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A convenient one-step method for the deprotection and esterification of triphenylmethyl ethers

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Abstract

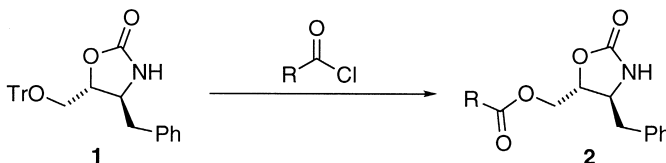
We have discovered a simple one-pot procedure to convert trityl ethers into esters, using the corresponding acid chloride as the only reagent. © 2000 Elsevier Science Ltd. All rights reserved.

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We had recently prepared a series of trityl ethers of 5-hydroxymethyl-oxazolidinone derivatives with varying alkyl or aryl substitutions in position 4 (e.g. **1**).¹ We wished to convert these trityl ethers (**1**) to a variety of different esters (**2**). In order to carry out such a transformation, we would usually remove the trityl ether, purify the alcohol and then acylate with an acid chloride or other acylating agent.

The trityl ether is an exceptionally useful protecting group in organic synthesis.² It is stable to a variety of reaction conditions, but can be readily removed by reduction (catalytic hydrogenation or dissolving metal reduction) or with acid.³

A common route to an ester is to treat an alcohol with an acid chloride. Since acid chlorides sometimes produce a small amount of HCl, we rationalized that we might be able to perform the conversion of a trityl ether to an ester in one step (Scheme 1).⁴ This was attempted using oxazolidinone **1** and 200 mol% of octanoyl chloride. To our delight, we found that this reaction gave **2** ($R = \text{CH}_3(\text{CH}_2)_6$) in 87% yield.



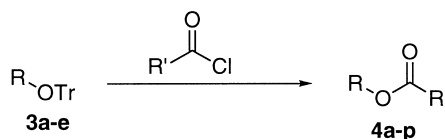
Scheme 1.

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Finding no examples of such a one-pot procedure dealing with trityl ethers, and since several one-pot interconversions of protecting groups have been reported in recent years,^{5–7} we set out to examine the limitations and the scope of this reaction. As a test system it was decided to use the trityl ether of 3-phenyl-1-propanol (**3a**).

The reaction of **3a** with an equimolar amount of acetyl chloride resulted in **4a** in 58% yield. Increasing the amount of acetyl chloride to 200 mol% resulted in a significant improvement in the yield (84%). Using 500 mol% gave **4a** in 93% yield. In all these cases, distilled acetyl chloride was used. However, if the acetyl chloride was used directly from the bottle without distilling, the yield improved to 98%, even for 200 mol% (Table 1).⁸ Our hypothesis was that HCl generated by the acid chloride was responsible for the cleavage of the trityl ether. In order to test this hypothesis, two additional reactions were carried out. The yield of **4a** dropped to 5% if Et₃N (200 mol%) was added to the reaction, while the starting trityl ether (**3a**) was recovered in 89% yield. Upon adding 100 mol% of HCl to the reaction prior to the addition of acetyl chloride, the yield improved significantly (from 58 to 85%), using only 100 mol% of acetyl chloride.

Table 1
Esterification of trityl ethers with acid chlorides^{8,9}



Entry	Cmpd.	R	R'	Mole %	Time	Product	Yield
1	3a	Ph(CH ₂) ₃	CH ₃	200	18 h	4a ¹⁰	98%
2	3a	Ph(CH ₂) ₃	(CH ₃) ₃ C	200	18 h	4b ¹⁰	100%
3	3a	Ph(CH ₂) ₃	CH ₃ (CH ₂) ₆	200	18 h	4c	99%
4	3a	Ph(CH ₂) ₃	(CH ₃) ₂ CH	200	18 h	4d ¹⁰	96%
5	3a	Ph(CH ₂) ₃	PhCH ₂ OCH ₂	200	18 h	4e	79%
6	3a	Ph(CH ₂) ₃	PhCH ₂ O	200	18 h	4f	NP ^a
7	3b	CH ₃ CH ₂ CH(CH ₃)	CH ₃ (CH ₂) ₆	200	18 h	4g	71%
8	3c ¹¹	PhCH ₂	CH ₃ (CH ₂) ₆	200	18 h	4h ¹²	90%
9	3d	TBSO(CH ₂) ₄	CH ₃ (CH ₂) ₆	200	18 h	4i	NP ^a
10	3e	AcO(CH ₂) ₄	CH ₃ (CH ₂) ₆	200	18 h	4j	NP ^a
11	3a	Ph(CH ₂) ₃	Ph	200	48 h ^b	4k ¹⁰	54%
12	3a	Ph(CH ₂) ₃	Ph	500	48 h ^c	4k ¹⁰	80%
13	3a	Ph(CH ₂) ₃	4-CF ₃ Ph	200	48 h	4l ¹⁰	55%
14	3a	Ph(CH ₂) ₃	4-NO ₂ Ph	200	96 h ^d	4m	77%
15	3a	Ph(CH ₂) ₃	3,4-Cl ₂ Ph	200	96 h ^d	4n	40%
16	3a	Ph(CH ₂) ₃	4-CH ₃ OPh	200	48 h ^b	4p	12%
17	3a	Ph(CH ₂) ₃	4-CH ₃ OPh	1000	18 h ^c	4p ¹⁰	68%

^a NP=No product formed

^b DMAP (10 mol%) was added

^c Heated to reflux

^d At room temperature for 2 days, then heated to reflux for 2 days

Other solvents can be used in the reaction. In THF, the reaction was complete after 8 h, giving **4a** in 85% yield. The reaction proceeded more slowly in toluene, but was complete after 120 h, giving **4a** in 85% yield. In DMF, the reaction did not go to completion, even after 120 h, giving **4a** in 25% yield and starting material **3a** in 33% yield. In comparison, the reaction generally takes 18 h to give **4a** in 98% yield in CH_2Cl_2 .

