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Metal-Free Oxidative Cross Esterification of Alcohols *via* Acyl Chloride Formation

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Abstract: A novel metal-free oxidative cross esterification of alcohols has been achieved using trichloroisocyanuric acid as an oxidant. The alcohols were converted *in situ* into their corresponding acyl chlorides, which were then reacted with primary and secondary aliphatic, benzylic and allylic alcohols and phenols. A wide variety of esters was obtained in satisfactory yields.

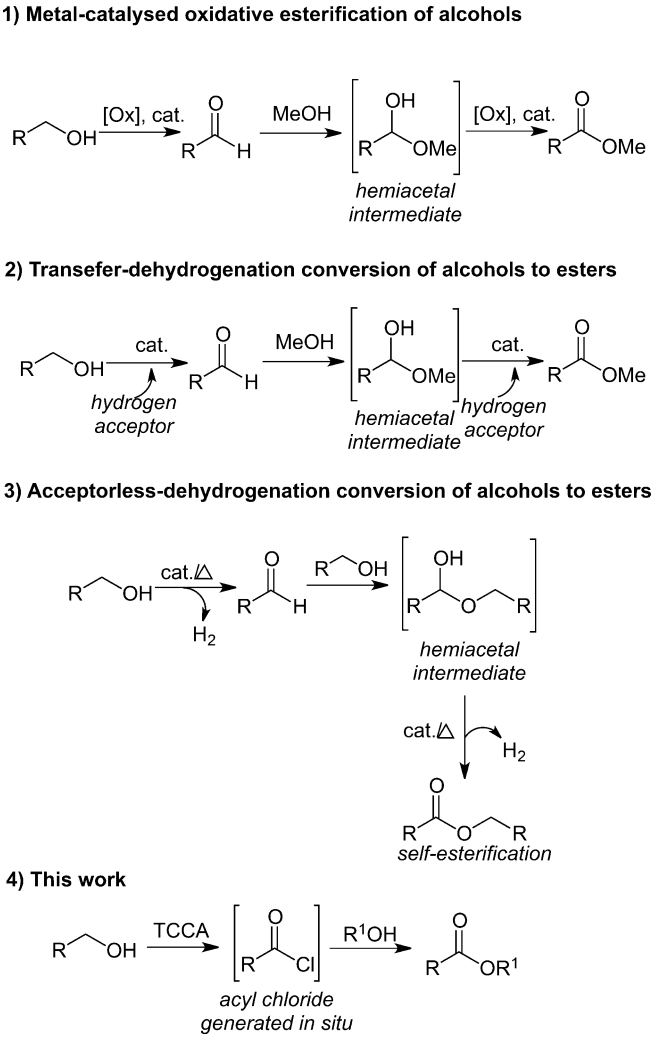
Keywords: acyl chlorides; alcohols; esters; metal-free reaction; trichloroisocyanuric acid

The ester group is one of the most significant and abundant functional group in organic chemistry and can be found in many natural products, polymers, pharmaceuticals and synthetic intermediates.[1] Traditionally, esters are prepared by a nucleophilic substitution between carboxylic acid derivatives (carboxylic halides, anhydrides and active esters) and alcohols.[2] A recent alternative approach is the oxidative esterification of aldehydes with alcohols, but the required aldehydes are normally obtained by selective oxidation of alcohols.[3] Alcohols are easily available and stable compounds, and are contained in many naturally occurring organic molecules. For these reasons, the direct conversion of alcohols to esters is a highlight of green and sustainable chemistry.[4]

A large number of metal-catalysed oxidative cross esterifications of alcohols have been reported (Scheme 1, pathway 1), but prevalently furnish methyl esters (methanol is used as a solvent),[5] require large excess of oxidants[6] and sometimes are limited with respect to catalyst accessibility.[7]

An important milestone in this context are the hydrogen transfer oxidations of primary alcohols to methyl esters (Scheme 1, pathway 2) catalysed by transition metals, such as Ru[8] and Ir.[9]

Currently, acceptorless alcohol dehydrogenations (AADs) are of great interest (Scheme 1, pathway 3). Although, with respect to atom economy, these transformations do not require a hydrogen acceptor, never-



