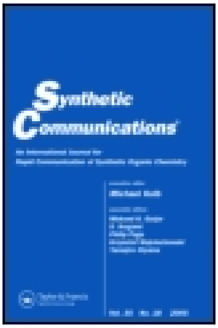

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$FeCl_3$-Catalyzed Tritylation of Alcohols in Ionic Liquids

B. Sreedhar [a], P. Radhika [a], B. Neelima [a], D. V. D. B. Chowdary [a] & M. V. Basaveswara Rao [b]
[a] Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology (Council of Scientific and Industrial Research), Hyderabad, India
[b] S.C. College of Arts and Science, Chikaluripet, Guntur, Andhra Pradesh, India

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$FeCl_3$-Catalyzed Tritylation of Alcohols in Ionic Liquids

**B. Sreedhar,[1] P. Radhika,[1] B. Neelima,[1] D. V. D. B. Chowdary,[1]
and M. V. Basaveswara Rao[2]**
[1]Inorganic and Physical Chemistry Division, Indian Institute of Chemical
Technology (Council of Scientific and Industrial Research),
Hyderabad, India
[2]S.C. College of Arts and Science, Chikaluripet, Guntur,
Andhra Pradesh, India

Abstract: A simple and efficient protection of alcohols as trityl ethers is described using trityl chloride in the presence of 5 mol% $FeCl_3$ as catalyst in ionic liquids at room temperature in shorter reaction times. This mild and efficient method gives access to the protection of a wide range of alcohols in good yields. The use of ionic liquid allows easy separation of the product and recycling of catalyst.

Keywords: Alcohols, $FeCl_3$, ionic liquids, recyclability, tritylation

INTRODUCTION

The hydroxyl group is the most important and versatile functional group in organic chemistry, the masking of which is often necessary in multistep synthetic manipulations.[1,2] Therefore, access to mild and efficient procedures for the installation of the desired protecting group followed by its removal is an important target for synthetic chemists. Triphenylmethyl (trityl) group is part of the most common, attractive approach for the protection of alcohols because of its stability under neutral or basic conditions. Further, the trityl group can be easily removed under mild acidic

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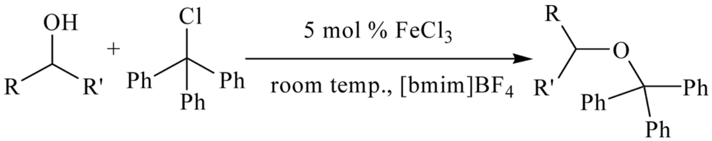
Address correspondence to B. Sreedhar, Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology, Hyderabad 500 607, India. E-mail: sreedharb@iict.res.in



Scheme 1. $FeCl_3$-catalyzed tritylation of alcohols in ionic liquids.

conditions using 1% trifluoroaceticacid (TFA) in dichloromethane (DCM) to regenerate the corresponding alcohol,[3] and it can also be employed in orthogonality with other protecting groups as well as functional groups.[4] Traditionally, tritylation is carried out with trityl chloride in the presence of a base.[5,6] The other methods include AgOTf–TrCl, TrODT–Tr1ATC15, tritylated pyridones, BnOTr–DDQ, TrOTMS–TMSOTf, *p*-methoxybenzyl trityl ether or prenyl trityl ether (PTE)–DDQ, and TrOH-B(C_6F_5)$_3$.[7–13] Most of these tritylating reagents require extensive preparation procedures from trityl chloride. Some of them also require harsh reaction conditions, longer times, and tedious workup procedures.[14–16] Furthermore, to the best of our knowledge, there are no reports for the trityl protection of alcohols using a recyclable catalytic system.

