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HETEROCYCLES IN FOCUS

Application of $BF_3 \cdot Et_2O$ in the synthesis of cyclic organic peroxides (microreview)

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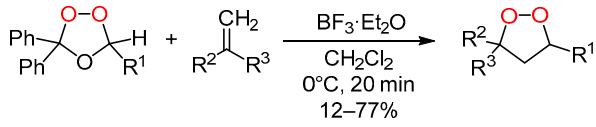
A summary of recent applications of Lewis acid $BF_3 \cdot Et_2O$ as a catalyst in the synthesis of cyclic organic peroxides is presented.

Introduction

Medicinal chemists and pharmacologists recognize cyclic peroxides as an uncharted chemical space for drug design. Cyclic peroxides exhibit antiparasitic,[1] anticancer,[2] antifungal,[3] and antiviral[4] activities. Ethanolic extract of *Artemisia annua* L. possesses antiviral activity against SARS-associated coronavirus.[5] Such properties have prompted the development of convenient and efficient methods for the synthesis of cyclic peroxides related to natural product – artemisinin. Brønsted acids are mainly used in the synthesis of cyclic peroxides.[6] However, these acids can lead not only to the formation of peroxides, but also promote their acid-catalyzed rearrangement.[7] Lewis acids disclose approaches toward synthesis of cyclic peroxides, which cannot be obtained using Brønsted acids.[8] Among Lewis acids, nonobvious $BF_3 \cdot Et_2O$ proved to be one of the most interesting tools for the selective synthesis of peroxides. This microreview describes recent achievements related to the application of $BF_3 \cdot Et_2O$ as a catalyst, which opens an efficient and atom-economical access to 1,2-dioxolanes, 1,2,4-trioxolanes, 1,2-dioxanes, derivatives of β- and γ-peroxylactones, 1,2,4-trioxanes, 1,2,4,5-tetraoxanes, and 1,2,4,5,7,8-hexaoxonanes.

Synthesis of 1,2-dioxolanes

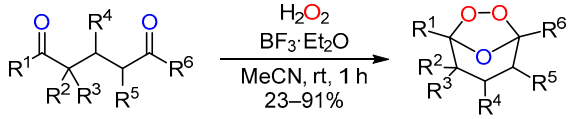
Substituted 1,2-dioxolanes were synthesized from 1,2,4-trioxolanes and olefins using $BF_3 \cdot Et_2O$ as a catalyst in CH_2Cl_2 at 0°C. In the presence of BF_3, the 1,2,4-trioxolane (ozonide) cycle decomposed with the formation of BF_3-coordinated carbonyl oxide, which attacked the corresponding alkene to yield 1,2-dioxolane.[9]



$R^1 = C_5H_{11}$, Ph; R^2 = Alk, Ph; R^3 = Alk, Ph; $R^2 + R^3 = (CH_2)_5$

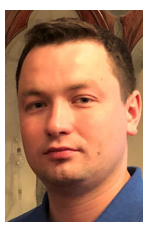
Synthesis of 1,2,4-trioxolanes

An ozone-free method for the synthesis of 1,2,4-trioxolanes from 1,5-diketones and H_2O_2 was developed.[10] In this case, $BF_3 \cdot Et_2O$ promoted selective assembly of the ozonide cycle rather than its destruction mentioned above.[9]



$R^1 = R^6$ = Me; $R^1 + R^2 = (CH_2)_4$; $R^1 + R^2 = R^5 + R^6 = (CH_2)_4$
R^2 = H, CO_2Et, $CO_2(t\text{-Bu})$; R^3 = H, Alk, Allyl, 4-$BrC_6H_4CH_2$, 4-$MeC_6H_4CH_2$; R^4 = H, Ph; R^5 = H

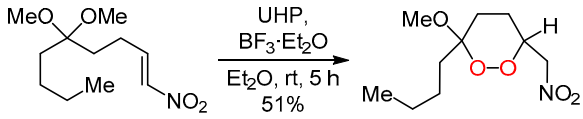
Peter S. Radulov graduated from the Mendeleev University of Chemical Technology of Russia in 2016. At present, he is a graduate student under the supervision of Prof. A. O. Terent'ev (N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences). His research interest is the chemistry of organic peroxides.



