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Friedel–Crafts catalysts as assistants in the tritylation of less reactive hydroxyls

Roberta Bernini [a], Maurizio Maltese [b,*]

[a] Dipartimento di Agrobiologia e Agrochimica, Università degli Studi della Tuscia, Via S. Camillo De Lellis, 01100 Viterbo, Italy
[b] Dipartimento di Chimica, Università degli Studi 'La Sapienza', P.le A. Moro 5, 00185 Rome, Italy

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ABSTRACT

Less reactive hydroxyls, such as those present in secondary alcohols and in some primary alcohols, phenols and carboxylic acids, were easily tritylated with the homogeneous assistance of equimolar quantities of chlorides of di- and trivalent metals in aprotic solvents. The metal ions allowed both high concentration of the effective reagent triphenylmethylcarbenium ion and mobilisation of the hydroxyl proton, thus giving rise to rapid, room temperature substitution reactions. The experimental conditions were so mild that other protected groups, such as alkyl- or trityl-protected carboxyls and (9-fluorenylmethoxycarbonyl)- or trityl-protected amino groups, remained unaffected.

1. Introduction

The triphenylmethyl (trityl) group is a common protecting group for hydroxyls, being easily introduced and successively removed by mild acidic treatment.[1] It is widely accepted that the tritylation reaction predominantly consists of an attack by the triphenylmethylcarbenium ion Tr^+ on the nucleophilic substrate through a S_N1 mechanism. The process rate depends on the capability of its components to favour the heterolytic cleavage of the Tr–X bond. With reference to the sole homogeneous methods, when triphenylcarbinol (X = OH) is employed as the reagent, the goal of increasing Tr^+ concentration is achieved by the action of strong Brønsted acids, for example, H_2SO_4.[2] However, as substrates suffer as a result of this treatment, milder procedures based on the use of Lewis acids such as $B(C_6F_5)_3$,[3] $ZnCl_2$,[3] $AlCl_3$,[3] $FeCl_3$[4,5] and $FeClO_4$[4] have been suggested. With the same aim, trityl ethers (X = OR, where R = benzyl, *p*-methoxybenzyl and prenyl) in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or DDQ/$Mn(OAc)_3$ have been employed.[6,7] Triphenylmethyl chlorides and bromides (X = Cl, Br) are used in association with an organic base such as pyridine,[8–10] dimethylaminopyridine (DMAP),[11] 2,4,6-*tert*-butyl pyridine,[12] 2,4,6-collidine[13] or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[14]

Tritylating reagents with ionic character (X = ClO_4^-,[10] PF_6^-,[13] BF_4^-[15,16]) alone or in association with a substituted pyridine have been employed with the aim of achieving a higher Tr^+ concentration. Trityl triflate (X = OTf) is widely used in hydroxyl tritylation. This reagent is prepared in situ by reaction of TrOH and trimethysilyl trifluoromethanesulfonate (TMSOTf) and used in association with 2,4,6-collidine[17] or by reaction of silver triflate (AgOTf) and TrCl in the presence of 2,6-di-*t*-butylpyridine or 1-methyl-2-pyrrolidinone.[18] *O*-Tritylation of alcohols, phenols and carboxylic acids is also achieved by acid-catalysed *trans*-etherification between trimethyltrityloxysilane and trimethylsilyl ethers.[19] As a further example of a tritylation procedure for aromatic hydroxyls, phenyltrityl ether has been prepared by treatment of phenol with triphenylmethyl pyridones[20] and with TrCl in the presence of DBU.[12] In contrast with the described protocols, the most widely used tritylation method for hydroxyls in carboxylic acids is chiefly based on the action of trityl bromide on their metal salts[21] and of trityl chloride on their silver[22] or cesium salts.[23] However, preparations of *N*-trityl glycine trityl ester by TrCl/triethylamine (TEA)[24] and of some pertritylated amino acids by TrBr/TEA[25] are also reported.

Recently, we devised a new route to *O*-tritylation[26] using reagent mixtures of the type TrCl/MCl_x (MCl_x is a Friedel–Crafts catalyst, $x = 2, 3$),[27] where M^{+x} is capable of giving rise to both high concentrations of triphenylmethylcarbenium ions, by acceptance of X^- and proton mobilisation on the functional group to be protected, through coordination of the metal ions themselves and formation of oxonium chlorides (Scheme 1). We reasoned that, in the presence of a substrate having hydroxyls as the functional groups, a complex equilibrium should be established in which all the positively charged ions present, namely H^+, Tr^+ and M^{+x}, compete for the donor site to be substituted. The introduction of a proton scavenger, such as TEA, should reduce the competition between Tr^+ and M^{+x} only. Thus, the success of tritylation should ultimately depend on the relative affinity of Tr^+ and M^{+x} for the donor atom to be substituted and on their relative concentrations.