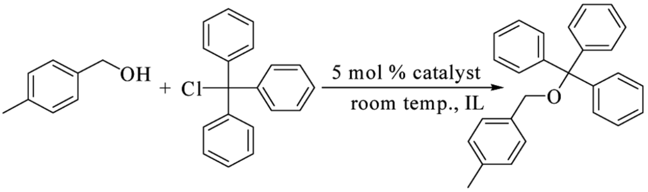
In recent years, ionic liquids (ILs) have received much attention as environmentally friendly alternatives to volatile organic solvents because of their unique properties such as low vapor pressure, wide liquid range, high thermal stability, and highly conductivity and solvation ability for a variety of organic substrates and catalysts including Lewis acids and enzymes.[17–20] The use of ILs offers the combined advantages of both homogeneous and heterogeneous catalysts. Reactions in ILs exhibit the high activity and selectivity of a homogeneous catalyst and also allow easy separation of the products and reusability of the catalyst, analogous to a heterogeneous catalyst.[21,22] Iron salts are well-known Lewis acid catalysts for various organic transformations because of their low cost, easy availability, environmentally benign nature, and exceptionally high reaction rates.[23]

Encouraged by the pioneering work of Tamura and Kochi on iron salts and our studies on ILs as recyclable media for various organic transformations,[24,25] we intend to study the protection of alcohols as trityl ethers under mild conditions in shorter reaction times using $FeCl_3$ as catalyst in ILs (Scheme 1).

RESULTS AND DISCUSSION

Initially, the protection of *p*-methyl benzyl alcohol with trityl chloride using various Lewis acid catalysts (5 mol%) in different ILs at room temperature was studied, and the results are presented in Table 1.

Table 1. Tritylation of *p*-methyl benzyl alcohol with different acid catalysts[a]



Entry	Catalyst	Time (min)	Conv. (%)[b]
1	$HAuCl_4$	135	60
2	$AlCl_3$	210	94
3	$CuCl_2$	180	98
4	$FeCl_3$	35	90
5	$MgCl_2$	210	—
6	$ZnCl_2$	240	—
7	$FeCl_3$	240	—[c]
8	$FeCl_3$	40	90[d]
9	$FeCl_3$	135	50[e]
10	—	240	—[f]

[a] Reaction conditions: catalyst (5 mol%), $[bmim]BF_4$ (1 mL), *p*-methyl benzyl alcohol (1 mmol), and trityl chloride (1 mmol) at room temperature.

[b] Conversions determined by ^1H NMR.

[c] Using [bmim]Cl and [bmim]OTf in place of $[bmim]BF_4$.

[d] Using $[bmim]PF_6$.

[e] CH_2Cl_2 was used as solvent in place of $[bmim]BF_4$.

[f] No reaction in the absence of catalyst.

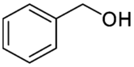
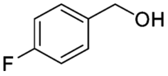
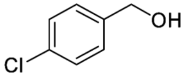
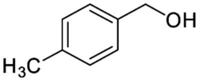
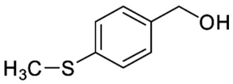
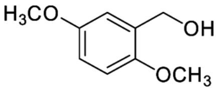
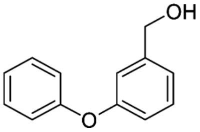
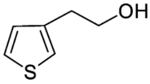
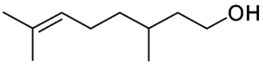
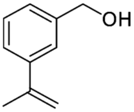
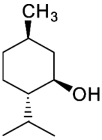
Among the different Lewis acids screened, $HAuCl_4$ gave the corresponding trityl ethers in moderate yield (entry 1), whereas $AlCl_3$, $CuCl_2$, and $FeCl_3$ displayed better activity with the formation of trityl ethers in good yields (entries 2–4). However, the reaction using $AlCl_3$ and $CuCl_2$ as catalysts in $[bmim]BF_4$ required longer reaction times when compared to the reaction using $FeCl_3$. On the other hand, other Lewis acids such as $MgCl_2$ and $ZnCl_2$ were ineffective for the reaction (entries 5 and 6). Further efforts were focused on the use of different ILs for the reaction. Three different imidazolium-based ILs, [bmim]Cl, [bmim]OTf, and $[bmim]PF_6$, were tested using $FeCl_3$ as catalyst. The reaction in ILs with chloride and triflate anions, [bmim]Cl and [bmim]OTf, gave no product, whereas $[bmim]PF_6$ gave conversions comparable to that of $[bmim]BF_4$ (entries 7 and 8). Therefore, changing the anion also has an influence on the reaction. To ascertain the superior performance of ILs over organic solvents, experiments were conducted using $FeCl_3$ as the catalyst separately in DCM (entry 9). It is interesting to note that the corresponding trityl ether was obtained in poor yield. Therefore, the reaction was significantly faster and more efficient in ILs. However, there was no reaction in the absence of catalyst (entry 10).