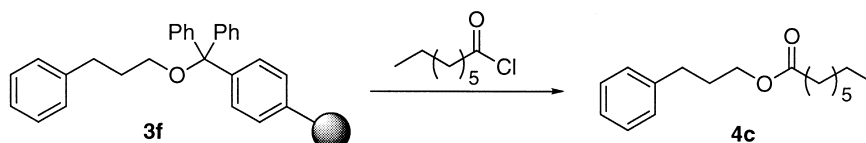
Other aliphatic acid chlorides worked quite well (Table 1). The sterically hindered trimethylacetyl chloride gave ester **4b** in 100% yield (Entry 2). Octanoyl chloride provided octanoate **4c** in 99% yield. Isobutyryl chloride also gave an excellent yield of ester **4d** (96%). Benzyloxyacetyl chloride afforded **4e** in reasonable yield (79%) as well. Benzyl chloroformate (CbzCl) formed no product at all.

2-Butyl trityl ether (**3b**) was readily converted to the ester (**4g**) in 71% yield, and the benzyl ether (**3c**) gave **4h** in 90% yield. However, a compound containing a silyl ether (**3d**) as well as one containing an acetate (**3e**) did not tolerate the reaction conditions and none of the desired product was formed. The silyl ether and the acetate were both cleaved under the reaction conditions, providing a mixture of esters.

Aromatic acid chlorides work as well, although the reaction took longer to go to completion, and yields were not as good when compared to the aliphatic acid chlorides. Upon heating, the reaction time was shortened and yields improved.⁹ Using the same reaction conditions that had been used for aliphatic acid chlorides (200 mol% PhCOCl , room temperature) resulted in very little product formation in 18 h. The reaction was then allowed to continue for a total of 4 days, which gave benzoate **4k** in 23% yield. The use of an acylation catalyst (DMAP) gave benzoate **4k** in 54% yield after 2 days. Addition of 100 mol% of HCl to the trityl ether, followed by addition of 200 mol% of PhCOCl , gave **4k** in 27% yield. We examined the use of larger amounts of benzoyl chloride (500, 800 and 1000 mol%) at both room temperature and reflux. While all of these provided improved yields (65–98%), the use of 500 mol% at reflux proved to be the most convenient method.

An electron-withdrawing group (4-trifluoromethyl) on the aromatic ring of the acid chloride gave **4l** in 55% yield after 2 days, even without heating. Using 200 mol% of either 4-nitrobenzoyl chloride, or 3,4-dichlorobenzoyl chloride, neither reaction was complete after 2 days at room temperature. Heating to reflux for an additional 2 days gave **4m** (77%) and **4n** (40%). An electron-donating group (4-methoxy), however, gave no product after 22 h at room temperature. Addition of DMAP only improved the yield of **4p** to 12%. Increasing the amount of acid chloride to 1000 mol% and heating to reflux for 18 h gave **4p** in 68% yield.

An additional application of this procedure is for the removal and subsequent acylation of an alcohol linked to a trityl-resin.^{13,14} The alcohol can be isolated directly as the ester. Using 3-phenyl-1-propanol as the model, the attachment to the trityl-resin and the removal to form the octanoate ester (**4c**) resulted in an overall yield of 70% (Scheme 2).¹⁵



Scheme 2.

We have discovered a simple one-step conversion of a trityl ether to an ester, using an acid chloride as the only reagent. This procedure works very well for aliphatic acid chlorides, even with secondary or benzylic trityl ethers. It is not compatible with acid-sensitive functionalities. It does not work as well for aromatic acid chlorides, although the reaction can be driven to completion by increasing the amount of acid chloride and/or by heating the reaction. Several variables were examined, including different trityl ethers, different acid chlorides, amount of acid chloride, solvent and the addition of an amine to the reaction.

Acknowledgements

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8. The trityl ether was dissolved in CH₂Cl₂ (0.5 M), cooled to 0°C and the aliphatic acid chloride (200 mol%) was added. After warming to room temperature and stirring for 18 h, the reaction was washed with saturated aqueous NaHCO₃ and water. The aqueous phase was extracted with CH₂Cl₂ and the combined organic phase was washed with brine. All new compounds showed satisfactory ¹H, ¹³C NMR and HRMS data.
9. The trityl ether was dissolved in CH₂Cl₂ (0.5 M), cooled to 0°C and benzoyl chloride (500 mol%) was added. The reaction was warmed to room temperature and then heated to reflux for 2 days. Same work-up as above.⁸
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15. 3-Phenyl-1-propanol was coupled to trityl chloride resin (copoly(styrene-1% DVB), 200–400 mesh; loading: 1.34 mmol/g) by stirring with DMAP and *i*Pr₂NEt in CH₂Cl₂ for 60 h. This resin was suspended in CH₂Cl₂ (19% w/v) and cooled to 0°C. Octanoyl chloride (200 mol%) was added, warmed to room temperature and stirred for 27 h. The resin was filtered and washed with CH₂Cl₂. Flash chromatography with 1% ethyl acetate in hexanes gave **4c** in 70% yield.