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Preparation of hexafluoroisopropyl esters by oxidative esterification of aldehydes using sodium persulfate†

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A simple, metal-free route for the oxidative esterification of aldehydes to yield hexafluoroisopropyl esters is reported. The methodology employs sodium persulfate and a catalytic quantity of a nitroxide and is applicable to aromatic, heteroaromatic, and aliphatic aldehydes.

Introduction

Of the oxidants in the synthetic chemist's toolkit, oxoammonium salts such as 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (AcNH-TEMPO$^+BF_4^-$, **1**) are attractive. They are shelf-stable, metal-free, recyclable, and can be used under mild conditions.[1] They and their nitroxide analogues, such as ACT (AcNH-TEMPO, **2**), have been employed extensively for the oxidation of alcohols to aldehydes, ketones, and carboxylic acids.[2] Moving beyond simple alcohol oxidation, oxoammonium salts can also be used as reagents for a range of oxidative functionalisation reactions. This includes the preparation of nitriles[3] and amides[4] from aldehydes, as well as an array of C–H functionalisation processes.[5] Another example is the oxidative esterification of aldehydes (Fig. 1a).[6] When performing this transformation, the nature of the coupling partner is important. It is not possible to use a simple alcohol since there is a propensity for it to undergo oxidation in the presence of the oxoammonium salt. One solution is to use a tertiary alcohol which could not itself be oxidised but previous methods have shown this to be difficult, due to the steric bulk of such species.[7] Under appropriate conditions, α-trifluoromethyl alcohols fail to oxidise when exposed to **1** and, based on this observation, we developed a methodology for the preparation of perfluoro esters from aldehydes and an excess of the requisite perfluoro alcohol (Fig. 1b).[6] Our attention focused primarily on the generation of hexafluoroisopropyl esters (HFIP esters). These compounds are valuable synthons that can easily be converted to other types of esters or to amides under mild conditions,[6,8] and can be used as starting materials for organocatalytic asymmetric reactions.[9,10] Additionally, they are themselves more lipophilic than their non-fluorinated analogues[11] and have other unique properties (*e.g.* they can be readily reduced with $NaBH_4$).[12] Other routes to HFIP esters include organocatalytic cross-coupling of aldehydes with hexafluoroisopropyl alcohol (HFIP),[13] palladium-catalysed alkoxycarbonylation,[14] or in a two-step process *via* the intermediacy of an acid anhydride.[15]

While successful and operationally simple, our route to HFIP esters does suffer from one significant drawback; a superstiochiometric quantity of **1** is required. In the presence of base, the hydroxylamine byproduct **3** initially formed undergoes a comproportionation reaction with a further aliquot of **1** to generate two equivalents of nitroxide **2**.[16,17] Thus a sacrificial equivalent of **1** is required to achieve complete esterification of the aldehyde substrate. To overcome this challenge, we wanted to turn to a method we have used for other oxidative

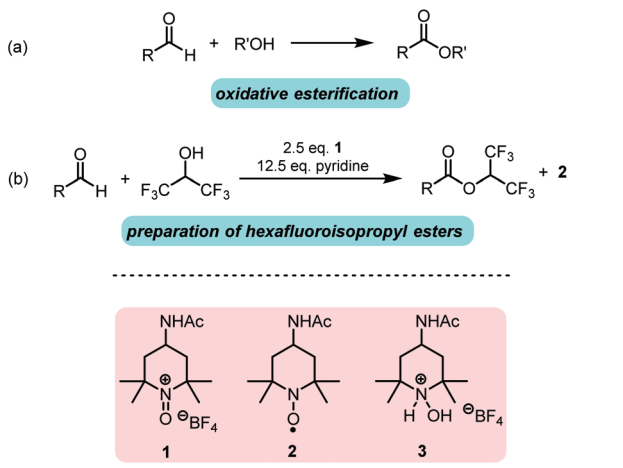

Fig. 1 Oxidative esterification of aldehydes.

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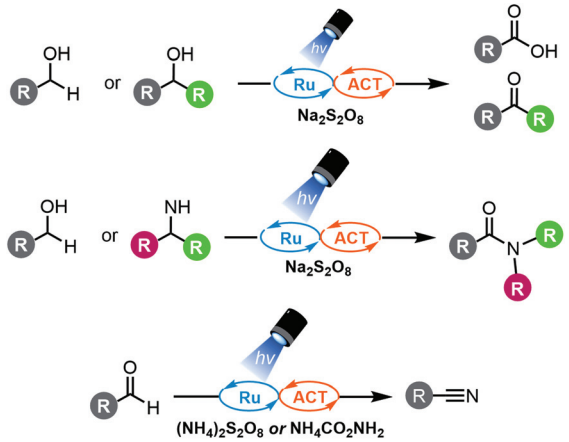


Fig. 2 Merger of oxoammonium cations and visible-light photoredox catalysis.

