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Oxidative Esterification of Aldehydes Using a Recyclable Oxoammonium Salt

Christopher B. Kelly,[†] Michael A. Mercadante,[†] Rebecca J. Wiles,[†] and Nicholas E. Leadbeater*[,†,‡]

Department of Chemistry, University of Connecticut, 55 North Eagleville Road, Storrs, Connecticut 06269-3060, United States, and Department of Community Medicine & Health Care, University of Connecticut Health Center, The Exchange, 263 Farmington Avenue, Farmington, Connecticut 06030, United States

nicholas.leadbeater@uconn.edu

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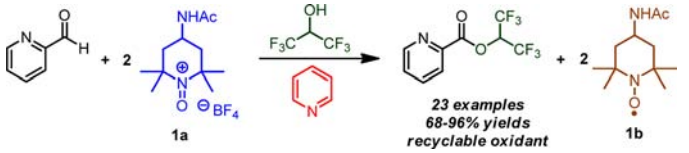
ABSTRACT



A simple, high yielding, rapid route for the oxidative esterification of a wide range aldehydes to hexafluoroisopropyl (HFIP) esters using the oxoammonium salt 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (1a) is reported. These esters can be readily transformed into a variety of other functional groups. The spent oxidant (1b) can be recovered and conveniently reoxidized to regenerate the oxoammonium salt, 1a.

Esters are highly attractive building blocks to the synthetic organic chemist. This functionality can readily be interconverted into a number of other functional groups, and they are frequently employed in industry as fragrances, medicines, or in polymer construction.[1] The classical route to ester preparation exploits reagent-based activation of carboxylic acids and subsequent treatment with the desired alcohol coupling partner.[1a] This activation can be performed *in situ* (e.g., using strong acids, $SOCl_2$, CDI,[2] DEAD/PPh_3,[3] DCC,[4] etc.) or in a stepwise fashion (e.g., carboxylic acid to acid chloride to ester).[5] Many of these processes employ reagents that can lack broad functional group tolerance as well as being toxic or hazardous to the user. Moreover, the byproducts that accompany these reactions are often difficult to separate from the desired ester.

An emerging alternative to ester synthesis is a tandem oxidation–esterification approach which offers greater flexibility in the requisite starting materials.[6] The most successful of these oxidative esterification methods is the conversion of an aldehyde to an ester. Several routes have been utilized to date such as those exploiting *N*-heterocyclic carbene activation,[7] transition metal-mediated processes,[8] and those simply using a stoichiometric oxidant[9] in the presence of the alcohol coupling partner. Of note is a recent report by Molander and co-workers that employs $Pd(OAc)_2$/XPhos with acetone as a terminal oxidant to accomplish oxidative esterification.[10]

Oxoammonium salts such as 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (**1a**) are environmentally benign, recyclable, metal-free species

[†] University of Connecticut.
[‡] University of Connecticut Health Center.