* Corresponding author. Tel.: +39 06 49913342; fax: +39 06 490324.
E-mail address: maurizio.maltese@uniroma1.it (M. Maltese).

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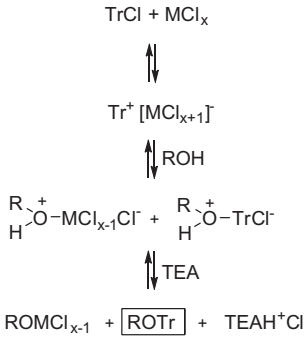
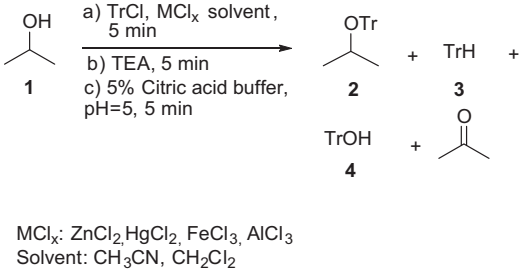


Scheme 1. Equilibria involved in the metal chloride-assisted *O*-tritylation.



Scheme 2. Procedure of tritylation of 2-propanol **1**.

Our preliminary experiments on the use of metal chlorides in assisting *O*-tritylations with TrCl showed that this procedure was in fact capable of increasing the reaction rate and that many of the less reactive hydroxyls reported in the literature, such as those of secondary alcohols, were susceptible to protection. These data prompted us towards the development of a protocol for a high rate, high yield and room temperature tritylation of this type of functionality and the experimental results are reported here.

2. Procedure and results

The organic solvent for the reaction needed to be a good solvent for the reagent mixture TrCl/MCl$_x$, in order to allow both high Tr$^+$ concentrations and low reaction volumes. Pyridine and its derivatives were excluded in order to avoid any overlap of the catalytic effect on tritylation, reported in the literature for these bases, with that of the metal acids we wanted to investigate in the present work. Our screening process indicated acetonitrile and dichloromethane as solvents and $HgCl_2$, $ZnCl_2$, $FeCl_3$ and $AlCl_3$ as metal chlorides.

As a general procedure, the substrate (1.0 mmol) was introduced into a solution of TrCl (1.0 mmol) and metal chloride (1.0 mmol) in the chosen solvent (6.0 mL) and the mixture was kept under magnetic stirring at room temperature for 5 min. Then, a solution of TEA (1.0 mmol) in the same solvent (2.0 mL) was added for 5 min. Finally, the reaction was quenched with aqueous 5% citric acid buffer at pH 5 (10.0 mL) and stirred for another 5 min. In the case of acetonitrile, the organic solvent was then evaporated under reduced pressure and the resulting suspension was extracted with diethyl ether. Organic extracts were combined, washed with water, dried on sodium sulfate and evaporated. In the case of dichloromethane, the organic solution was directly isolated, dried and evaporated.

Owing to the high Tr$^+$ concentration employed in this procedure, the oxidation of secondary alcohols due to hydride abstraction should be expected.[28–30] The amount of triphenylmethane (TrH) produced in this reaction is a measure of its importance. This is the reason why, in order to evaluate how much this competitive reaction could hamper the tritylation of secondary alcohols by the present methodology, we used 2-propanol **1**, known to be susceptible to oxidation, as a model substrate (Scheme 2).

The yields of 2-trityloxypropane **2**[31] and triphenylmethane **3** are listed in Table 1; the data on triphenylcarbinol **4**, resulting from unreacted TrCl through water workup, have been omitted for the sake of brevity. Blank reactions performed in the absence of TEA led to undetectable amounts of trityl ether **2**. Analogously, an equimolar mixture of TEA, $ZnCl_2$ and TrCl was not able to tritylate substrate **1**.