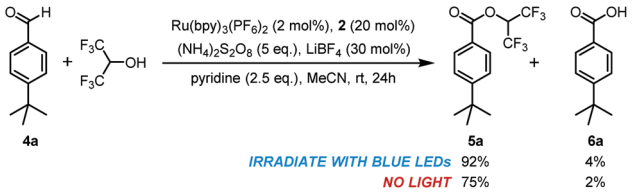


Fig. 3 Employing visible-light photoredox catalysis to prepare HFIP esters.

functionalisation processes; namely merging oxoammonium-cations and visible-light photocatalysis.[18] We employed a dual catalytic system comprising of $Ru(bpy)_3(PF_6)_2$ as a photocatalyst and **2** as the primary oxidant.[19] Cheap, readily available sodium persulfate is used as a terminal oxidant.[20] This approach proved successful for the preparation of nitriles and amides from alcohols and aldehydes,[21] and for the oxidation of alcohols to ketones, and carboxylic acids (Fig. 2).[22] We believed that such an approach might allow us to prepare a series of HFIP esters from aldehyde precursors. We therefore embarked on a program of study focused on this transformation. We report here how we started this endeavour and how it led to a simpler, easier approach that does not require photocatalysis but instead simply uses sodium persulfate as a primary oxidant, in conjunction with a catalytic quantity of **2**.

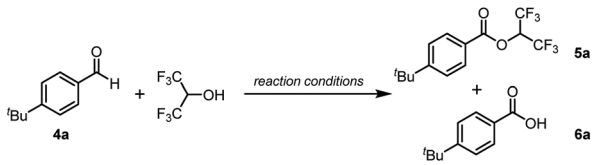
Results and discussion

With development of a photocatalytic route to HFIP esters in mind, we embarked on reaction optimisation. Using 4-*tert*-butylbenzaldehyde (**4a**) as a test substrate, we used as our starting point the reaction conditions developed previously by our group for the photoamidation of alcohols.[22] This involved employing $Ru(bpy)_3(PF_6)_2$ as the photocatalyst and **2** as the pro-oxidant that would be converted to the active oxoammonium cation oxidant (**1**) *in situ*. Pyridine was used as the base, and lithium tetrafluoroborate as an additive to activate the aldehyde towards nucleophilic attack by pyridine. Using sodium persulfate as the terminal oxidant resulted in a mixture of the desired HFIP ester (**5a**, 92%) and 4-*tert*-butylbenzoic acid (**6a**, 4%) after irradiating with blue LED light for 24 h (Fig. 3). Buoyed by this encouraging result, we moved to explore the effects of changing the parameters of the reaction. As part of this, we undertook a series of baseline experiments to confirm the need for each component in the reaction. One such trial involved performing the reaction in the absence of light. Surprisingly, we obtained a 75% conversion to **5a**. This result showed that the reaction was not wholly photomediated and motivated us to develop a simpler approach for the reaction.

We first re-ran the reaction in the absence of light having removed the ruthenium photocatalyst and obtained an identical result (Table 1, entry 1). We next removed the lithium tetrafluoroborate additive and again obtained a comparable conversion to the HFIP ester (entry 2). Extending the reaction time from 24 h to 48 h led to an improved conversion (entry 3). Operating for 24 h but reducing the quantity of sodium persulfate used had a deleterious effect on product conversion, showing that 5 eq. was optimal (entries 4 and 5). The same was true when we attempted to reduce the amount of pyridine used (entry 6). Increasing the loading of **2** to 30 mol% did improve the outcome of the reaction (entry 7), but changing the persulfate salt to the potassium analogue did not (entry 8). Returning to sodium persulfate as the terminal oxidant, and using 20 mol% **2**, we next probed the effect of increasing the temperature at which the reaction was performed (entries 9 and 10). Operating at 50 °C proved to be optimal, especially if the loading of **2** is increased to 30 mol% (entry 10). To confirm that the nitroxide, **2**, plays a key role in the reaction, we performed a trial in its absence. While we did obtain some product, this came at the cost of selectivity; a significant amount of off-target carboxylic acid (**6c**) being formed (entry 11). In some of our previous work, and in other literature reports, the use of lutidine as a base was advantageous,[6,17,23] but in this case changing from pyridine to 3,5-lutidine did not improve the outcome of this reaction (entry 12). Returning to pyridine as the base but reducing the reaction time showed us that a good conversion to **5** could be obtained after 3.5 h at 50 °C (entries 13–15).