Ivan A. Yaremenko received his PhD in organic chemistry in 2013 under the supervision of Prof. A. O. Terent'ev. At present, he is a Senior Researcher in the N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences. His research interests are chemistry of organic peroxides, medicinal and agrochemistry.

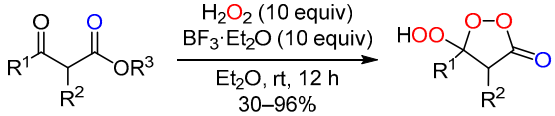
Synthesis of 1,2-dioxanes

Peroxidation of acetal containing Michael acceptor fragment afforded 1,2-dioxane (nitro analog of plakoric acid). Urea–H_2O_2 complex (UHP) and $BF_3{\cdot}Et_2O$ in Et_2O allowed nucleophilic substitution of only one methoxy group.[11]



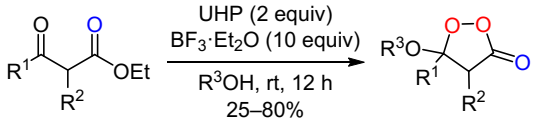
Synthesis of β-hydroperoxy- and β-alkoxy-β-peroxylactones

$BF_3{\cdot}Et_2O$ was used as effective catalyst for the synthesis of β-hydroperoxy-β-peroxylactones from β-keto esters, their silyl enol ethers, enol acetates, or cyclic acetals and H_2O_2.[12]



R^1 = Alk, CH_2CO_2Alk, Bn, Ph; $R^1 + R^2 = (CH_2)_3$, $(CH_2)_4$
R^2 = H, Alk, Ad, CH_2CO_2Et, Bn, 4-$BrC_6H_4CH_2$; R^3 = Alk

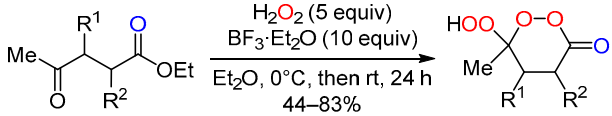
Furthermore, $BF_3{\cdot}Et_2O$–UHP–alcohol system provided β-alkoxy-β-peroxylactones from β-keto esters.[13]



R^1 = Alk; R^2 = Alk, Ad, $(CH_2)_2CN$, Bn, 4-$ClC_6H_4CH_2$, 4-$BrC_6H_4CH_2$, 4-$MeOC_6H_4CH_2$; R^3 = Alk

Synthesis of γ-hydroperoxy-γ-peroxylactones

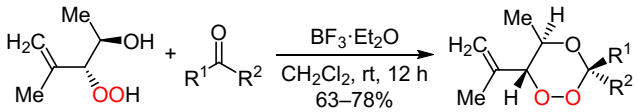
Peroxidation of γ-keto esters under action of $BF_3{\cdot}Et_2O$ afforded γ-hydroperoxy-γ-peroxylactones in moderate to high yields. It should be noted that application of Brønsted acids as catalysts led to the formation of target peroxides in 15–24% yields.[14]



R^1 = H, Alk, Bn, 2-$ClC_6H_4CH_2$, 4-$ClC_6H_4CH_2$, 4-$BrC_6H_4CH_2$, 3-$MeC_6H_4CH_2$, 4-$MeC_6H_4CH_2$, 4-$O_2NC_6H_4CH_2$; R^2 = H, Alk