The use of $ZnCl_2$, in both acetonitrile and dichloromethane, gave a significant yield of trityl ether **2** (50% and 46%, respectively, entries 1 and 2). A better result (yield: 66%) was obtained by using $HgCl_2$ in acetonitrile (entry 3), whilst the low solubility of this salt in dichloromethane did not allow the relative solvent effect to be studied (entry 4). $FeCl_3$ and $AlCl_3$ were inactive concerning the production of the trityl ether in acetonitrile (entries 5 and 7), the former chloride exclusively leading to substrate oxidation in this solvent. In dichloromethane, in the presence of $FeCl_3$, the desired product was obtained at a better yield compared to $AlCl_3$ (entry 6 vs entry 8). Finally, in dichloromethane, despite comparable yields of the produced trityl ether, the amount of TrH was relatively lower for $ZnCl_2$ than for $FeCl_3$ (entry 2 vs entry 6).

Table 1
Evaluation of several metal chlorides and their concentration on the tritylation of 2-propanol **1** in acetonitrile and dichloromethane

Entry	MCl$_x$	Solvent	**2**[a] (yield %)	**3**[a] (yield %)
1	$ZnCl_2$	CH_3CN	50	10
2	$ZnCl_2$	CH_2Cl_2	46	14
3	$HgCl_2$	CH_3CN	66	8
4	$HgCl_2$	CH_2Cl_2	—	—
5	$FeCl_3$	CH_3CN	—	77
6	$FeCl_3$	CH_2Cl_2	43	29
7	$AlCl_3$	CH_3CN	—	—
8	$AlCl_3$	CH_2Cl_2	23	—
9	$ZnCl_2$[b]	CH_3CN	36	8
10	$ZnCl_2$[b]	CH_2Cl_2	32	11
11	$FeCl_3$[b]	CH_3CN	—	26
12	$FeCl_3$[b]	CH_2Cl_2	—	6

[a] Determined by GC–MS analysis of the organic extracts obtained after the workup.
[b] $ZnCl_2$ and $FeCl_3$ at 0.5 mmol.

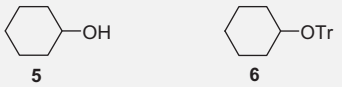
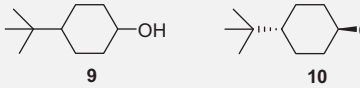
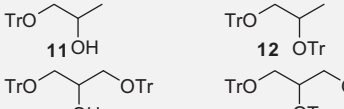
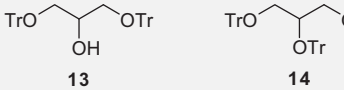
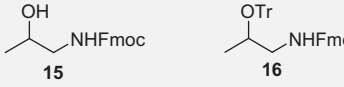
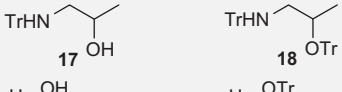
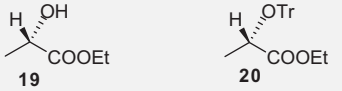
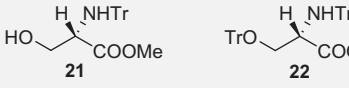
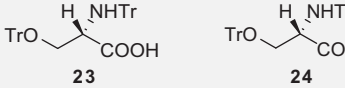
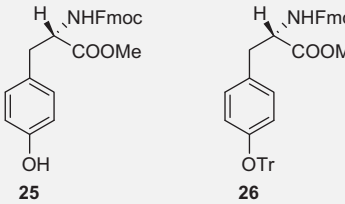
With the aim of reducing the quantity of the metal chloride employed, we investigated reactions on substrate **1** with less than equimolar concentrations of metal chloride. The results, as illustrated in Table 1 by the use of 0.5 mmol of $ZnCl_2$ (entries 9 and 10) and of $FeCl_3$ (entries 11 and 12), indicated that the yield of the trityl ether formed decreased. The production of TrH followed the same trend (entries 9–10 vs entries 1–2 and entries 11–12 vs entries 5–6). We have ascribed this result to the effect produced on the chloride ion transfer equilibrium by the addition of TEA. In fact, the base acts as a proton scavenger only if the substrate hydroxyls release protons at a reasonable rate. Otherwise, its addition to the reaction mixture reduces the concentration of the metal ion by complexation, progressively precluding both the chloride ion transfer mechanism and the catalytic effect on the mobility of the substrate protons. Furthermore, the base may directly quench the reactive species Tr$^+$ through N-quaternisation.

In principle, this hampering effect may be reduced by a slower addition of TEA, but as we wanted to develop a rapid procedure for the formation of trityl ethers, we did not pursue this. Since we wanted to develop an environmentally friendly procedure, we also attempted to reduce the amount of metal chloride by employing other bases; however, the use of pyridine, 2,4,6-collidine, DMAP

or DBU, in place of TEA, in the metal-assisted tritylation of 2-propanol **1** did not produce remarkable changes in the yield of 2-trityloxypropane **2** produced.