(1) (a) Otera, J. *Esterification: Methods, Reaction and Application*, 2nd ed.; Wiley-VCH: Weinheim, 2010. (b) Riemenschneider, W., Bolt, H. M. Esters, Organic. *Ullmann's Encyclopedia of Industrial Chemistry*: Wiley-VCH: Weinheim, 2005. (c) Rosato, D. V.; Rosato, D. V.; Rosato, M. V. *Plastic Product Material and Process Selection Handbook*: Elesevier Inc.: New York, 2004.
(2) Staab, H. A.; Mannschreck, A. *Chem. Ber.* **1962**, *95*, 1284.
(3) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763.
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(6) Ekoue-Kovi, K.; Wolf, C. *Chem.—Eur. J.* **2008**, *14*, 6302.
(7) Example: Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4331.
(8) Example: Kiyooka, S.; Wada, Y.; Ueno, M.; Yokoyama, T.; Yokoyama, R. *Tetrahedron* **2007**, *63*, 12695.
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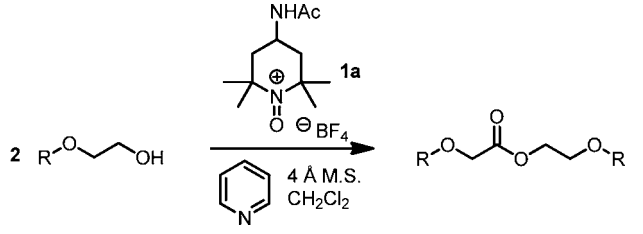
that can facilitate oxidation under extremely mild conditions. As such, they have gained recent popularity as alternatives to more traditional oxidizing reagents.[11] Much of the literature involving oxoammonium salts centers around the conversion of alcohols to corresponding carbonyl species.[12] As part of a broad program to enhance the profile of oxoammonium salt-based transformations,[13] we became interested in the possibility of synthesizing esters by means of oxidative esterification utilizing **1a** as the oxidant. Currently, there is little precedence for oxoammonium salt-mediated oxidative esterification.[14] Bobbitt and co-workers recently reported that alcohols could be converted into their dimeric esters under basic oxidative conditions (Scheme 1).[12] However, the reaction was limited in that the dimerization process was unique to alcohols bearing β-oxygen substituents.[12] At high concentrations in dichloromethane as solvent, dimeric esters of non-β-oxygen alcohols could be observed, albeit in suboptimal conversion.[12]

Scheme 1. Dimeric Ester Synthesis by Oxidative Esterification

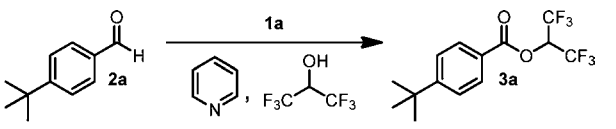


Seeking to expand the utility of this process, we posited that a coupling reaction in which an aldehyde and an alcohol partner could be joined to form an ester in the presence of **1a** could be possible. However, because of the propensity for alcohols to undergo oxidation themselves when exposed to **1a** under basic conditions,[15] it would be very unlikely that the oxidative esterification pathway would predominate. One solution would be to use as a coupling partner a tertiary alcohol which could not itself be oxidized. However, previous methods have shown this to be very difficult, likely because of the steric bulk of these species.[10,14b] We had previously shown that, in the presence of pyridyl bases, aliphatic α-trifluoromethyl alcohols fail to oxidize when exposed to **1a**.[13a] With this finding we wondered if perfluoroesters could be synthesized from aldehydes and an excess of the requisite perfluoroalcohol. If successful, such a methodology would have several advantages. Fluorinated esters are valuable synthons that can easily be converted to other types of esters or to amides under mild conditions. Additionally, they are themselves more lipophilic than their nonfluorinated analogs[16] and have other unique properties (e.g., they can be readily reduced[17] with $NaBH_4$). Perfluoroalcohols are very easy to remove, thus facilitating product isolation (e.g., hexafluoroisopropanol, HFIP, has a boiling point of 57 °C). Despite these advantages, limited examples exist for the preparation of this type of ester and those that are known either require large excesses of the oxidant[18] or report poor yields.[6]

Initially, we investigated whether hexafluoroisopropyl (HFIP) esters could be synthesized by way of oxidative esterification. Using **2a** as a model aldehyde, 2.2 equiv of pyridine as the base, 2.5 equiv of **1a** as the oxidant, and 1.5 equiv of HFIP in CH_2Cl_2 (0.5 M), we obtained 70% conversion by GC/MS to the desired ester **3a** in 12 h. To improve both the conversion and reaction time, we then increased the loading of HFIP (3 equiv) and utilized pyridine as both the base and solvent (12.75 equiv). Gratifyingly we were able to achieve complete conversion to **3a** in 1 h (Scheme 2). Isolation proved facile, giving an excellent yield of **3a** (96%). Reducing the HFIP loading led to extended reaction times being required to obtain comparable product conversion. We therefore opted to use 3 equiv. We also screened 4-picoline and 2,6-lutidine as potential solvents and bases for the reaction, but these pyridyl systems failed to affect appreciable oxidative esterification of **2a**.

