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HETEROCYCLES IN FOCUS

Synthesis of cyclic aza-peroxides (microreview)

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A summary of approaches developed for the synthesis of stable cyclic aza-peroxides is presented.

Introduction

Now there is no doubt that cyclic organic peroxides are a promising class of compounds for the development of drugs. Stable cyclic peroxides like artemisinin for discovery of which the Nobel Prize was awarded, possess high antimalarial activity.[1] Drugs based on artemisinin are recommended by WHO for the treatment of malaria. Over the past two decades, a whole spectrum of biological activity has been identified for organic peroxides.[2] Furthermore, artemisinin,[3] artesunate, OZ418, and OZ277 have an inhibitory ability to SARS-CoV-2.[4] However, for a long time, aza-peroxides were kept in the shadow of organic peroxides because of their instability associated with self-oxidation due to the presence of both oxidizing and reducing moieties in one molecule. Discovery of two natural cyclic aza-peroxides verruculogen[5] and fumitremorgin A[6] as well as the synthesis of 6(11)-azaartemisinins, which exhibit promising antimalarial[7] and anticancer[8] activity, gave impetus to the development of methods for the synthesis of nitrogen-containing peroxides.[9] However, the synthesis of stable and readily available cyclic peroxides fused with a nitrogen heterocycle is a challenge. This microreview describes recent achievements in the synthesis of cyclic aza-peroxides: 1,2,4-dioxazolidines, 1,2,4-dioxazinanes, peroxy-bridged indolizidinones, 1,2,4-dioxazepanes, 1,2,4,5,7-tetraoxazocanes, 1,2,4,5,7,8-hexaoxa-10-azacycloundecanes.

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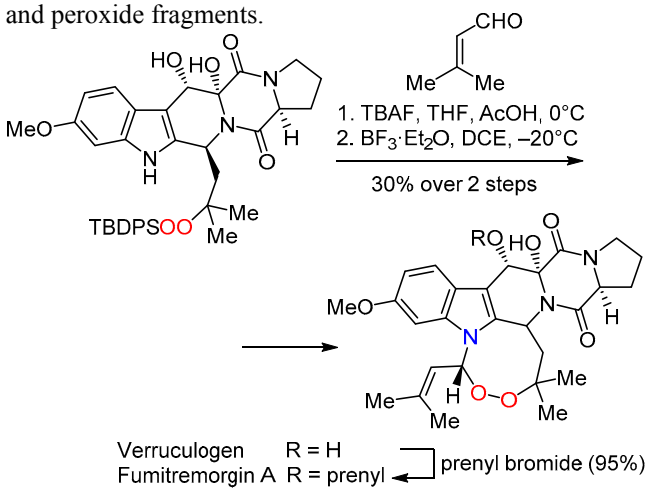
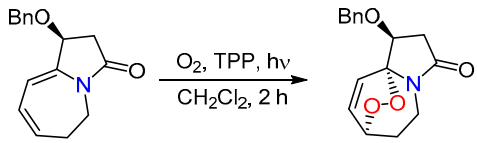
Synthesis of verruculogen

Only two bioactive natural aza-peroxides verruculogen and fumitremorgin A are known (isolated from *Aspergillus fumigatus* in the 1970s). First total synthesis of verruculogen and fumitremorgin A was developed only in 2015 by the Baran group.[10] The final step included catalyzed by $BF_3 \cdot Et_2O$ condensation of aldehyde, amine and peroxide fragments.