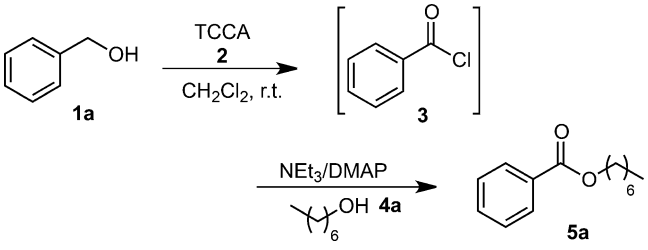
Scheme 1. Esters from alcohols.

theless they necessitate elevated temperatures to remove H_2 from the equilibrium and prevalently are self esterifications of primary alcohols.[10]

The methods outlined above consist of the formation of a hemiacetal intermediate, which is subsequently oxidised to the ester (Scheme 1, pathways 1, 2 and 3). Many drawbacks, connected to the formation and reactivity of the hemiacetal, limit the substrate scopes of these reactions. For these reasons we have investigated the possibility to develop a more general methodology to transform directly primary alcohols into esters. We have envisioned use of an alternative method to bypass the hemiacetal formation and to avoid the use of a large excess of oxidant and alcohols. Our goal was to carry out a general metal-free methodology that would be able to transform alcohols into acyl chlorides, which would then react with all classes of alcohols providing the corresponding esters (Scheme 1, pathway 4). Due to our interest in the oxidative transformations of alcohols[11] and in relation to our recently reported metal-free oxidative esterification of aldehydes,[12] we tested the possibility to transform directly primary alcohols into esters by the use of trichloroisocyanuric acid (TCCA). TCCA is an economical, commercially available, and non-toxic oxidising[13] and chlorinating[14] reagent, frequently used for swimming-pool, dishware, house, hotel and public places disinfection, and in fruit and vegetable preservation.[15] To the best of our knowledge, no similar transformation of alcohols to esters *via* acyl chloride formation are known to date.

We began our investigation by treating benzyl alcohol (Table 1, **1a**, 2.0 mmol) with TCCA (Table 1, **2**, 3.0 mmol) in dichloromethane (3.25 mL) at room temperature.

Table 1. Screening of the reaction conditions.