Following reaction optimization, we next subjected a variety of aldehydes to our oxidative esterification conditions. Both electron-rich (Table 1, entries 1–2, 4, 6–7) and electron-poor (entries 3, 5, 8 and 9) functionalized derivatives of benzaldehyde all underwent rapid oxidation and gave excellent yields of their corresponding HFIP esters. Notably, substrates bearing electron-deficient aryl systems reached completion at a much faster rate than those bearing electron-donating groups. In certain cases (entries 3, 4, 9, 16, 18, 23, and 24), we were unable to achieve complete conversion using our optimized conditions. However, by simply increasing loadings of both **1a** and HFIP, we were able to ensure that the starting material was completely consumed.

Scheme 2. Model Oxidative Esterification of Aldehydes



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We then probed whether polycyclic and heterocyclic systems would be amenable to esterification. Furyl and pyridyl substituted aldehydes (entries 11, 12, and 13 respectively) were compatible with our optimized conditions giving their ester products in excellent yield. Our representative polycyclic species, 1-napthaldehyde (entry 10), similarly tolerated our reaction conditions, the HFIP ester being obtained in good yield.

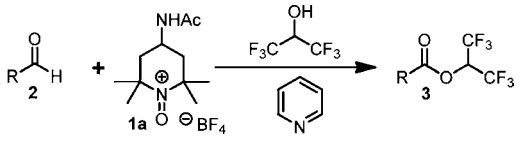
Wondering whether this oxidative esterification could be extended to aliphatic aldehydes, we initially screened a representative straight-chain system (entry 14). We were delighted to find this system readily underwent oxidative esterification in good yield. We next screened a variety of aliphatic systems. Those with α-substitution (entries 16 and 23) proved to react slower and required additional **1a** and HFIP to achieve complete conversion. This retardation in rate is likely due to the steric encumbrance caused by the α-substituents. Interestingly, **2o** was not impeded by α-substitution, likely due to the restricted rotation of the cyclohexyl system (entry 15). By moving the substituent to the *β*-position (entries 17−19 and 21), the reaction proceeds readily, giving good to excellent yields of the desired esters. Of note is the α-diphenyl substituted substrate **2t** whose failure to react could be attributed to the enhanced acidity of its α-proton (entry 20). When treated under the optimized conditions, neither starting material nor product was obtained, but rather a tar-like polymeric material. This could be the result of either an α-alkylation reaction between an enol form of the aldehyde and **1a** or a series of aldol-like reactions.

Moving to α,*β*-unsaturated and propargylic systems, we explored several olefinic species (entries 22 and 24−26). While cinnamyl (entry 22) and furylacryl (entry 24) aldehydes were successfully oxidized in good yield, α-methyl cinnamylaldehyde failed to go to complete conversion (not shown), despite increased addition of both **1a** and HFIP. Interestingly, a nonconjugated α,*β*-unsaturated aldehyde and a representative alkynyl aldehyde both afforded no product (entries 25 and 26 respectively). Only polymeric material and a trace amount of starting material were recovered each time.

In an attempt to expand the utility of this transformation, we investigated whether trifluoroethanol (TFE)-based esters could be prepared using our oxidative esterification. We chose three representative benzaldehyde derivatives (**2b**, **2c**, **2d**) to probe the efficacy of this transformation as compared to the preparation of the HFIP analogs. Unfortunately, even at the higher loadings of **1a** and trifluoroethanol, we failed to achieve greater than 30% conversion with any of these aldehydes.