Despite the moderate yields of **2** obtained in the preliminary screening, we considered these data promising enough to extend the procedure to other substrates. The experimental data suggested the use of $HgCl_2$ in acetonitrile (highest yield of **2** and relatively low production of **3**); however, in view of the demand for efficient, economic, reliable and environmentally friendly processes, $ZnCl_2$ was chosen as the chloride and acetonitrile as the solvent for the *O*-tritylation of several secondary alcohols and some primary alcohols, carboxylic acids and phenols of low reactivity (listed in Table 2).

Table 2
Scope of $ZnCl_2$-promoted tritylation of secondary alcohols, phenols and carboxylic acids[a]

Entry	Substrate	Product	Yield[b] (%)
1	 **5**	**6**	80
2	 **7**	**8**	72
3	 **9**	**10**	92[c]
4	 **11**	**12**	79
5[d]	 **13**	**14**	67
6	 **15**	**16**	83
7	 **17**	**18**	82
8	 **19**	**20**	83
9	 **21**	**22**	92
10	 **23**	**24**	83
11	 **25**	**26**	80

[a] Tritylation reactions were performed according to the general procedure described for the screening experiments (see text).
[b] Isolated yield.
[c] Yield based on *trans*-4-*t*-butylcyclohexanol present in the commercial product **9** (mixture of *cis*/*trans* 33/67).
[d] Reaction performed in dichloromethane as substrate **13** was insoluble in acetonitrile.

Alcohols **5**, **7** and **9** were chosen on the grounds of their low reactivity; 1-trityloxy-2-propanol **11** and 1,3-di-trityloxy-2-propanol **13** were investigated to evaluate the role of steric hindrance against the installation of the voluminous trityl group; and substrates with functionalities protected by other groups (**15, 19, 21** and **25**) or the same trityl group (**11**, **13**, **17**, **21** and **23**) were included to investigate the stability of previously introduced protections to the manipulations of the proposed method. Finally, optically active compounds **19** and **23** were examined to check if the present method, as compared with other tritylation procedures, affects the enantiomeric purity of the tritylated derivatives (**20** and **24**).

In general, the reactions proceeded smoothly for all cases, in good to excellent yields, within the very short reaction time chosen for screening. The oxidation reaction of the secondary alcohol function was observed for cyclohexanol **5**, amounting to about 10% of the employed TrCl, but a satisfactory yield of tritylated compound **6**[32] was observed (entry 1). In contrast, we did not isolate TrH in the preparation of compound **8**[7] (entry 2) and **10** (entry 3). In this case, only the *trans*-isomer **10** was obtained, as previously observed.[14]

The success of the tritylation of secondary alcohol groups in propylene glycol and glycerol trityl derivatives **11** and **13** to prepare compounds **12**[33] and **14**[34] indicated a minor role of steric hindrance on the final yield of these reactions (entries 4 and 5).

Since in this method, the substrate experiences acidic conditions until the addition of the base is accomplished, *O*-detritylation of **11** and **13** (entries 4 and 5), N-detritylation of **17**, **21** and **23**[27] (entries 7, 9 and 10) and *trans*-esterification of **19** and **21** (entries 8 and 9) could be expected. However, we found no evidence for such processes and the high yield of reaction for these substrates confirmed this. In our opinion, the accelerated tritylation rate of this procedure does not affect the previously protected groups present in the molecule.

The *N*-Fmoc group present in compounds **15** and **25**[35] (entries 6 and 11) remained unaffected after the present tritylation protocol.

In contrast, when the tritylation of this kind of substrate is performed with procedures based on the use of TrCl in the presence of a base, the *N*-Fmoc moieties may suffer deprotection.[1] Thus, the present procedure seems to offer a suitable route for orthogonally protected substrates of the Fmoc/Tr type.

The optical activities of the trityl derivatives **20**[14] and **24**[36] (entries 8 and 10) were in agreement with the literature data.

3. Conclusion

In summary, we have developed a new simple and high rate procedure for preparing trityl ethers and esters under very mild reaction conditions and easy workup. The reactions are performed at room temperature, thus preventing or reducing the impact of secondary reactions and allow the use of non-chlorinated solvents. The method offers the opportunity of tritylating hydroxyls in the presence of base-sensitive functions, such as esters or Fmoc-protected amino groups, and does not give rise to racemisation in amino acid derivatives. Further investigation of the scope of this methodology is currently underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.144.

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