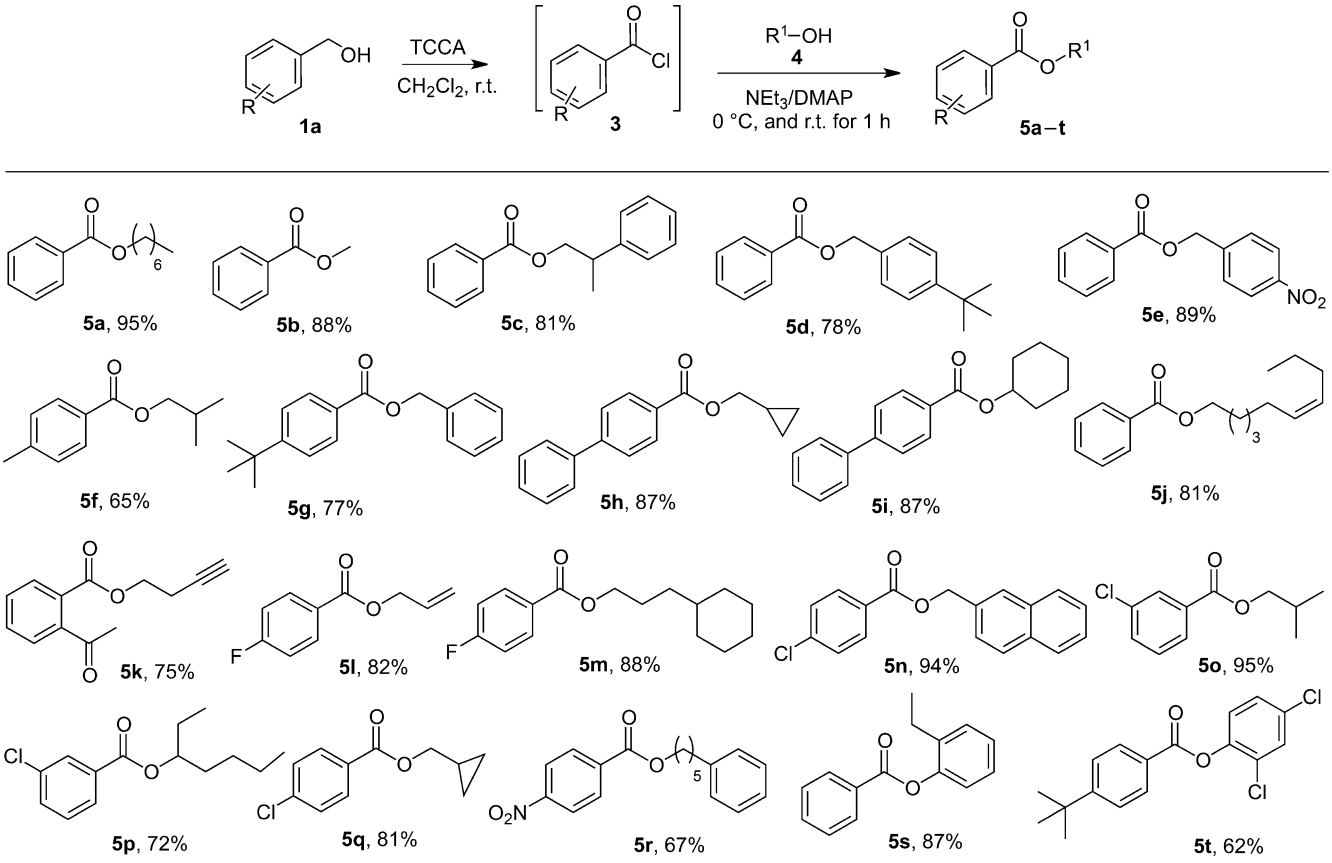


Entry	**1a** (mmol)	TCCA (mmol)	Yield [%][a]
1	2.0	3.0	97[b]
2	1.1	3.0	96[b]
3	1.1	2.0	95[b]
4	1.1	1.1	95[b]
5	1.1	1.1	–[c]
6	1.1	1.1	–[d]

[a] Isolated yields.
[b] Reaction performed at room temperature.
[c] Reaction performed at 80 °C (MWI) for 2 h.
[d] Reaction performed at 80 °C (MWI) for 4 h.

The reaction was monitored by TLC until the disappearance of the alcohol, and after 5 days, the corresponding benzoyl chloride (Table 1, **3**) was quantitatively formed. This reaction mixture, containing the acyl chloride generated *in situ*, was treated with heptanol (Table 1, **4a**, 1 mmol) and NEt_3 in the presence of a catalytic amount of DMAP (2 mmol/10 mol%) at 0 °C, and after 1 h at room temperature the desired ester was formed in 97% yield (Table 1, **5a**, entry 1). In order to decrease the amount of the benzyl alcohol **1a**, the same reaction was carried out employing 1.1 mmol of **1a** and the desired ester **5a** was obtained in 96% yield (Table 1, **5a**, entry 2). Then the reduction of the TCCA amount was investigated. When 2.0 mmol (Table 1, **2**, entry 3) and 1.1 mmol (Table 1, **2**, entry 4) of TCCA were used the ester **5a** was obtained with comparable and satisfying yields. After the optimised stoichiometric ratio of the reactants was established, in order to shorten the reaction time, the first step of the methodology was carried out under microwave dielectric heating at 80 °C for 2 h (Table 1, entry 5) and for 4 h (Table 1, entry 6) but a mixture of unreacted benzyl alcohol **1a**, benzaldehyde and benzoyl chloride **3** was recovered. After the reaction conditions were optimised, the scope of the reaction was tested (Scheme 2). In general, all reactions proceeded without any significant side products, and the corresponding esters **5a–t** were obtained in satisfying yields.[16]

The methodology was applied to variously substituted benzylic alcohols, affording a wide range of esters. Neither the electronic properties nor steric effects of substituents on the aromatic ring of the benzylic alcohols were found to have any effect on the reaction. Both electron-donating groups, such as benzylic C–H (Scheme 2, product **5f**), aliphatic groups (Scheme 2, products **5g** and **5t**) and phenylic residues (Scheme 2, products **5h** and **5i**), and electron-withdrawing groups, such as NO_2 (Scheme 2, product **5r**), were well tolerated providing the desired esters in good yields. Benzylic alcohol with carbonyl substituents like a ketone gave good results too (Scheme 2, product **5k**). The reaction carried out on alcohols with halide substituents on the aromatic ring gave the corresponding esters, which could be further transformed by traditional cross-coupling reactions (Scheme 2, products **5l–q**). We studied the reaction of benzylic alcohols with various primary and secondary alcohols. Primary linear (Scheme 2, products **5a** and **5b**) and branched aliphatic alcohols (Scheme 2, products **5c**, **5f**, **5h**, **5m**, **5o** and **5q**) furnished the corresponding esters in satisfactory yields. Notably, more sterically hindered secondary alcohols, such as cyclohexanol (Scheme 2, product **5i**) and heptan-3-ol (Scheme 2, product **5p**) were also suitable for delivering the corresponding esters.[17] Benzylic alcohols, which may quickly oxidise to the corresponding aldehydes, in-

