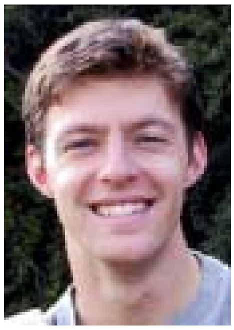
SYNLETT
Spotlight 79

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

$R_3O^+BF_4^-$: Meerwein's Salt

Compiled by Stefan Pichlmair



Stefan Pichlmair was born in 1976 in Zeltweg, Austria. After completing his diploma thesis in 2000 under the supervision of Prof. U. Jordis at the Technical University of Vienna, he joined the research group of Prof. J. Mulzer (University of Vienna) to pursue a PhD. His primary research interests revolve around stereoselective reactions and the total synthesis of natural products.

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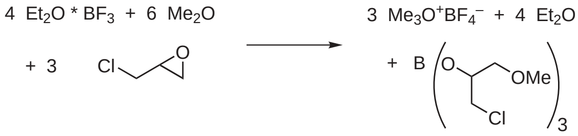
Introduction

The discovery of trialkyloxonium salts with the general formula $R_3O^+BF_4^-$ is credited to Meerwein,[1] who also investigated much of their chemistry.[2] Today, many different oxonium salts are known. The most important cations are Me_3O^+ and Et_3O^+ whereas the most important anion is the tetrafluoroborate species followed by the more stable SbF_6^-, $SbCl_6^-$ or PF_6^- analogues.[1,3a,b] Trialkyloxonium salts are well known for their excellent alkylating properties, particularly when applied to the alklyation of relatively weakly nucleophilic functional groups. Oxonium salts have also been employed as quarternizing agents for a variety of heterocyclic amines. One of the most significant drawbacks of Meerwein salts can be their insolubility in certain organic slovents, in which case, the use of the more soluble $MeSO_2CF_3$ (magic methyl) can be employed. The electrophilicity of several alkylating reagents have been demonstrated to decrease in the order of $Me_2Cl^+SbF_6^- > (MeO)_2CH^+BF_4^- > Me_3O^+X^- > Et_3O^+X^- > MeSO_2CF_3 > MeSO_2F > (MeO)_2SO_2 > MeI$.[4]

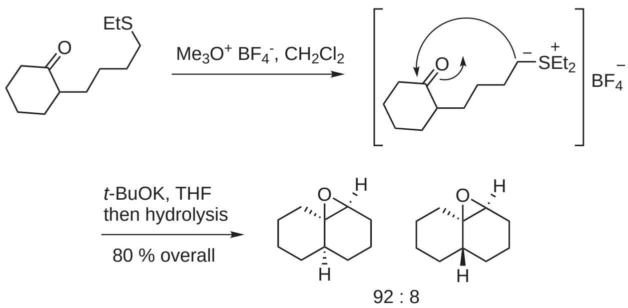
Preparation and Handling of $Et_3O^+BF_4^-$ and $Me_3O^+BF_4^-$

$Et_3O^+BF_4^-$ and $Me_3O^+BF_4^-$ are both commercially available. They can, however, be readily prepared from epichlorhydrin and $BF_3{\cdot}OEt_2$.[5a,b] It is recommended that triethyloxonium tetrafluorborate be stored in diethyl ether or dichloromethane at 0–5 °C due to its very hygroscopic properties, whereas the trimethyl salt can be stored neat in a desiccator over drierite at –20 °C for over a year without change in reactivity. Trimethyloxonium salts are non-hygroscopic, and may be easily handled in air for a short period of time.



Abstracts

(A) Thioethers can be quantitatively transformed into their corresponding sulfonium salts, which display increased leaving group ability properties. In the depicted example below, deprotonation of a ketosulfonium salt leads to the sulfonium ylide, which then undergoes a highly diastereoselective epoxy-annulation. In this case epoxidation of a corresponding alkene with MCPBA gives only a 3:1 mixture of diastereomers.[6]



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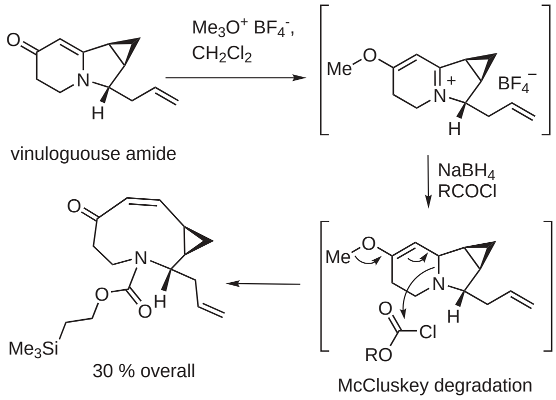
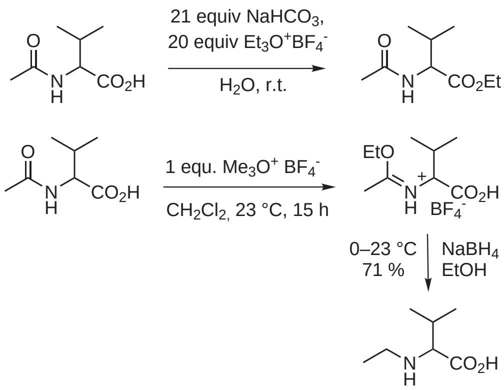
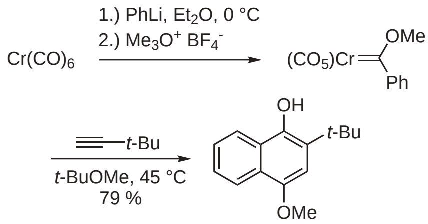
(B) O-Alkylation of amides[7] and *S*-alkylation of thioamides[8] leads to iminoesters which are much more reactive than their corresponding amide towards nucleophiles. As an example Meldrum's acid undergoes a condensation reaction with an iminoester species. In Danishefsky's total synthesis of indolizomycin, O-alkylation of a vinylogous amide was sucessfully achieved. The iminium species obtained was then reduced by $NaBH_4$. A McCluskey type fragmentation led to the nine-membered ring of the natural compound.[9]



(C) Carbonic acids can be esterified with Meerwein's salt in aqueous media in the presence of proton acceptors. Under these conditions O-alkylation of amides doesn't occur.[10] In non-protic media without addition of base, only O-alkylation is observed and the carboxyl group is not esterified.[11]



(D) One important method to form Fisher carbene complexes utilizes the methylating properties of $Me_3O^+BF_4^-$. They are made by one-pot reactions of suitable nucleophiles (e.g. alkyl, aryl, alkynyllithium, or lithiumdialkylamide) with chromiumhexacarbonyl and subsequent O-alkylation with Meerwein's salt, furnishing alkoxycarbene complexes. In the depicted example a Fisher carbene complex undergoes a unique benzannulation reaction known as the 'Doetz reaction'.[12]



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