By employing the optimized reaction conditions, a variety of alcohols have been subjected to trityl protection. The tritylation is quite simple, fast, and efficient, with the formation of corresponding trityl ethers in good yields. The reaction of electronically and structurally diverse aliphatic primary benzylic alcohols such as *p*-fluoro, *p*-chloro, *p*-methyl, and *p*-methylthio benzyl alcohols with trityl chloride gave the desired products in quantitative yields (entries 1–5). A lignin-like structure containing 2,5-dimethoxy benzyl alcohol could be easily protected into corresponding trityl ethers in 95% yield, whereas 3-phenoxy benzyl alcohol afforded the product in 55% yield (entries 6 and 7). It should be noted that the heteroatom-containing substrate, thiophene-2-ethanol, could also be smoothly converted into tritylated product (entry 8). Natural acyclic and cyclic monoterpenoids such as β-citronellol, perillyl alcohol, and L-menthol were equally effective as substrates for the reaction with trityl chloride to give the corresponding trityl ethers in excellent yields (entries 9–11). Tritylation of hydroxyl group present in steroidal alcohols such as cholesterol resulted in the formation of corresponding product in 83% yield but required a longer reaction time (entry 12). Similarly, the reaction succeeded well with aliphatic cyclic alcohols such as cyclopentanol and norborneol (entries 13 and 14). The aliphatic diols and secondary alcohols reacted slowly at room temperature; however, at slightly elevated temperature (40°C), the resulting diether products were obtained in good yields (entries 15–19). Nevertheless, diols required 2 equivalents of trityl chloride for complete conversion. Further, to check the compatibility and to confirm the mildness of the reagent, we studied the protection of amino alcohols such as L-lucinol and DL-alaninol. These substrates underwent selective O-tritylation in shorter reaction times and in good yield (entries 20 and 21).

The plausible catalytic cycle may be explained by the more stable trityl cation formed in the reaction of trityl chloride with $FeCl_3$ in IL, which in the presence of alcohol facilitates the S_N1 reaction to form the desired trityl ethers under mild reaction conditions.

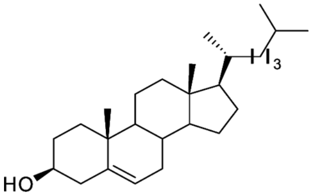
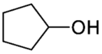
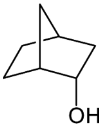
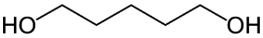
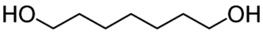
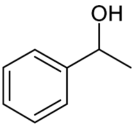
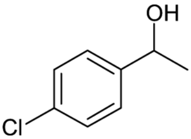
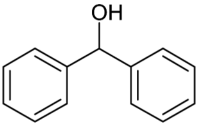
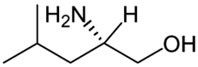
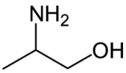
Finally, upon completion of the reaction, the IL phase containing $FeCl_3$ was almost quantitatively recovered by simple extraction of the product with organic solvent. The recovered IL phase containing the catalyst was reused for five cycles with consistent activity (Table 2, entry 4).

