio: 1:4) to give white crystals (0.70 g, 60%); mp 113-115°C (lit.[11], 114-115°C); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45-7.55 (m, ArH, 5H), 7.25-7.35 (m, ArH, 10H), 3.40 (t, J = 6.0 Hz, 2H), 2.50 (t, J = 6.0 Hz, 2H), 1.70 (br, OH, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.70, 129.45, 127.72, 126.54, 66.13, 60.27, 34.47; Anal. Calcd for ($C_{21}H_{20}OS$) (320.45): C, 78.75; H, 6.25; S, 9.60. Found C, 78.67; H, 6.34; S, 9.30; IR (KBr, cm^{-1}) 3542, 3401, 2923, 2360, 1685, 1621, 1590, 1484, 1440, 1139, 875.

Results[12] and Discussion

In this work, we analyze the oxygen reactivity versus the nitrogen and sulfur reactivity in an ambident nucleophile of *o*-aminophenol (**2**), *m*-aminophenol (**5**), *p*-aminophenol (**8**) and 2-mercaptoethanol. In preliminary work, we found that the nitrogen and sulfur atoms are the reactive center and are protected easily compaired with the oxygen atoms.

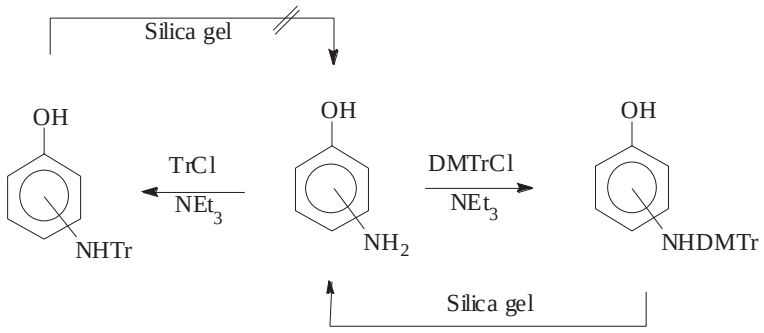
It is noteworthy that NH-DMTr, unlike O-Tr, in compounds **3, 6** and **9** (Scheme 3) led to its decomposition using the silica column during the purification, but was not decomposed in the alumina column. It subsequently proves that it is generally possible to alkylate NH-DMT substituted alkyl or aryl-alcohols on oxygen and then remove the substituted *p*-methoxytrityl group in a small silica gel column in high yield (Scheme 2). The way will be open for the use of substituted trityl as a protecting group in a general flexible synthesis of O-alkyl ambident nucleophiles [1], or protecting the oxygen with trityl and removing the DMT group in a small silica gel column to give O-protecting alkyl or aryl-amines [2] (Scheme 2).



Scheme 2

Scheme 3 shows the protection of *o*-aminophenol (**2**) with TrCl and DMTrCl. The nitrogen was protected by TrCl to give compound **1** and by DMTrCl to give compound **3**.

According to Scheme-3, the nitrogen of *m*-aminophenol was selectively protected by TrCl and DMTrCl to give compounds **4** and **6**, respectively. Proton and carbon NMR studies of compounds **4** and **6** indicated formation of the assigned structures.



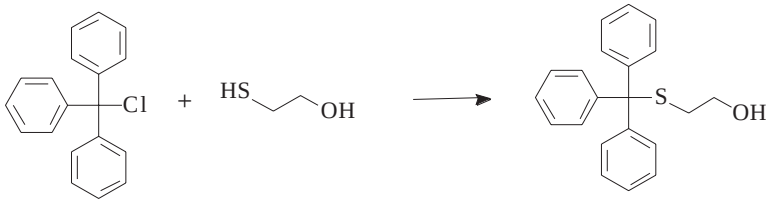
1; *o*-NHTr **2**; *o*-NH_2 **3**; *o*-NHDMTr
4; *m*-NHTr **5**; *m*-NH_2 **6**; *m*-NHDMTr
7; *p*-NHTr **8**; *p*-NH_2 **9**; *p*-NHDMTr

Scheme 3

p-Aminophenol was selectively protected by TrCl and DMTrCl to give compounds **7** and **9**, respectively (Scheme 3). These compounds were identified using carbon and proton NMR spectra.

Proton and carbon NMR studies of compounds **1**, **3**, **4**, **6**, **7** and **9** indicated the formation of the assigned structures. The infrared spectra of compound **4** clearly show the highest frequency band due to O-H and N-H stretching vibration at around 3519 and 3397 cm^{-1}, respectively.

Compound **12** was synthesized by the reaction of TrCl with 2-mercaptoethanol (Scheme 4). The FTIR, elemental analyses, proton and carbon NMR of compound **12** were completely in agreement with the proposed structure.



