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Mild and Adaptable Silver Triflate-Assisted Method for Trityl Protection of Alcohols in Solution with Solid-Phase Loading Applications

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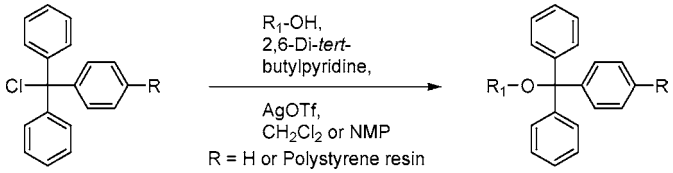
ABSTRACT



Trityl ethers were prepared in solution in a matter of minutes by treating trityl chloride with silver triflate in the presence of alcohols. Yields were comparable or better than known literature methods. The method was compatible with the base-labile Fmoc protecting group of amino alcohols and adapted for trityl protection of halo-containing alcohols. These base- and nucleophile-sensitive intermediates were anchored on trityl resin and further functionalized, displaying the utility of this approach for future combinatorial applications.

The masking of hydroxyl functionalities early in a synthetic route is often necessary to successfully perform subsequent multistep synthetic manipulations.[1] The ability to easily install the desired protecting group, followed by facile removal at the end of synthesis, is paramount in the design of any synthesis. The conditions to peform these operations should ideally be compatible with other functional groups in the molecule and display orthogonal reactivity patterns with other protective groups.

The triphenylmethyl (trityl) functionality represents an attractive alcohol protecting group since it is readily removed under mildly acidic conditions[2] (1% TFA in dichloromethane) to regenerate the alcohol. Furthermore, the additional chromophore in the trityl group, along with increased lipophilicity can aid in intermediate purification. The trityl protecting group can be employed orthogonally with blocking groups that can be removed with stronger acidic conditions or basic conditions.[2] Given these advantages, the formation of trityl ethers is not always straightforward, with some procedures requiring extensive preparation of reagents.[3] Additionally, some methods require harsh or basic reaction conditions and/or lengthy reaction times.[4]

Our initial focus was aimed at the development of a rapid and mild solution-phase protocol for trityl ether formation. This milder method, facilitated by utilizing silver triflate (AgOTf), was compared with conventional methods with use of simple alcohol substrates and alcohols which are potentially unstable to the conventional conditions. The results were used to tailor solid-phase applications. The advantages of this approach on the solid phase, with base-labile protecting groups or with reactive electrophilic functionalities, are highlighted with two applications detailed in this paper.

(1) For a review of hydroxyl protection and deprotection, see: (a) Jarowicki, K.; Kocienski, P. *Contemp. Org. Chem.* **1996**, *3*, 397−431. (b) Greene, T. W.; Wutts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley and Sons: New York, 1999. (c) Robertson, J.; Stafford, P. M. Selective Hydroxyl Protection and Deprotection. In *Carbohydrates*; Osborn, H. M. I., Ed.; Elsevier Science: Oxford, England, 2003; pp 9−68.

(2) Rothman, D. M.; Vazquez, M. E.; Vogel, E. M.; Imperiali, B. *J. Org. Chem.* **2003**, *68*, 6795−6798.

(3) (a) Hanessian, S.; Staub, A. P. A. *Tetrahedron Lett.* **1973**, *14*, 3555−3558. (b) Murata, S.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 2107−2108.

(4) (a) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *20*, 95−98. (b) Hernandez, O.; Chaudhary, S. K.; Cox, R. H.; Porter, J. *Tetrahedron Lett.* **1981**, *22*, 1491−1494. (c) Colin-Messager, S.; Girard, J.-P.; Rossi, J.-C. *Tetrahedron Lett.* **1992**, *33*, 2689−2692.

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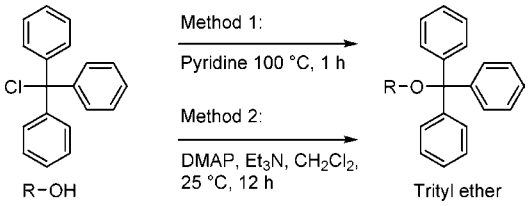
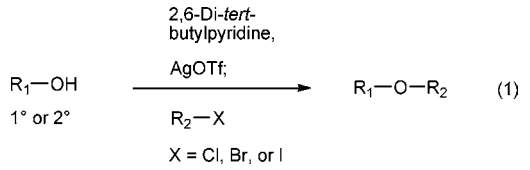
Two established methods for trityl protection of alcohols are displayed in Scheme 1.[4a] Method 1 uses pyridine as the