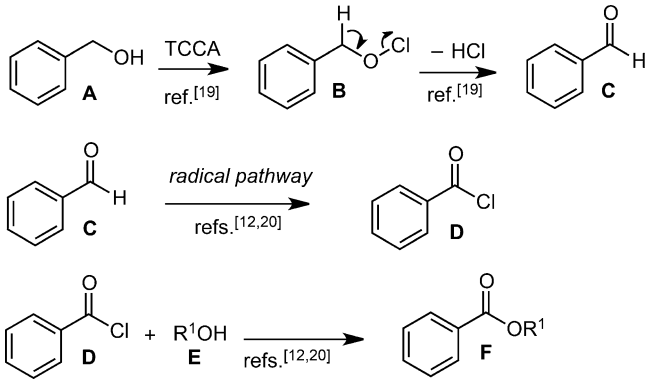


Scheme 2. Investigation of the substrate scope of the reaction.

stead reacted successfully providing the desired esters (Scheme 2, products **5d**, **5e**, **5g** and **5n**). Alcohols with unsaturation, such as (*Z*)-dec-6-en-1-ol, but-3-yn-1-ol and prop-2-en-1-ol were also effectively employed in this oxidative esterification (Scheme 2, products **5j**, **5k** and **5l**). We were delighted to notice that phenols, which are weak nucleophiles, reacted successfully (Scheme 2, products **5s** and **5t**).[18]

A possible reaction mechanism is reported in Scheme 3. Alcohol **A** reacts with TCCA, generating a hypochlorite compound **B** which readily loses hydrogen chloride to form the aldehyde **C**.[19] On the basis of previously published papers, aldehyde **C** is then converted into the acyl chloride **D** following a radical pathway.[12,20] In the last step, the acyl chloride **D** reacts with alcohol **E** to give the corresponding ester **F**.[21]

In conclusion, a novel example of metal-free cross oxidative esterification of alcohols to esters is reported. The transformation *in situ* of benzyl alcohols to acyl chloride provides the methodology with a very wide scope. Notably the methodology has an optimal stoichiometric molar ratio of reactants, and makes use of mild reaction conditions and cheap and easily available reagents. In no case was the self coupling product formation observed. Additional studies on the mechanistic details are currently underway in our laboratory.



Scheme 3. A plausible reaction mechanism.

Experimental Section

Heptyl Benzoate (5a); Typical Procedure

TCCA (0.256 g, 1.1 mmol) was portionwise added over a period of 1–2 min to a solution of benzyl alcohol (0.119 g, 1.1 mmol) in 3.25 mL dichloromethane under a dry argon at-

mosphere and at room temperature. The resulting suspension was stirred at room temperature for 5 days under dry argon (the reaction was monitored by TLC until disappearance of benzyl alcohol). Then the reaction mixture was cooled to 0 °C, stirred under an inert atmosphere of dry argon and heptanol (0.116 g, 1.0 mmol) was dropwise added *via* syringe followed by dropwise addition of NEt_3 (0.202 g, 2.0 mmol) and then DMAP (0.012 g, 10 mol%) at once. After completion of the addition, the reaction mixture was left to stir at room temperature until disappearance of the heptanol (monitored by TLC, the reaction is usually complete in about 1 h). Then the solvent was removed under vacuum, and the residue purified by flash chromatography (hexane/ethyl acetate = 4.5/0.5). The expected ester **5a** was then obtained as a colorless oil; yield: 0.209 g (95%); R_f = 0.593 (hexane/ethyl acetate = 4.5/0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, J = 8.0 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 4.31 (t, J = 6.7 Hz, 2H), 1.80–1.73 (m, 2H), 1.48–1.26 (m, 8H), 0.89 (t, J = 6.6 Hz, 3H);[22] ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 132.7, 130.5, 129.5, 128.3, 65.1, 31.7, 28.9, 28.7, 26.00, 22.6, 14.0;[22] IR (neat): ν = 2956, 2929, 2857, 2359, 2341, 1721, 1602, 1585, 1467, 1453, 1275, 1112, 1027, 711 cm^{-1}.[2,3]

Acknowledgements

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