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Zinc chloride homogeneous catalysis in the tritylation of hydroxyl- and amide-bearing molecules

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ABSTRACT

A tritylation protocol based on the transfer of the triphenylmethylcarbenium ion from trityl acetate to substrates having hydroxyls, in the presence of catalytic amounts of $ZnCl_2$, is described. The advantages of this method are broad scope, mild conditions, and easy handling. The comparison with the procedure based on the use of equimolar mixture of TrCl and $ZnCl_2$ in the presence of TEA shows that comparable results are obtained. However, only this method allows reactions of secondary or benzylic alcohols such as oxidation or formation of symmetric ethers to be suppressed. Both procedures are successfully extended to simple and substituted amides. Irrespective of its low solubility in acetonitrile, even asparagine can be directly tritylated on its amide group.

1. Introduction

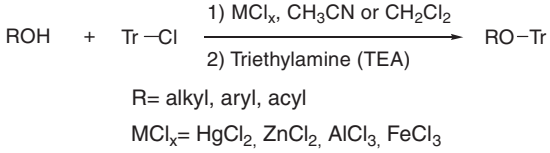
Comparable reactivity of functional groups is usually discriminated by selective protection[1] and this practice plays a prominent role in multistep syntheses of complex products. The choice of the most suitable protecting group for each function frequently holds the key to success. Among the several available protecting groups for the hydroxyl, the trityl group is one of the most advantageous because of its easy installation and cleavage. The trityl protecting functionality is introduced on hydroxyl by many homogeneous procedures[1] through the use of reagents, such as triphenylcarbinol (TrOH), trityl ethers (TrOR), and trityl halides or tritylium salts. H_2SO_4,[2] $B(C_6F_5)_3$,[3] $ZnCl_2$,[3] $AlCl_3$,[3] $FeCl_3$,[4,5] and $Fe(ClO_4)_3$[4] have been proposed as acid catalysts for TrOH, while trityl ethers TrOR (R = benzyl-, *p*-methoxybenzyl- and prenyl-) have been used as sources of triphenylmethylcarbenium ions coming from the benzylic carbon oxidation by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[6,7]

The use of TrCl or TrBr is frequently assisted by organic bases, such as pyridine,[8–10] dimethylaminopyridine (DMAP),[11] 2,4,6-*tert*-butyl pyridine,[12] 2,4,6-collidine,[13] and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU),[14] while reagents with more ionic character, such as $TrClO_4$,[10] $TrPF_6$,[13] $TrBF_4$,[15,16] and trityl triflate[17,18] are rarely used in the presence of substituted pyridines.

Metal salts have been sporadically employed in tritylation protocols. In the Tr^+ production from benzyl trityl ethers,[7] $Mn(OAc)_3$ works as an oxidant in the regeneration cycle of DDQ. Silver triflate[18] or hexafluorophosphate,[19] in association with TrCl is the tool to produce in situ trityl triflate or hexafluorophosphate, instead of being effective catalysts for the reaction. In contrast, iron trichloride effectively catalyzes *O*-tritylation by TrCl in ionic liquids.[5]

Recently, we have reported a procedure for the tritylation of less reactive hydroxyls in high yields and short reaction times, based on the use of equimolar mixture of trityl chloride and some Friedel–Crafts catalysts, with the subsequent addition of a strong nitrogen base as the proton scavenger (hereafter cited as method A, Scheme 1).[20]

After that work, our aim was to reduce the amount of the metal chloride employed, in order to obtain a more eco-friendly procedure, and to overcome some drawbacks of the protocol, such as the substrate oxidation processes, which hardly affected the tritylation yield of the secondary alcohols and of those of benzylic type. In this procedure, the rate and the efficiency of the reaction are due to the high equilibrium concentration and production rate of the triphenylmethylcarbenium ion. The high Tr^+ concentration is ensured by the favorable chloride transfer process from TrCl to MCl_x



Scheme 1. *O*-Tritylation in Friedel–Crafts conditions (method A).