We turned our attention next to isolating the HFIP ester product. This proved challenging since it is necessary to remove any unspent aldehyde starting material as well as the corresponding carboxylic acid formed as a byproduct. In addition, HFIP esters are generally volatile and prone to hydrolysis in an aqueous acidic environment. Exploring a number of product isolation protocols, isolation of the HFIP ester from the aldehyde starting material proved particularly troublesome. Using a standard method involving washing with sodium bisulfite to remove unreacted aldehyde impacted the recovery of the desired ester product.[24] We decided to return to

Table 1 Optimisation of reaction conditions[a]



Entry	Conditions[b]	**4a** (%)	**5a** (%)	**6a** (%)
1	$Na_2S_2O_8$ (5 eq.), **2** (0.2 eq.), $LiBF_4$ (0.3 eq.), pyridine (5 eq.), 25 °C, 24 h	23	75	2
2	$Na_2S_2O_8$ (5 eq.), **2** (0.2 eq.), **no $LiBF_4$**, pyridine (5 eq.), 25 °C, 24 h	28	71	1
3	$Na_2S_2O_8$ (5 eq.), **2** (0.2 eq.), **no $LiBF_4$**, pyridine (5 eq.), 25 °C, **48 h**	7	90	3
4	**$Na_2S_2O_8$ (2.5 eq.)**, **2** (0.2 eq.), **no $LiBF_4$**, pyridine (5 eq.), 25 °C, 24 h	60	39	1
5	**$Na_2S_2O_8$ (4 eq.)**, **2** (0.2 eq.), **no $LiBF_4$**, pyridine (5 eq.), 25 °C, 24 h	50	50	0
6	$Na_2S_2O_8$ (5 eq.), **2** (0.2 eq.), **no $LiBF_4$**, **pyridine (2.5 eq.)**, 25 °C, 24 h	33	59	8
7	$Na_2S_2O_8$ (5 eq.), **2 (0.3 eq.)**, **no $LiBF_4$**, pyridine (5 eq.), 25 °C, 24 h	13	87	0
8	**$K_2S_2O_8$ (5 eq.)**, **2** (0.2 eq.), **no $LiBF_4$**, pyridine (5 eq.), 25 °C, 24 h	48	52	0
9	$Na_2S_2O_8$ (5 eq.), **2** (0.2 eq.), **no $LiBF_4$**, pyridine (5 eq.), **30 °C**, 24 h	17	81	2
10	$Na_2S_2O_8$ (5 eq.), **2 (0.3 eq.)**, **no $LiBF_4$**, pyridine (5 eq.), **50 °C**, 24 h – optimised conditions taken forward	0	88	12
11	$Na_2S_2O_8$ (5 eq.), **no 2**, **no $LiBF_4$**, pyridine (5 eq.), 50 °C, 24 h	0	60	40
12	$Na_2S_2O_8$ (5 eq.), **2** (0.2 eq.), **no $LiBF_4$**, **3,5-lutidine (5 eq.)**, **50 °C**, 24 h	37	63	0
13	$Na_2S_2O_8$ (5 eq.), **2** (0.2 eq.), **no $LiBF_4$**, pyridine (5 eq.), **50 °C**, **3.5 h**	16	81	3
14	$Na_2S_2O_8$ (5 eq.), **2** (0.2 eq.), **no $LiBF_4$**, pyridine (5 eq.), **50 °C**, **1 h**	44	55	Trace
15	$Na_2S_2O_8$ (5 eq.), **2 (0.3 eq.)**, **no $LiBF_4$**, pyridine (5 eq.), **50 °C**, **3.5 h**	6	91	3

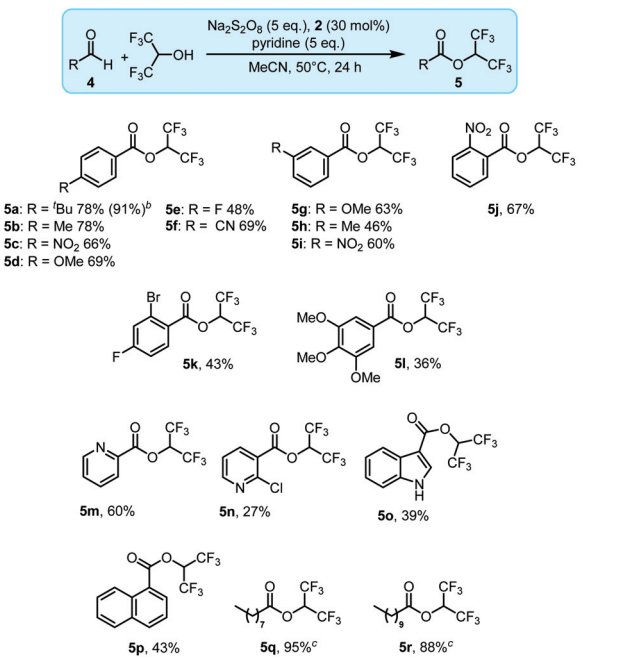
[a] Reactions performed in acetonitrile (2 mL) using **3a** (1 mmol, 1 eq.) and 2.5 eq. HFIP in a sealed vial; conversion determined by GC-MS. [b] Conditions changed from entry 1 are highlighted in **bold**.