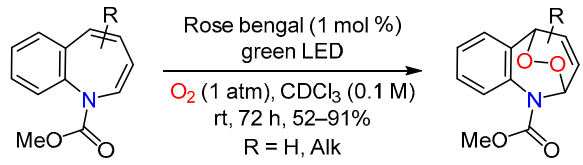


Synthesis of 1,2,4-dioxazepanes

Diene was converted to the endoperoxide upon treatment with singlet oxygen (O_2, *meso*-tetraphenylporphyrin (TPP), UV light 500 W). Pure endoperoxide was isolated with the use of column chromatography.[11]

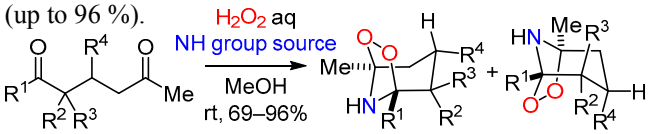


The Schenck ene reaction of 1-benzazepines in the presence of rose bengal as a photosensitizer provided endoperoxides in high yields. Several obtained endoperoxides are valuable precursors for the synthesis of *d*-fused 1-benzazepines with antitumor activity.[12]



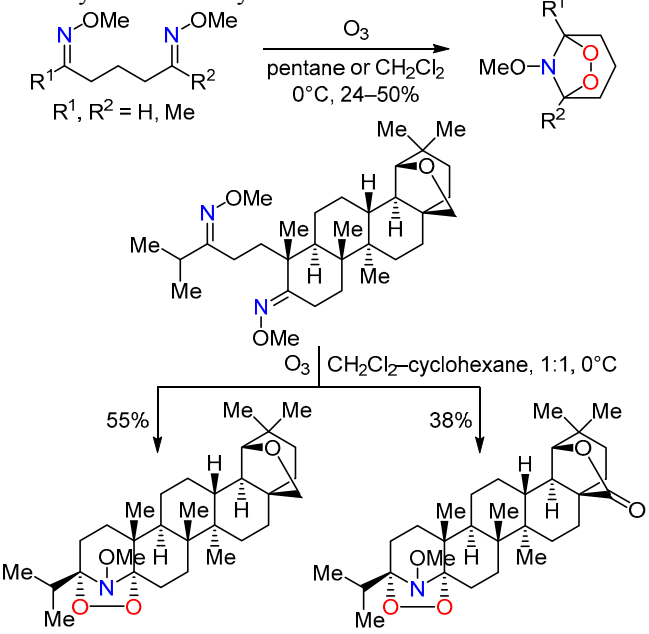
Synthesis of bridged 1,2,4-dioxazolidines

A selective and atom-efficient method for the synthesis of stable cyclic bridged 1,2,4-dioxazolidines (azaozonides) without the use of a catalyst through the three-component condensation of 1,5-diketones, hydrogen peroxide, and aqueous ammonia or ammonium salts as NH group source was described.[13] Azaozonides were obtained in high yield (up to 96 %).



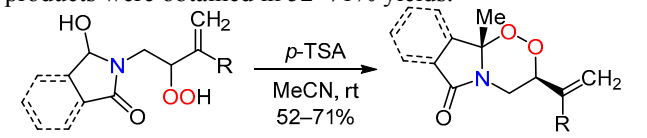
R^1 = Me; R^2 = H, C(O)OEt, C(O)OAd
R^3 = H, Alk, allyl, Bn, CH_2Ar; R^4 = H, Ar
NH group source = NH_3 aq, $(NH_4)_2CO_3$, NH_4OAc, $HCOONH_4$

N-Methoxy-1,2,4-dioxazolidines can be obtained by the ozonolysis of *O*-methylated dioximes.[14]



Synthesis of 1,2,4-dioxazinanes

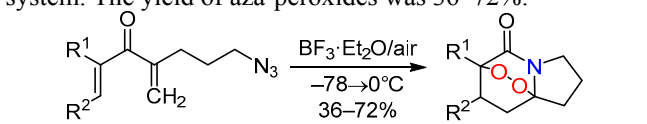
A diastereoselective synthesis of 1,2,4-dioxazinanes based on acid-catalyzed intramolecular cyclization of the corresponding hydroperoxides was carried out. The desired products were obtained in 52–71% yields.[15]