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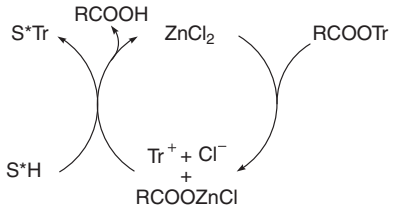


Scheme 2. Trityl transfer from a trityl ester to a protic substrate S*H catalyzed by $ZnCl_2$ (method B).

(Scheme 1), while its high production rate in the course of the proton substitution depends on the intrinsically high rate of this same transfer process.

In our opinion, if the counter-anions liberated in the production of Tr^+ would be less nucleophilic than Cl^-, the Tr^+ production should be more controlled in equilibrium concentration and production rate. Along with other Lewis acids, the metal chlorides easily give *O*-detritylation of trityl-ethers[21,22] and -esters,[23] leading to equilibrium concentrations of Tr^+ depending on the relative amount of the metal chloride employed. Thus, their mixtures could be useful sources of trityl cations to be transferred as protecting group on other donor sites.[24]

Furthermore, in this procedure, the production of Tr^+ is accompanied by that of anions whose basic strength and nucleophilic character can be modulated, offering an alternative to the use of the strong nitrogen base, as we have previously proposed.[20] The protons produced by the substrate in the tritylation reaction would then react with the in situ formed zinc alcoholate or carboxylate, liberating an alcohol or a carboxylic acid and regenerating the zinc catalyst (Scheme 2, where the transfer from a trityl ester has been taken into account).

The use of TrOTMS–TMSTf,[25] TrODT–TrATC,[15,26] and tritylated pyridones[27] in *O*-tritylation represent previous schemes of trityl transfer. However, these protocols did not employ metal catalysis.

2. Procedure and results

We soon wanted to check these ideas and firstly set up conditions with reagents, catalyst, solvents, and reaction temperature through an application to a model substrate. We have chosen trityl esters as reagents (as in Scheme 2) for their being more prone to dissociate under acid catalysis. Trityl formate **1b**[28] and trityl acetate **2b**[29] have been selected because they can be prepared by a simple, rapid, and economic procedure.[30] The metal chloride of choice was $ZnCl_2$, for the satisfying results soon observed in the preliminary screening of this work and in view of the excellent results previously obtained in *O*-tritylation.[20] Acetonitrile and dichloromethane were selected as solvents also in order to compare the present results with the previous ones.[20]

The efficiency of method B was firstly tested on *N*-Fmoc-ethanolamine **3a** as a model substrate, also to obtain information on the compatibility of this procedure with the presence of other protecting groups in the reactant. Firstly, a blank of the reaction in the absence of $ZnCl_2$, both in acetonitrile and dichloromethane, did not give any product, pointing to the catalytic action of the metal acid.

In both solvents, with equimolar concentrations of $ZnCl_2$, the reactions at room temperature were complete in few minutes and with relevant yields. With lower salt concentrations, we could obtain satisfying yields only with longer reaction times or by increasing the temperature. Even if a blank has excluded a Ritter reaction of acetonitrile with formation of *N*-tritylacetamide,[31] we have preferred room temperature procedures, always for the sake of comparison with the results obtained with method A[20] and have chosen reaction times of 1 h.

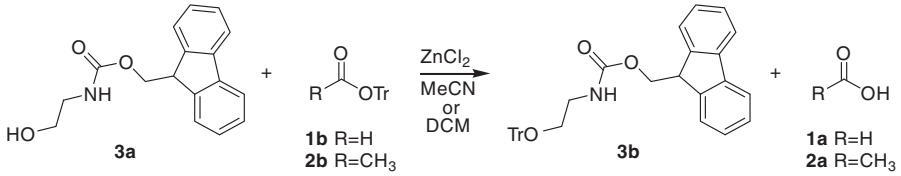
Table 1 reports the results relative to the use of $ZnCl_2$, both in MeCN and DCM, in concentrations ranging from equimolar to catalytic. The results of this Table have been obtained following this general procedure: *N*-Fmoc-ethanolamine **3a** (1.0 mmol) was added to the solution of the tritylating agent **1b** or **2b** (1.0 mmol) in 5 mL of acetonitrile containing 1.0, 0.5 or 0.1 mmol of $ZnCl_2$, the mixture was stirred for 1 h at room temperature. The product is recovered by filtration, washed with 3 mL of MeCN/H_2O 1:1, then with 3 mL of pure MeCN, dried, and weighted. In case of DCM, the final solution was washed with 5% citric buffer at pH 6, dried, and evaporated under vacuum. The pure solid **3b** was precipitated by addition of 5 mL of acetonitrile to the crude residue.