Scheme 1. Established Methods for Trityl Ether Formation



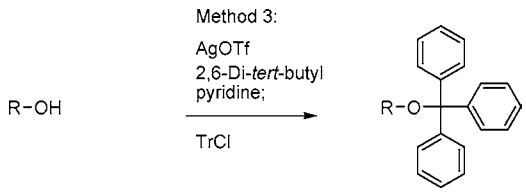
solvent, with heating. Method 2, also performed under basic conditions, requires a longer reaction time, but occurs at ambient temperature. Formation of the reactive pyridinium intermediates is the rate determining step in the formation of trityl ethers with these methods. We realized that the basic conditions used in these methods may preclude the use of alcohols containing base-labile or electrophilic functionalities and sought to develop a milder protocol.

The rationale for an alternative method of trityl protection was derived from a general method for alcohol alkylation. The literature method[5] for etherification of alcohols with primary alkyl halides in the presence of AgOTf is displayed in eq 1. Reported yields were between 39% and 96% for primary halides. In addition, the reaction was also applied to the secondary halide, isopropyl iodide, for which a yield of 25% was reported.



It was envisioned that treatment of trityl chloride with AgOTf could easily generate the more stable trityl cation in the presence of alcohols to facilitate the S_N1 reaction to form the desired trityl ethers under milder conditions.[6,7] When trityl chloride and an alcohol were treated with AgOTf (Scheme 2) a bright red to yellow color was initially observed, which indicated formation of the trityl cation. Usually, the color disappeared within 5 min indicating that the cation had been quenched and formation of the trityl ether was complete. When the reactions were run for 1 h, no difference in the crude LC/MS traces were observed when compared to those

Scheme 2. Silver Triflate-Assisted Trityl Protection of Alcohols[a]



[a] Procedure: trityl chloride (1.0−1.1 mmol) was added to alcohol (R−OH) (1 mmol), AgOTf (1.1−1.2 mmol), and 2,6-di-*tert*-butylpyridine (1.5 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After 1 h the reaction was filtered and purified (see the Supporting Information for details).

taken after 5 min, indicating rapid ether formation. The methods for trityl ether formation detailed in Schemes 1 and 2 were employed with a variety of alcohols and are compared in Table 1.

Yields of trityl ethers **1**−**4**, which were prepared with simple alcohols and AgOTf (Method 3), were generally comparable to or better than the literature procedures (Methods 1 and 2) with the advantage of a shorter reaction time and milder conditions. For the secondary alcohol used to prepare **1**, 2 equiv of alcohol provided a slightly better yield with Method 3. Attempts with several tertiary alcohols failed to provide useful results for all three methods probably due to steric hindrance.

For the halo-containing ethers, **5**−**9**, Method 3 was modified in some cases. With more reactive halides (for ethers **5**, **7**, **8**,[8] and **9**[9]) the halo alcohol was added 5 min after trityl cation formation, leading to better yields. This improvement can be attributed to preventing competition for AgOTf by the halide on the alcohol substrate, since AgOTf is consumed rapidly by trityl chloride. For solubility purposes the yield for **8** was improved significantly by using 1-methyl-2-pyrrolidinone (NMP) as the solvent. Addition of the halo alcohol 5 min post cation formation for ethers **5** and **8** improved the yield from the 20% range to the 60% range; similarly the yield for **7** was improved from 0% to 67%. Overall for **5**−**9**, Method 3 was superior to Methods 1 and 2, and provided products in 63% to 73% yield.

The base-labile 9-fluorenylmethoxycarbonyl (Fmoc) amine protecting group is widely used in orthogonal solid-phase peptide syntheses. This group is readily cleaved by a variety of inorganic and organic bases.[10] To determine if an orthogonal trityl/Fmoc strategy could be suitably developed, trityl protection of two Fmoc-protected amino alcohols (for ethers **10** and **11**) was attempted with use of the basic

(5) Burk, R. M.; Gac, T. S.; Roof, M. B. *Tetrahedron Lett.* **1994**, *35*, 8111−8112.

(6) 4,4′-Dimethoxytrityl triflate (DMTOTf) has been used in excess with pyridine to protect hydroxyl groups of monomers with the DMT functionality in the preparation of oligonucleotide analogues. For examples, see: (a) Egger, A.; Leumann, C. J. *Synlett* **1999**, *S1*, 913−916. (b) Ahn, D.-R.; Egger, A.; Lehmann, C.; Pitsch, S.; Leumann, C. J. *Chem. Eur. J.* **2002**, *8*, 5312−5322. (c) Renneberg, D.; Leumann, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 5993−6002.