R = Ph, 4-HalC_6H_4, 4-MeC_6H_4, 4-CyC_6H_4, 4-PhC_6H_4

Synthesis of peroxy-bridged indolizidinones

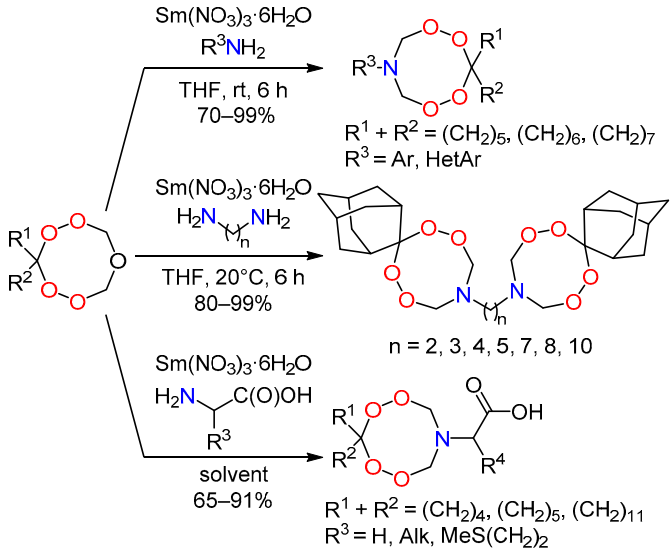
Peroxy-bridged indolizidinones were obtained by the intramolecular cyclization of cross-conjugated dienones with pendent azide side chain under the action of $BF_3 \cdot Et_2O$/air system. The yield of aza-peroxides was 36–72%.[16]



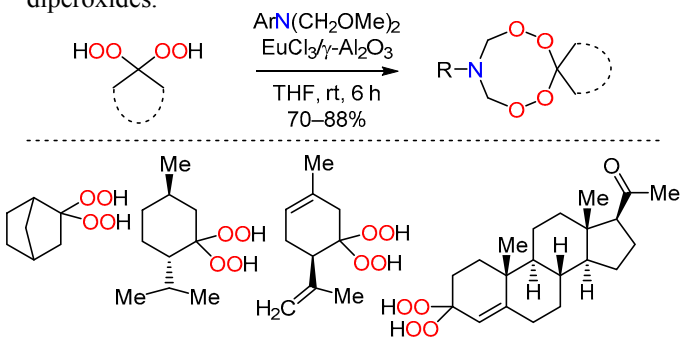
R^1 = Me, R^2 = H, Ph; $R^1 + R^2 = (CH_2)_3$

Synthesis of 1,2,4,5,7-tetraoxazocanes

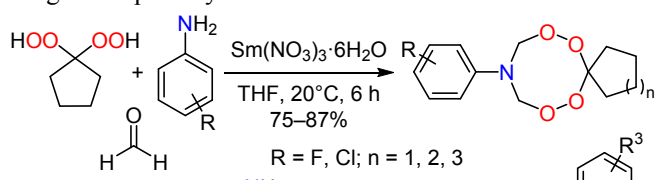
An efficient synthesis of *N*-substituted tetraoxazaspiroalkanes can be carried out on the basis of $Sm(NO_3)_3 \cdot 6H_2O$-catalyzed transformation of pentaoxaspiroalkanes with primary arylamines,[17] diamines,[18] or amino acids.[19]

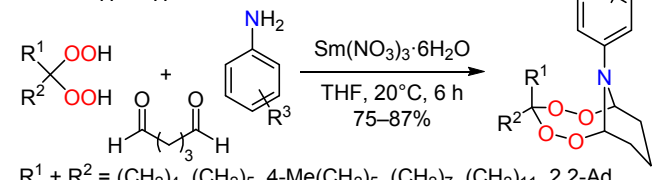


Heterocyclization of terpene bishydroperoxides with *N*-aryl-*N*,*N*-bis(methoxymethyl)amines in the presence of $EuCl_3$/γ-Al_2O_3 as a catalyst afforded new spiro terpene aza-diperoxides.[20]



