

SYNLETT Spotlight 423

2,2,6,6-Tetramethylpiperidine-Based Oxoammonium Salts

Compiled by Christopher B. Kelly

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

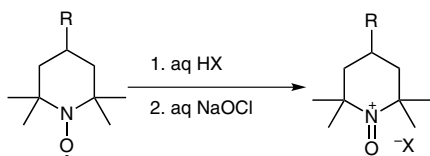
Christopher Kelly studied chemistry at Stonehill College in Easton, Massachusetts, USA, where he received his B.S. in Biochemistry in 2010. That same year, he joined the University of Connecticut in Storrs, where he is currently working towards his Ph.D. under the supervision of Dr. Nicholas Leadbeater. His research focuses on the development of new methods for incorporating fluorine into organic molecules as well as novel oxidation methods using oxoammonium ions.

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Introduction

Oxoammonium salts have recently attracted much attention as environmentally friendly, shelf-stable alternatives to traditional oxidants.¹ In addition to being more sustainable, these salts have several advantages: 1) the spent oxidant is easily recovered and recyclable; 2) oxidations are performed under mild conditions and are simple to conduct; 3) oxidations are typically colorimetric processes and reaction progress can be monitored visually.²



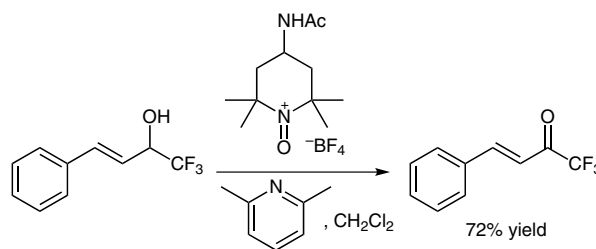
R = NHAc, OH, OMe, =O, H

X = Cl, Br, NO₃, ClO₄, BF₄, PF₆, SbF₆

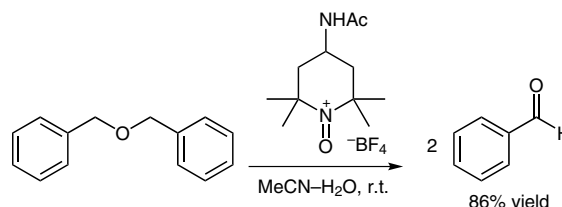
Scheme 1 Preparation of oxoammonium salts

Abstracts

(A) Trifluoromethylketones (TFMKs) are valuable synthons both as enzyme inhibitors and as critical intermediates in constructing a variety of fluorinated pharmacons. However, their preparation is complicated by the notoriously difficult to oxidize nature of α -CF₃ alcohols, a property that can likely be attributed to their electron-deficient nature. Using 4-NHAc-TEMPO⁺ BF₄⁻ (Bobbitt's salt) in the presence of a pyridyl base, α -CF₃ alcohols are readily oxidized in excellent yield to their corresponding TFMKs.⁶



(B) Bailey et al. reported¹¹ that Bobbitt's salt can be utilized to cleave benzyl ethers. Like the cross dehydrogenative couplings (CDCs), this oxidative reaction relies on the formal hydride transfer from the benzylic carbon to the oxoammonium salt, leading to a reactive oxonium ion. This ion then decomposes to the corresponding aldehyde and alcohol via water substitution. The alcohol subsequently undergoes oxidation to a carbonyl derivative.



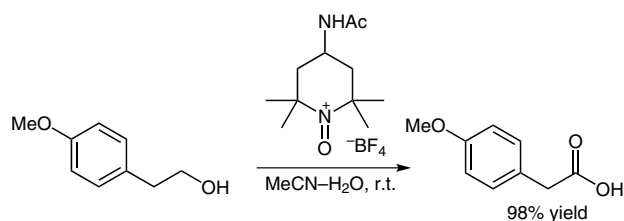
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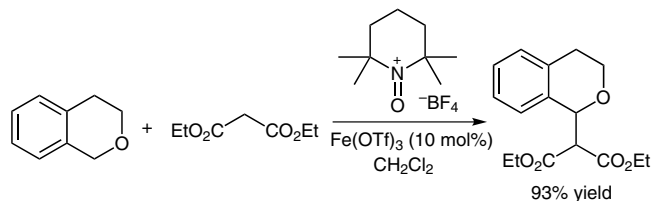
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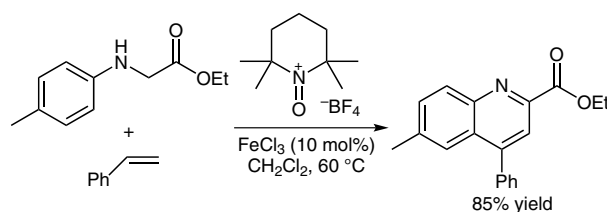
(C) During their previous benzyl ether cleavage study, Bailey et al. noticed that if the resulting alcohol was primary aliphatic, the carbonyl derivative obtained was a carboxylic acid.¹¹ However, if the alcohol was primary benzylic, the aldehyde was obtained instead. Seeking to understand this disparity and capitalize on its potential utility, they explored this transformation using a variety of alcohols.³ Ultimately, they found the rate of oxidation was controlled by the rate of hydration of the intermediate aldehyde.³



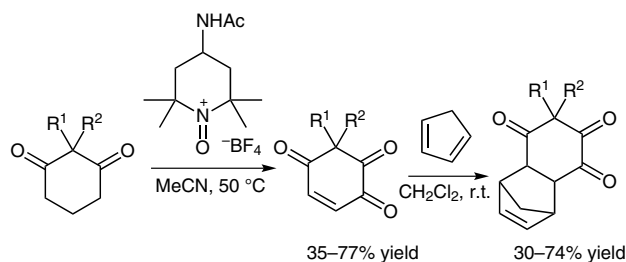
(D) Cross dehydrogenative coupling (CDC) has emerged as powerful C–H bond functionalization strategy. Particular attention has been given to CDCs involving C(sp³)–H bonds, likely due to the difficulty in accomplishing this task. A CDC of benzylic C–H bonds adjacent to an oxygen or nitrogen with an enolizable carbonyl, mediated by Fe(OTf)₃ and TEMPO⁺ BF₄⁻, has recently been reported by Richter and García Mancheño.¹⁰ This mild method affords the rapid functionalization of biologically relevant structural classes such as isochromanes or tetrahydroisoquinolines.



(E) Following the successful development of the previous CDC process, the García Mancheño group pursued another CDC methodology for the synthesis of highly functionalized quinolines.⁸ Using FeCl₃ and TEMPO⁺ BF₄⁻, a variety of substituted quinolines could be synthesized via a one-pot dehydrogenative Povarov–oxidation tandem reaction from N-alkyl anilines and styrenes.



(F) Ene-triketones represent densely functionalized, versatile building blocks for more complicated systems. However, they are sparsely described in the literature, likely owing to difficulty in their preparation. Starting from 1,3-cyclohexanediones, ene-triketones can be obtained in 40–80% yield via the exhaustive oxidation with Bobbitt's salt.⁷ The reactivity of these oxidized products was explored via Diels–Alder reactions.



References

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