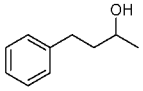
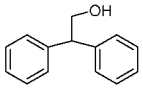
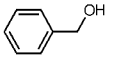
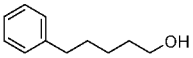
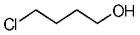
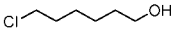
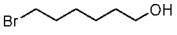
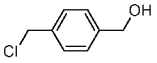
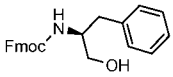
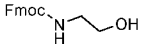
(7) Trityl triflate (TrOTf) has been used as a hydride ion acceptor to generate the 1-adamantyl cation intermediate leading to 1-adamantyl derivatives: Bochkov, A. F.; Kalganov, B. E. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1987**, *11*, 2560−2563.

(8) Pierce, M. E.; Harris, G. D.; Islam, Q.; Radesca, L. A.; Storace, L.; Waltermire, R. E.; Wat, E.; Jadhav, P. K.; Emmett, G. C. *J. Org. Chem.* **1996**, *61*, 444−450.

(9) (a) Stumpp, M. C.; Schmidt, R. R. *Tetrahedron* **1986**, *42*, 5941−5948. (b) Krakowiak, K. E.; Bradshaw, J. S.; Huszthy, P. *Tetrahedron Lett.* **1994**, *35*, 2853−2856.

(10) For a review of the use of Fmoc protection in peptide synthesis, see: Atherton, E.; Sheppard, R. C. The Fluorenylmethoxycarbonyl Amino Protecting Group. In *The Peptides*; Udenfriend, S., Meienhofer, J., Eds.; Academic Press: Orlando, FL, 1987; Vol. 9, pp 1−38.

Table 1. Comparison of Trityl Ether Formation Methods with Selected Alcohols

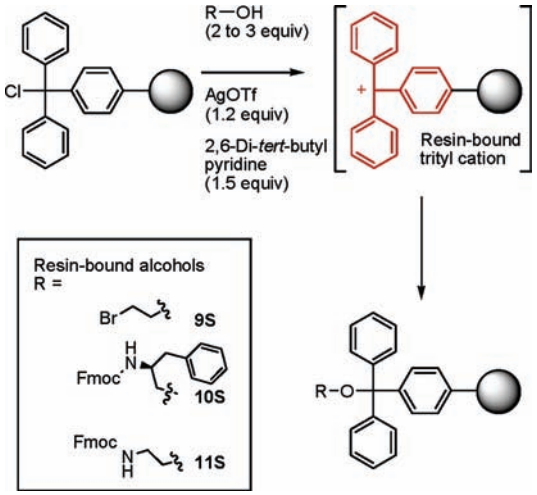
trityl ether	alcohol	method / yield (%) 1[a]	2[b]	3[c]
1		49	59	56 69[d]
2		83	N.D.	80
3		82	59	81
4		88	N.D.	76
5		57	N.D.	22 63[e]
6		74	50	73
7		26	50	0.0 67[e]
8		14	36	21[e] 68[e,f]
9		9	60	73[e]
10		60	N.D.	76
11		1.6	0.0	10 60[f]

[a] Method 1 as detailed in Scheme 1. [b] Method 2 as detailed in Scheme 1. [c] Method 3 as detailed in Scheme 2. [d] 2 equiv of alcohol used. [e] Alcohol added 5 min after reaction of AgOTf with TrCl. [f] NMP used as a solvent instead of CH_2Cl_2. N.D. = not determined.

conditions of the standard methods and compared to the milder conditions of Method 3. For ether **10**, the yields were slightly better with Method 3 when compared with Method 1. For ether **11** the improvement in yield for Method 3 (60%, using NMP as solvent for solubility of alcohol) was even more dramatic in comparison to Method 1 (1.6%). Overall, the good yields for Method 3 led to the realization that a solid-phase orthogonal trityl resin/Fmoc protection strategy could potentially be developed.

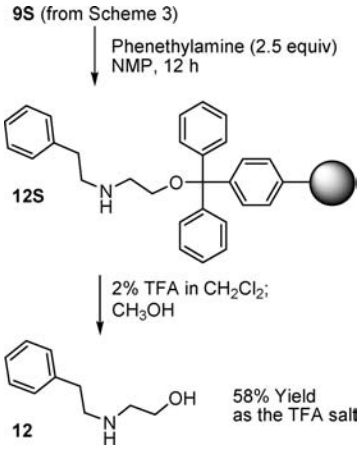
Common methods for solid-phase trityl ether formation with trityl chloride resin use either excess pyridine in combination with heating[11] or pyridine as the solvent at ambient temperature for 2 to 5 days.[12] The favorable results obtained in solution prompted adaptation of our milder AgOTf method to the solid phase (Scheme 3). With use of commercially available trityl chloride resin, ether formation can be driven quickly to completion by using excess alcohol equivalents to provide **10S** and **11S**. Upon completion, excess alcohol and reagents were easily removed by washing the resin. Additionally, 2-bromoethanol was successfully loaded onto the trityl resin, providing **9S** by addition of the alcohol after the trityl cation was preformed.