The results in Table 1 have shown that the yields of the trityl ether **3b** were significant and comparable in both solvents. In order to have a comparison with our previous results,[20] we have chosen acetonitrile for further experiments on trityl transfer. Convincingly, the experimental results on Table 1 have suggested AcOTr as the reagent of choice.

These preliminary results pointed to the effective existence of a metal chloride catalytic route to trityl ethers. Thus, at first, we wanted to check the catalytic procedure on primary alcohols. Afterward, since an important feature of the tritylation method A is the activation of scarcely reactive hydroxyls, we wanted to check the catalytic procedure B on the less reactive secondary alcohols. Further, we have planned to extend the comparison of methods A and B to substrates having more acidic hydroxyls than in alcohols, in order to evaluate the effect of the substrate acidity on the final equilibrium in the reaction of trityl transfer. Finally, we wanted to extend the scope of the method by checking the assistance of $ZnCl_2$ in the tritylation of other less reactive protic groups such as the amide group, chosen also to evaluate if the method is efficient toward protons bound to nitrogen instead of an oxygen atom.

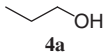
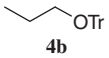
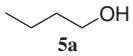
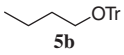
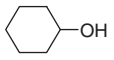
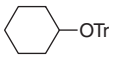
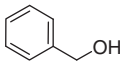
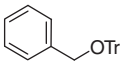
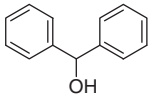
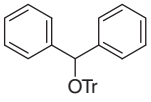
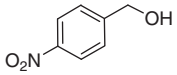
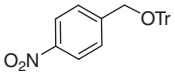
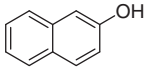
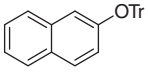
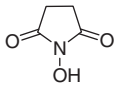
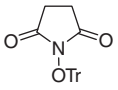
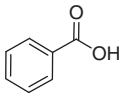
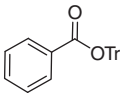
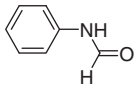
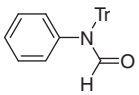
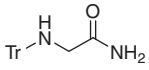
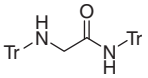
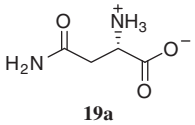
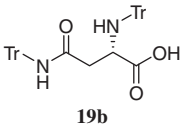
The results of the application of catalytic method B are listed in Table 2 and compared with those obtained in Friedel–Crafts conditions (method A). Both protocols are detailed as follows: (*Method*

Table 1
Evaluation of trityl formate **1b** and trityl acetate **2b**, respectively, as tritylating agents of *N*-Fmoc-ethanolamine **3a** in the presence of 1, 0.5 and 0.1 equiv of $ZnCl_2$



Tritylating agent	Yields (%) of **3b** in MeCN			Yields (%) of **3b** in DCM		
	1	0.5	0.1	1	0.5	0.1
1b	77	68	53	75	64	50
2b	89	84	59	85	81	56

Table 2
Scope of tritylations according to Tr^+-transfer from trityl acetate (method B, Scheme 2) and comparison with the results obtained with method A (Scheme 1)