Table 2. Tritylation of various alcohols using $FeCl_3$ in [bmim]BF_4[a]

Entry	Alcohol	Time (min)	Yield (%)[b]
1		10	99
2		30	95
3		60	95
4		35	98, 95[c]
5		120	97
6		120	95
7		195	55
8		195	92
9		150	90
10		180	92
11		230	93

(*Continued*)

Table 2. Continued

Entry	Alcohol	Time (min)	Yield (%)[b]
12		300	83
13		220	92
14		255	95
15		255	99[d,e]
16		190	99[d,e]
17		150	89[d]
18		180	85[d]
19		195	98[d]
20		180	80
21		170	69

[a] Reaction conditions: catalyst (5 mol%), [bmim]BF_4 (1 mL), *p*-methyl benzyl alcohol (1 mmol), and tritylchloride (1 mmol) at room temperature.

[b] Isolated yield.

[c] Isolated yield after fifth cycle.

[d] Reaction temperature at 40°C.

[e] Two equivalents of trityl chloride.

EXPERIMENTAL

General Remarks

All chemicals were purchased from Aldrich Chemicals and S.D. Fine Chemicals Pvt. Ltd., India, and used as received. All the solvents used were laboratory-reagent (LR) grade and used as received from S.D. Fine Chemicals Pvt. Ltd, India. ACME silica gel (100–200 mesh) was used for column chromatography, and thin-layer chromatography (TLC) was performed on Merck precoated silica-gel 60-F254 plates. Melting points were recorded on a Barnstead electrothermal 9200 instrument and are uncorrected. CHNS analysis was performed on a Vario EL analyzer. The infrared (IR) spectra of all compounds were recorded on a Nexus 670 Fourier transform (FT)-IR spectrometer (Nicolet Corporation Ltd., USA) using KBr pellets or neat. The IR values are reported in reciprocal centimeters (cm^{-1}). The ^{1}H and ^{13}C NMR spectra were recorded on Varian-Gemini 200-MHz and Bruker-Avance 300-MHz spectrometers. Mass spectra were obtained at an ionization potential of 70 eV [scanned on VG 70–70H (micromass)]. Thermogravimetric (TG) and differential thermal analysis (DTA) were studied on a TGA/SDTA Mettler Toledo 851_e system using open alumina crucibles containing samples weighing about 8–10 mg with a linear heating rate of 10°C min^{-1}. Nitrogen was used as purge gas for all these measurements.

Synthesis of Ionic Liquids

ILs synthesized according to the procedures reported in the literature, and the purity was confirmed by ^{1}H NMR and TGA–DTA analysis.[20]

General Procedure for the Preparation of Trityl Ethers

Alcohol (1 mmol) and trityl chloride (1 mmol) were added to a solution of $FeCl_3$ (0.008 g, 5 mol%) in IL (1 mL). The mixture was stirred at room temperature for the given time (see Tables 1 and 2). After completion of the reaction, as monitored by TLC, the crude product was extracted with organic solvent (3×10 mL). The combined organic extracts were concentrated in vacuo, and the resulting product was purified by column chromatography on silica gel with ethyl acetate–n-hexane (2:8) as eluent to afford the desired product. The products were characterized by comparison of their nuclear magnetic resonance (NMR) and mass spectra with those reported in the literature.[7,12,13] The IL containing $FeCl_3$

was dried under vacuum and preserved for the next run. The physical data and the spectroscopic data of selected cyanohydrins reported in Table 2 are given here.

Data

1-Fluoro-4-[(trityloxy)methyl]benzene (Entry 2, Table 2)

Solid; mp 138–140°C; yield 95%; ^{1}H NMR (CDCl$_3$) δ 7.65–6.91 (m, 19H), 4.21 (s, 2H); MS (EI) *m/z* 259, 243, 137, 125, 109, 95, 77; IR (KBr): υ 3058, 2924, 2882, 2853, 1583, 1489, 1447, 1373, 1223, 1078, 1031, 932, 837, 762, 702, 629 cm^{-1}. Anal. calcd. for $C_{26}H_{21}OF$: C, 80.62; H, 5.426. Found: C, 80.55; H, 5.40.