10 **11** **12**

Scheme 4

The main focus of this reaction is to understand the previous mechanism of the same reaction and a different product, Tr-S$(CH_2)_2$-Cl[13]. In this reaction, pyridine or triethylamine was used as a base.

As stated previously[1], trityl and *p*-methoxytrityl tetrafluoroborate salts were recommended as reagents superior to the corresponding chlorides because of their ease of preparation in highly pure form and relative stability. Therefore, 4,4'-dimethoxytrityl tetrafluoroborate salt ($DMTrBF_4$) was prepared by the reaction of DMTOH, prepared using the grignard reaction, and aqueous tetrafluoroboric acid in acetic anhydride with high yield (94%).

According to our Beilstain search, our novel compounds of parent and *p*-methoxy-substituted trityl aminophenols (**1**, **3**, **4**, **6** and **9**) and known compounds of *N*-trityl-*p*-aminophenol (**7**)[14] and *S*-trityl-2-mercapto ethanol (**12**)[11] were straightforward and are sufficiently described in the experimental section. We have found that, in general, the introduction of a single trityl group onto the nitrogen and sulfur in ambident nucleophiles is straightforward using trityl chloride or 4,4'-dimethoxytrityl chloride in pyridine as solvent. Yields are good and crystalline products well characterized.

The parent trityl group is the most easily introduced (using trityl chloride) but the least easy to remove, requiring acidic conditions. *p*-Methoxy substituted analogues, conveniently prepared using tetrafluoroborates, are much easier to deprotect. We found that the removal of parent trityl groups from nitrogen requires relatively strong acidic conditions in which the perchloric acid of molarity is in the range 8 to 4 and takes at least an hour. Figure 1 shows the maximum absorbance of the Tr^+ cation at 270 nm. The aqueous substrate includes 2% of acetonitrile as an organic solvent to avoid the solubility problem of amines.

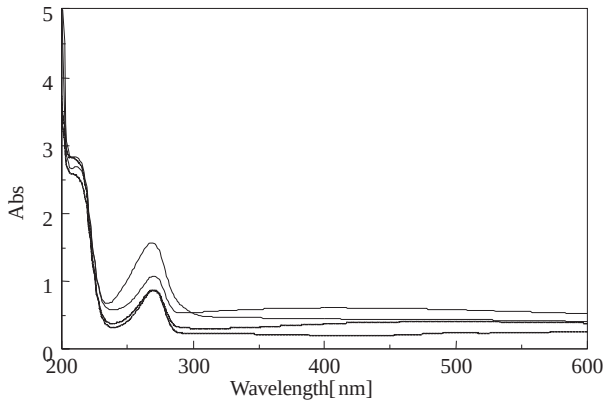


Figure 1. Scanning of the carbocation (Tr^+) of N-trityl-*m*-aminophenol (**4**) in perchloric acid at different concentrations.

However, the acid-induced removal of DMTr from the corresponding amine needs only mildly acidic conditions (up to 4 M) and a few seconds. A complete absorption spectrum was recorded in wavelengths from 200 nm to 600 nm. Figure 2 shows that there is a large increase in absorbance at 498 nm indicating the formation of the $DMTr^+$ cation.

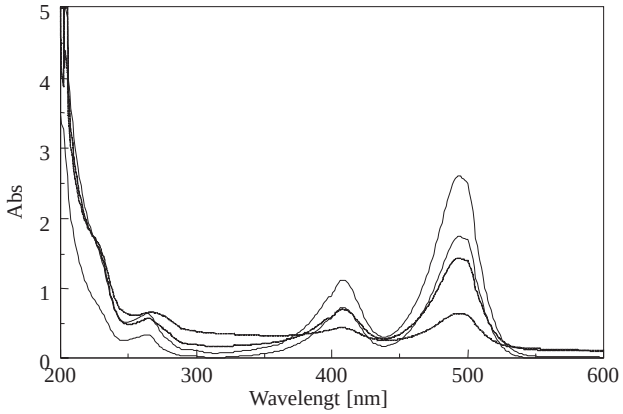


Figure 2. Spectra of the reaction mixture of N-4,4'-dimethoxytrityl-*m*-aminophenol (**6**) at different acid concentrations, [$HClO_4$] 1M, 2M, 3M and 4M, 2% CH_3CN.

Conclusion

The results described in this paper lead us to recommend the wider use of TrCl and DMTrCl (preferably, $DMTBF_4$) protecting groups for primary and secondary amino and sulfur groups in ambident nucleophiles in the presence of hydroxyl groups. The DMTrCl group is not only selective because of its stability in air, but also because of its relative ease of removal from protected nitrogen.

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