To further demonstrate the utility of the HFIP esters synthesized in this study, we conducted several subsequent reactions using **3q** as a representative ester (Scheme 3). To investigate the reported propensity toward reduction,[16] we treated **3q** with sodium borohydride. We found that it could indeed be reduced quite readily, giving the corresponding alcohol in excellent yield. We next explored amidation, finding that the desired benzylamide could be readily synthesized. In contrast to the traditional amidation of esters,[1] no strong base was required in our case. Of additional note is that, unlike a previous report by Studer[19] in which HFIP esters were made from aldehydes *in situ* prior to amidation, using our protocol, aliphatic systems

Table 1. Scope of Oxidative Esterification of Various Aldehydes with HFIP[a]



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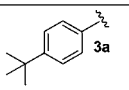
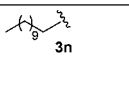
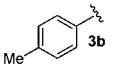
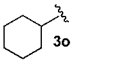
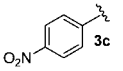
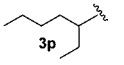
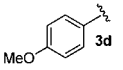
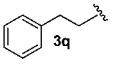
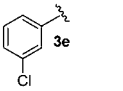
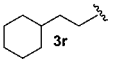
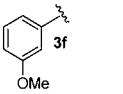
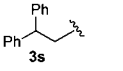
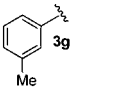
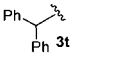
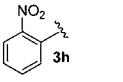
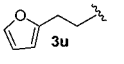
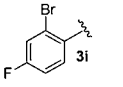
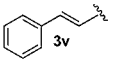
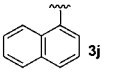
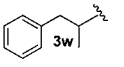
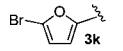
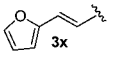
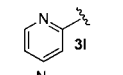
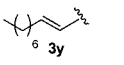
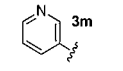
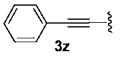
1	 3a	96	14	 3n	79
2	 3b	94	15	 3o	75
3	 3c	89[b]	16	 3p	86[b]
4	 3d	95[b]	17	 3q	87
5	 3e	94	18	 3r	71
6	 3f	79	19	 3s	87
7	 3g	90	20	 3t	-
8	 3h	94	21	 3u	68
9	 3i	96[b]	22	 3v	78
10	 3j	86	23	 3w	91[b]
11	 3k	91	24	 3x	90[b]
12	 3l	88	25	 3y	-
13	 3m	95	26	 3z	-

[a] Reaction conditions unless otherwise noted: Aldehyde (1 equiv), **1a** (2.5 equiv), HFIP (3 equiv), pyridine (12.75 equiv). [b] Required 3 equiv of **1a** and 3.5 equiv of HFIP.

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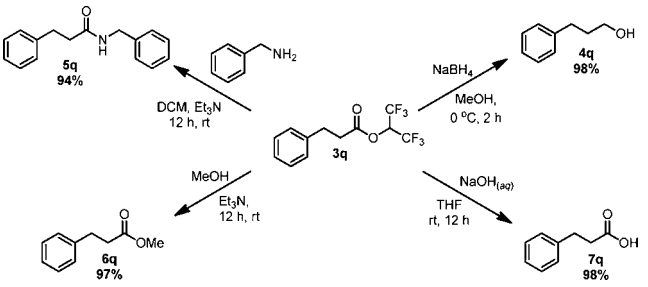
(19) Sarkar, S. D.; Studer, A. *Org. Lett.* **2010**, *12*, 1992.

can be utilized without competitive aldol processes. We also conducted a transesterification of **3q**, again under very mild conditions, giving a good yield of the desired methyl ester **6q**. Finally, hydrolysis of **3q** proceeded quite rapidly giving the carboxylic acid **7q** in excellent yield.

Scheme 3. Applications of HFIP Esters



In summary, we have disclosed a methodology for the oxoammonium salt-mediated oxidative esterification of aldehydes in the presence of HFIP to furnish a range of HFIP esters. Using pyridine as the solvent and **1a** as the oxidant, the ester products can be obtained in good to near-quantitative yields. The reaction is compatible with a range of functionalities, and the byproducts of the reaction can be removed with ease. Moreover, the spent oxidant, 4-acetylamino-2,2,6,6-tetramethyl-1-piperidinyloxy (**1b**), can be recovered and recycled (see Supporting Information). Finally, HFIP esters can be easily converted to other valuable products under very mild reaction conditions. Further oxoammonium-mediated oxidative functionalization reactions are currently being investigated as is a mechanistic study on this transformation.

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Supporting Information Available. Experimental procedures, characterization data, and spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.