Entry	Substrates	Products	Yield[a] (%)	
			Method A: TrCl + $ZnCl_2$ in MeCN, TEA	Method B: AcOTr + 10% $ZnCl_2$ in MeCN
1	 **4a**	 **4b**	87	88
2	 **5a**	 **5b**	82	86
3	 **6a**	 **6b**	80[b]	87
4	 **7a**	 **7b**	50[b]	83
5	 **8a**	 **8b**	0	83
6	 **9a**	 **9b**	0	89
7	 **10a**	 **10b**	67	88
8	 **11a**	 **11b**	80	81
9	 **12a**	 **12b**	87	90
10	 **13a**	 **13b**	81	58
11	 **14a**	 **14b**	85	77
12	 **15a**	 **15b**	78	75
13	 **16a**	 **16b**	80	73
14	 **17a**	 **17b**	83	80
15	 **18a**	 **18b**	78	75
16	 **19a**	 **19b**	61[c]	0

[a] Isolated yield of pure product.
[b] Previous results from Ref. 20.
[c] With 2 equiv of TrCl and 3 equiv of TEA.

A): the substrate (1.0 mmol) was added to a solution of TrCl (1.0 mmol) and $ZnCl_2$ (1.0 mmol) in acetonitrile (6.0 mL) and the mixture was stirred at room temperature for 5 min. Then, a solution of TEA (1.0 mmol) in the same solvent (2.0 mL) was added during 5 min. After quenching with aqueous 5% citric acid buffer at pH 5–6 (10.0 mL) and stirring for other 5 min, the organic solvent was evaporated under reduced pressure and the resulting suspension extracted with diethyl ether or dichloromethane. (*Method B*): the substrate (1.0 mmol) was added to a solution of trityl acetate **2b** (1.0 mmol) in 5 mL of acetonitrile containing 0.1 mmol of $ZnCl_2$, the mixture was stirred for 2 h at rt (substrates **4a**–**13a**) or refluxed for 3 h (substrates **14a**–**18a**), then the reaction was quenched with 5% citric buffer at pH 5–6 and the solvent evaporated under vacuum. The product was recovered by filtration or extraction with diethyl ether or dichloromethane.

We first checked if other primary alcohols than **3a** could be protected by procedure B (Table 2, entries 1 and 2), obtaining a confirmation of the utility of this method. Secondary alcohols, as well, were easily protected (entries 3 and 4) and the higher yields obtained with the present method, as compared with those of method A, have immediately pointed to the lack of any substrate oxidation.[20] In fact, in case of cyclohexanol **6a** (entry 3) and 2-propanol **7a** (entry 4), so prone to oxidation by hydride abstraction,[20] we did not detect any triphenylmethane in the crude reaction product.[32–34] This result met our expectation that catalytic method B could allow a better control of the protection reaction, with suppression of the substrate oxidation reaction. This good result was immediately checked with benzyl alcohol **8a** and benzhydrol **9a** (entries 5 and 6, respectively), which represented an effective drawback in the application of our previous procedure. Method A completely failed in the tritylation of these alcohols, which, in the presence of equimolar zinc chloride, very rapidly are transformed into mixtures of the corresponding symmetric ethers and, respectively, in benzaldehyde and benzophenone, with only traces of the desired trityl ethers.[35] In both cases, relevant quantities of triphenylmethane have been recovered in the crude product of the reaction. These results are due to the high stability of the benzyl- and benzhydryl- carbocations produced by these substrates under the action of the reagent TrCl/$ZnCl_2$. In the catalytic method B, the lower production rate and equilibrium concentration of the triphenylmethylcarbenium ions prevent both the oxidation and the symmetric etherification of the reactant. In contrast, the intrinsic lower stability of 4-nitrobenzyl-carbocation allowed the tritylation of **10a** to occur in moderate to high yield both with procedure A and B (entry 7).

We wanted to explore if and how much the acidity of the hydroxyl could affect the yield of the reaction by comparing the yields of tritylation of 2-naphthol **11a** (entry 8), *N*-hydroxy succinimide **12a** (entry 9), and benzoic acid **13a** (entry 10), three hydroxyl-bearing compounds having increasing acidity along the series, with the last substrate having almost the same pK_a of the acetic acid. With method A, the yields of protection are all noticeable. In contrast, with method B, the yields obtained for **11a** and **12a** were good (entry 8 and 9, respectively), while that obtained with benzoic acid **13a** is near 50%, showing that the equilibrium concentrations of trityl benzoate **13b** and trityl acetate were almost equal (entry 10). Thus, in this procedure, the acid strength of the hydroxyl has a negative effect on its tritylation only when the pK_a of the substrate approximates that of the acetic acid.