1-(Methylsulfanyl)-4-[(trityloxy)methyl]benzene (Table 2, Entry 5)

Solid; mp 144–145°C; yield 97%; ^{1}H NMR (CDCl$_3$) δ 7.50–7.20 (m, 19H), 4.10 (s, 2H), 2.47 (s, 3H); MS (EI) *m/z* 243, 165, 137, 122, 91, 47; IR (KBr): υ 3475, 3061, 3021, 2923, 2854, 1958, 1891, 1733, 1596, 1490, 1443, 1372, 1325, 1213, 1154, 1073, 1009, 895, 801, 757, 699, 635 cm^{-1}. Anal. calcd. for $C_{27}H_{24}OS$: C, 81.81; H, 6.06; S, 8.08. Found: C, 81.74; H, 5.99; S, 8.12.

1,4-Dimethoxy-2-[(trityloxy)methyl]benzene (Table 2, Entry 6)

Solid; mp 158–160°C; yield 95%; ^{1}H NMR (CDCl$_3$) δ 7.50–6.60 (m, 18H), 4.13 (s, 2H), 3.79 (s, 3H), 3.64 (s, 3H); MS (EI) *m/z* 243, 165, 137, 121, 105, 91, 77; IR (KBr): υ 3476, 3061, 2937, 2835, 1679, 1594, 1441, 1276, 1217, 1154, 1006, 933, 888, 756, 696, 635, 581 cm^{-1}. Anal. calcd. for $C_{28}H_{26}O_3$: C, 81.95; H, 6.34. Found: C, 81.89; H, 6.21.

3-(2-Trityloxy-ethyl)-thiophene) (Table 2, Entry 8)

Solid; mp 130–132°C; yield 92%; ^{1}H NMR (CDCl$_3$) δ 7.40–7.18 (m, 15H), 7.10 (d, 1H), 7.40–6.89 (d, 1H), 6.79 (d, 1H), 3.32 (t, 2H, $J = 6.6$ Hz), 3.07 (t, 3H, $J = 6.6$ Hz); MS (EI) *m/z* 243, 139, 111, 97, 77 cm^{-1}; IR (KBr): υ 3466, 3058, 3022, 2920, 2865, 1953, 1594, 1488, 1445, 1374, 1268, 1216, 1150, 1079, 929, 896, 756, 697, 631, 588 cm^{-1}. Anal. calcd. for $C_{25}H_{22}OS$: C, 81.08; H, 5.94; S, 8.64. Found: C, 81; H, 5.82; S, 8.51.

1-[Phenyl(trityloxy)methyl]benzene (Table 2, Entry 19)

Solid; mp 96–98°C; yield 98%; ^1H NMR ($CDCl_3$) δ 7.40–7.26 (m, 25H), 5.36 (s, 1H); MS (EI) *m/z* 183, 167, 105, 91, 77; IR (KBr): υ 3468, 3060, 2923, 2853, 1954, 1741, 1595, 1489, 1443, 1326, 1154, 1079, 1007, 889, 758, 698, 635, 579 cm^{-1}. Anal. calcd. for $C_{32}H_{26}O$: C, 90.14; H, 6.10. Found: C, 90.2; H, 6.15.

CONCLUSION

In conclusion, a facile, recyclable, and clean protection of alcohols as trityl ethers using a catalytic amount of $FeCl_3$ in ILs at room temperature in shorter reaction times has been demonstrated. The simplicity of operation, mild conditions, easy recyclability of the catalyst, and the environmentally benign nature of the reaction allows easy application to a wide range of substrates.

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