running the reaction for 24 h rather than the shorter time because at this juncture all the aldehyde was consumed (Table 1, entry 10). Therefore, our optimal reaction conditions were: HFIP (2.5 eq.), **2** (30 mol%), pyridine (5 eq.), $Na_2S_2O_8$ (5 eq.), in acetonitrile at 50 °C for 24 h.

With the optimised reaction conditions in hand, we moved to assessing the substrate scope of the methodology with respect to aldehydes that varied in electronic properties as well as substitution patterns (Table 2). We were pleased to find that the oxidative esterification was effective for both electron rich and electron poor *ortho*-, *meta*-, and *para*-substituted benzaldehydes (**5a–j**), polysubstituted benzaldehydes (**5k** and **5l**), as well as representative heteroaromatic substrates (**5m–o**) and an extended aromatic example (**5p**). While aliphatic aldehydes could be converted to the corresponding HFIP esters, product isolation proved problematic due to the volatility of the ester products (**5q** and **5r**). Substrate screening was performed on the 1 mmol scale. To show the scalability of the reaction, we performed the reaction using **4a** at a tenfold scale. A 91% isolated yield of the desired HFIP ester, **5a**, was obtained.

From a mechanistic standpoint (Fig. 4), the initial step of the reaction in likely the thermally-mediated homolytic cleavage of sodium persulfate to yield two equivalents of the oxygen-centred sulfate radical anion for which there is literature precedent in other classes of reaction.[25,26] This radical anion can then oxidise nitroxide **A** in a single-electron transfer (SET) process to yield the oxoammonium cation **B** which then performs the oxidative esterification process. In so doing, hydroxylamine **C** is formed and then **A** can be regenerated by hydrogen-atom transfer (HAT) to another sulfate radical anion. The oxidative esterification process itself take place *via* the intermediacy of an acyl pyridinium ion. Such intermediates have been identified previously when performing oxidative functionalisation reactions using **1**.[4,6,17]

Table 2 Scope of the oxidative esterification protocol[a]



[a] Reactions performed on the 1 mmol scale; isolated yield after purification unless noted otherwise. [b] Reaction performed on the 10 mmol scale. [c] Product conversion determined by GC-MS.

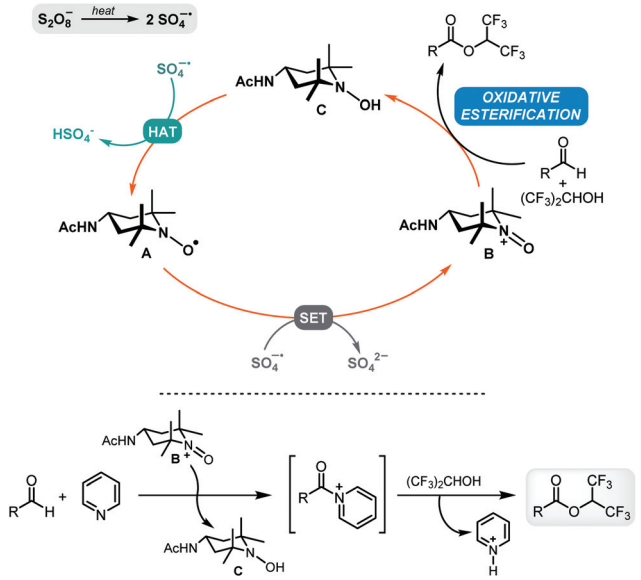


Fig. 4 Envisioned catalytic cycle for oxidative esterification.

Conclusion

In summary, a simple, metal-free route for the oxidative esterification of aldehydes to yield hexafluoroisopropyl esters is presented. The methodology employs sodium persulfate as the primary oxidant and a catalytic quantity of a nitroxide as an additive. It can be applied to aromatic, heteroaromatic, and aliphatic aldehyde substrates.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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