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 verruculogen⁵ and fumitremorgin A⁶ as well as the synthesis of 6(11)-azaartemisinins, which exhibit promising antimalarial⁷ and anticancer⁸ 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.

**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 BF₃·Et₂O condensation of aldehyde, amine and peroxide fragments.

The Schenck ene reaction of 1-benzazepines in the presence of rose bengal as a photosensitizer provided endoperoxides with antitumor activity.¹²

**Synthesis of 1,2,4-dioxazepanes**

Diene was converted to the endoperoxide upon treatment with singlet oxygen (O₂, 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 anticancer 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 (azaazoides) 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. Azaazoides were obtained in high yield (up to 96%).

\[
\text{(R^1 = Me; R^2 = H, C(O)OEt, C(O)OAc; R^2 = H, Alk, alyl, Bn, CH}_2\text{Ar; R}^4 = \text{H, Ar; NH group source = NH}_2\text{aq, (NH}_2\text{)C}_2\text{O, NH}_4\text{OAc, HCOONH}_4, N-Methoxy-1,2,4-dioxazolidines can be obtained by the ozonolysis of O-methylated dioximes.14}
\]

\[
\text{R}^1\text{, R}^2 = \text{H, Me}
\]

\[
\text{O}_3 \quad \text{CH}_2\text{Cl}_2-\text{cyclohexane, 1:1, 0°C}
\]

55% 38%

Synthesis of 1,2,4-dioxazinanines

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

\[
R = \text{Ph, 4-HalC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{CyC}_6\text{H}_4, 4-\text{PhC}_6\text{H}_4
\]

\[
\text{p-TSA} \quad \text{MeCN, rt 52–71%}
\]

Synthesis of peroxy-bridged indolizidinones

Peroxyl-bridged indolizidinones were obtained by the intramolecular cyclization of cross-conjugated dienones with pendent azide side chain under the action of BF\(_3\)-Et\(_2\)O/air system. The yield of aza-peroxides was 36–72%.16

\[
\text{R}^1 = \text{Me, R}^2 = \text{H, Ph; R}^1 + \text{R}^2 = (\text{CH}_2)_b
\]

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

An efficient synthesis of N-substituted tetraoxaspiroalkanes can be carried out on the basis of Sm(NO\(_3\))\(_3\)-H\(_2\)O-catalyzed transformation of pentaoxaspiroalkanes with primary arylamines,17 diamines,18 or amino acids.19

\[
\text{THF, rt, 6 h} \quad 70–99%
\]

Heterocyclization of terpene bishydroperoxides with N-aryl-N,N-bis(methoxymethyl)amines in the presence of EuCl\(_3/-\gamma\text{-Al}_2\text{O}_3\) as a catalyst afforded new spiro terpene aza-diperoxides.20

\[
\text{THF, rt, 6 h} \quad 70–88%
\]
Synthesis of 1,2,4,5,7,8-hexaoxa-10-azacyclodecanes

Sm salts catalyzed the reaction of heptaoxaspiroalkanes with arylamines affording N-aryloxaazaspiroalkanes.25 The reaction of heptaoxacyclodecanes with hydrazine derivatives (3-chlorophenylhydrazine, phenylhydrazine, 2,4-dinitrophenylhydrazine, and tert-butylhydrazine)24 or amino acids25 in the presence of Sm-containing catalysts gave the corresponding N-substituted hexaoxaspiroalkanes 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(pirocyeloalkane)-substituted α,α-(1,2,4,5,7,8-hexaoxa-10-azacyclodecan-10-yl)-alkanes via the reaction between heptaoxacyclodecanes 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 azatriperoxides exhibited high cytotoxic activity against Jurkat, K562, and U937 tumor cultures.25

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