An efficient route to cyclic aza-diperoxides based on Sm salts ($SmCl_3 \cdot 6H_2O$, $Sm(NO_3)_3 \cdot 6H_2O$, $SmCl_3/\gamma$-Al_2O_3, and $Sm(NO_3)_3/\gamma$-Al_2O_3) catalyzed three-component condensations of 1,1-bis(hydroperoxy)cycloalkanes with formaldehyde[21] or pentanedial[22] and primary arylamines was developed. The chemoselectivity of this reaction depends on the position of the substituent (F, Cl, Br) in the phenyl ring of the primary amine.

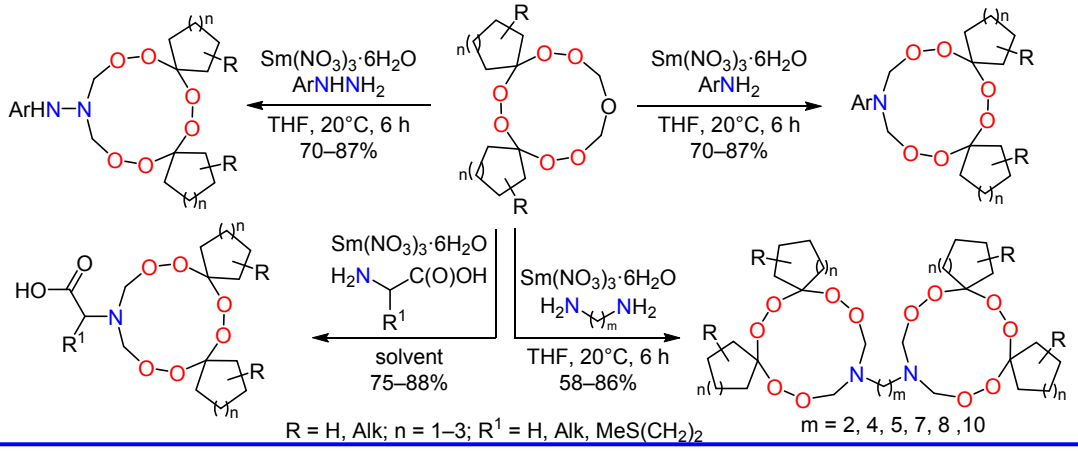




$R^1 + R^2$ = $(CH_2)_4$, $(CH_2)_5$, 4-Me$(CH_2)_5$, $(CH_2)_7$, $(CH_2)_{11}$, 2,2-Ad
R^3 = F, Cl, Br

Synthesis of 1,2,4,5,7,8-hexaoxa-10-azacycloundecanes

Sm salts catalyzed the reaction of heptaoxaspiroalkanes with arylamines affording *N*-arylhexaoxazadispiroalkanes.[23] The reaction of heptaoxacycloundecanes with hydrazine derivatives (3-chlorophenylhydrazine, phenylhydrazine, 2,4-dinitrophenylhydrazine, and *tert*-butylhydrazine)[24] or amino acids[19] in the presence of Sm-containing catalysts gave the corresponding *N*-substituted hexaoxazaspiroalkanes in high yields. It was found that cycloaza-triperoxide-substituted amines possessed high cytotoxicity against Jurkat, K562, and U937 tumor cell lines and normal fibroblast cell line. A useful one-pot synthesis of tetra(spirocycloalkane)-substituted α,ω-(1,2,4,5,7,8-hexaoxa-10-azacycloundecan-10-yl)-alkanes *via* the reaction between heptaoxacycloundecanes and α,ω-alkanediamines (1,4-butane-, 1,5-pentane-, 1,7-heptane-, 1,8-octane-, and 1,10-decanediamines) catalyzed by Sm compounds was developed. It was shown that synthesized dimeric aza-triperoxides exhibited high cytotoxic activity against Jurkat, K562, and U937 tumor cultures.[25]



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