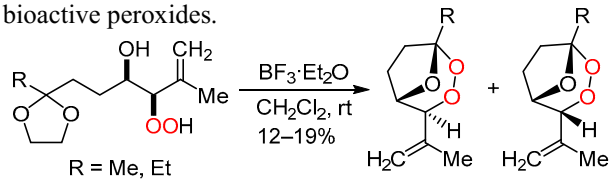
Synthesis of 1,2,4-trioxanes

$BF_3{\cdot}Et_2O$-catalyzed peroxyacetalization of hydroperoxy alcohol with aldehydes or ketones provided 1,2,4-trioxanes in high yields.[15]



$R^1 = R^2$ = Me, Et, cycloC_5H_9, cycloC_6H_{11}; R^1 = Me, R^2 = Et, OMe; R^1 = H, R^2 = Me, Et, Ph

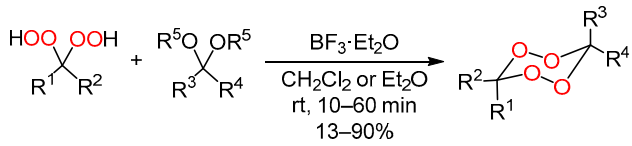
Bridged 1,2,4-trioxanes were synthesized in low yields *via* intramolecular cyclization of peroxyketals under action of $BF_3{\cdot}Et_2O$.[16] Such an approach could disclose access to new bioactive peroxides.



R = Me, Et

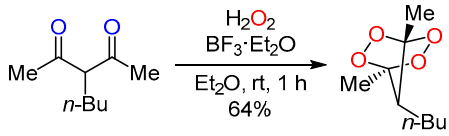
Synthesis of 1,2,4,5-tetraoxanes

Interaction of *gem*-bishydroperoxides and acetals in the presence of $BF_3{\cdot}Et_2O$ is a versatile synthetic route toward substituted unsymmetrical 1,2,4,5-tetraoxanes.[17]



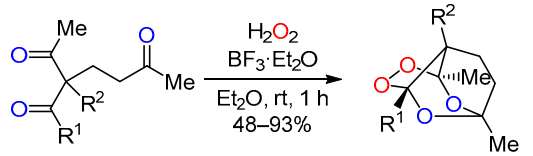
R^1 = Alk; R^2 = H; $R^1 + R^2$ = Ad, $(CH_2)_5$; R^3 = Alk, Ph
R^4 = H, Alk; $R^3 + R^4$ = Ad, $(CH_2)_5$; R^5 = Me, Et

$BF_3{\cdot}Et_2O$ was also used for the synthesis of bridged 1,2,4,5-tetraoxanes from β-diketones.[18]



Synthesis of tricyclic monoperoxides

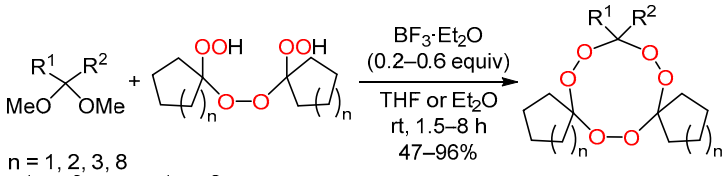
Peroxidation of β,δ'-triketones in the presence of $BF_3{\cdot}Et_2O$ led to the formation of tricyclic monoperoxides in moderate to excellent yields. Despite the presence of three carbonyl groups, peroxidation was selective.[19]



R^1 = H, Alk, $(CH_2)_2CN$, $(CH_2)_2CO_2Et$, Bn, 4-$MeC_6H_4CH_2$, 4-$O_2NC_6H_4CH_2$; R^2 = Me, Ph, 4-BrC_6H_4, 4-MeC_6H_4

Synthesis of 1,2,4,5,7,8-hexaoxonanes

A method for the synthesis of 1,2,4,5,7,8-hexaoxonanes based on $BF_3 \cdot Et_2O$-catalyzed reaction of acetals and 1,1'-peroxybis(1-hydroperoxycycloalkanes) was developed. This approach significantly expanded the structural diversity of 1,2,4,5,7,8-hexaoxonanes and, in most cases, permitted to prepare these compounds in high yields.[20]



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