Table 2 reports also the results of the extension of both procedures to simple and substituted amides (entries 11–14). Preliminary blanks on these substrates with TrCl in the presence of TEA failed. Attempts with method B showed that the protection occurs very slowly at ordinary temperature; satisfying results have been obtained only keeping the reaction mixtures at refluxing temperature. After these experiments, we turned back to the room temperature method A, which, in contrast, gave excellent yields of the expected products, smoothly and rapidly. Previous methods in the homogeneous tritylation of amides required the reaction of their metal salts with TrCl[27] or prolonged warming of mixtures of the pure amides with TrCl or TrOH[36] or of their solutions in aromatic solvents with TrOH in the presence of TsOH[37] or in a solution of TrOH in AcOH, in the presence of H_2SO_4.[38–41]

As compared with the harsh experimental conditions employed in these methods, this was a very nice result of protocol A.[42]

Finally, in order to put in evidence possible steric hindrance between bulky protecting groups, we attempted the trityl-protection of the amide group of *N*-trityl glycinamide **18a** with both procedures (entry 15). The yields obtained, good and comparable, seem to confirm that the installation of the trityl group chiefly depends on the reactivity of the functional group to be protected while steric hindrance plays a secondary role.

The protection of the amide group by the trityl group has synthetic relevance in relation with peptide synthesis, where the side-chain amide groups of the amino acids asparagine and glutamine have often given rise to undesired side reactions in the course of the synthesis, such as dehydration to the nitrile function, intramolecular cyclization to the imide and others. Furthermore, many of the known protecting groups for the amide function, others than trityl, cause side reactions during their cleavage, producing carbocations capable of reacting irreversibly with tryptophan.[43,44] The good results obtained in the tritylation of the amide group, chiefly with method A, has prompted us to try to protect asparagine with our methodologies. Since the amino acids have very low solubility in organic solvents, we have devised firstly an indirect route, via the esterification of the carboxylic group. However, the attempt of using the amino acid itself as the substrate for application of method A has shown that it dissolves quite easily in acetonitrile containing 2 equiv of the reagent. The addition of 3 equiv of TEA and the usual water work up have given a crude material which, suspended in ether and treated with diethylamine, has led to the isolation of a moderate but significant yield of the bis tritylated Tr-Asn(Tr)-OH **19b**.[45] In contrast, an analogous experiment with method B was ineffective, because the amino acid did not dissolve in the reagent solution, even under prolonged warming. Since methods of selective N_α-detritylation of amino acids are in our hands,[23] this result opens an original route to an indirect synthesis of the side-chain protected asparagine H-Asn(Tr)-OH.[39–41] Investigations in this direction are in progress in this laboratory.

3. Conclusion

We have reported the results of a tritylation protocol based on the transfer of the triphenylmethylcarbenium ion from trityl esters to substrates having hydroxyl and amide groups, in the presence of catalytic $ZnCl_2$. This method leads to a better control in the production of the reactive species Tr^+ and, as a consequence, in case of secondary and benzylic alcohols, it is a powerful tool in avoiding secondary reactions such as oxidation or formation of symmetric ethers. With respect to the previously described procedure based on the use of equimolar mixtures of TrCl and $ZnCl_2$ (the Friedel–Crafts conditions), the capability of installing the trityl group on hydroxyls of low reactivity is preserved. In contrast with the harsh conditions reported in the literature, simple and substituted amides can be smoothly tritylated under Friedel–Crafts conditions at room temperature, while the catalytic procedure requires warming. Accordingly, irrespective of its low solubility in acetonitrile, asparagine can be directly tritylated on the amide group only in the presence of stoichiometric $ZnCl_2$.

Supplementary data

Supplementary data (melting points, microanalysis and NMR) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.095.

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