Scheme 3. Silver Triflate-Assisted Trityl Resin Loading



The preparation of amino alcohols from halo-containing alcohols can prove difficult with solution-phase methodology. Some concerns include over-alkylation of the amine and the need for a protection of the hydroxyl functionality with a group that can be easily removed and separated from the polar crude product. The following solid-phase approach on trityl resin addresses both issues (Scheme 4). The alkylating agent **9S** is separated on the resin by pseudoinfinite dilution,

Scheme 4. Solid-Phase Synthesis of a Secondary Amino Alcohol

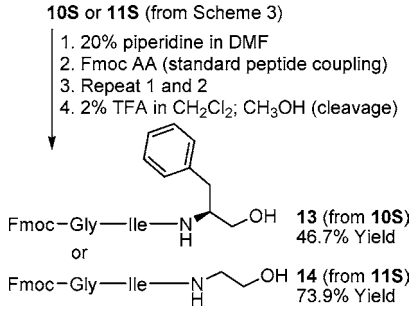


(11) For a review of the use of trityl resins, see: *Novabiochem Catalog, Reagents for Peptide and High-Throughput Synthesis*; Novabiochem: San Diego, CA, 2004; pp 2.16−2.20.

preventing excessive alkylation of the secondary amine product **12S**, which forms upon treatment with phenethylamine. In this case, after washing away excess amine, the crude product **12**[13] was easily isolated after cleavage from the trityl resin in good yield and purity.

Another useful solid-phase application is displayed in Scheme 5. With **10S** and **11S** as starting points, two tripeptides containing C-terminal alcohols (**13** and **14**) were synthesized by using a standard Fmoc peptide solid-phase synthesis protocol.[14] Reactions were monitored with the Kaiser test[15] and the products were isolated in respectable yields following resin cleavage. These examples display the ease with which the structure−activity relationship (SAR) for the replacement of a C-terminal carboxyl group with an alcohol can be explored by incorporating this modification at the beginning of the synthesis.

Scheme 5. Synthesis of Tripeptides Containing a C-Terminal Alcohol Functionality



In conclusion, a mild method for trityl ether formation (Method 3) was developed in solution and gave equal or better yields than standard trityl protection methods for alcohols (Methods 1 and 2). The rate for the S_N1 reaction was improved by using AgOTf to generate the stable trityl cation, decreasing the reaction time to minutes rather than hours. The method was adapted for use with reactive halo alcohols by preforming the trityl cation and was also compatible with the base-labile Fmoc protecting group. The use of AgOTf was successful when dichloromethane or NMP was employed as the solvent to accommodate alcohols with different solubility properties. In addition, this method can easily be applied in any chemistry lab, since all of the necessary reagents are available from commercial suppliers.

The method was also adapted to anchor alcohols on solid support by forming the trityl ether linkage. The scope of this approach was expanded by taking advantage of a solid-phase strategy to prepare the amino alcohol (**12**) and tripeptides containing C-terminal alcohol functionalities (**13** and **14**). These relatively simple examples display the ease of this approach and offer promise for future parallel and combinatorial applications.

Acknowledgment. A.D.S. thanks the Wyeth Research Summer Intern Program for support. We thank the Chemical Technologies group at Wyeth for analysis of compounds.

Supporting Information Available: Full experimental details for **1**−**11**, as well as experimental details for solid-phase trityl resin loading and preparation of **12**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Fréchet, J. M. J.; Haque, K. E. *Tetrahedron Lett.* **1975**, *16*, 3055−3056. (b) Chen, C.; Ahlberg Randall, L. A.; Miller, R. B.; Jones, A. D.; Kurth, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 2661−2662.

(13) Chan, D. C. M.; Laughton, C. A.; Queener, S. F.; Stevens, M. F. G. *J. Med. Chem.* **2001**, *44*, 2555−2564.

(14) (a) Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404−3409. (b) Wang, S. S. *J. Am. Chem. Soc.* **1973**, *95*, 1328−1333. (c) Meienhofer, J.; Waki, M.; Heimer, E. P.; Lambros, T. J.; Makkofske, R.; Chang, C. C. *Int. J. Peptide Protein Res.* **1979**, *13*, 35−42.

(15) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595−598.