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HETEROCYCLES IN FOCUS

Synthetic application of oxiranecarbonitriles (microreview)

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The microreview covers synthetic applications of oxiranecarbonitriles that are summarized in five distinct categories: ring opening, ring expansion, Meinwald rearrangement, cycloaddition, and enzyme hydrolysis.

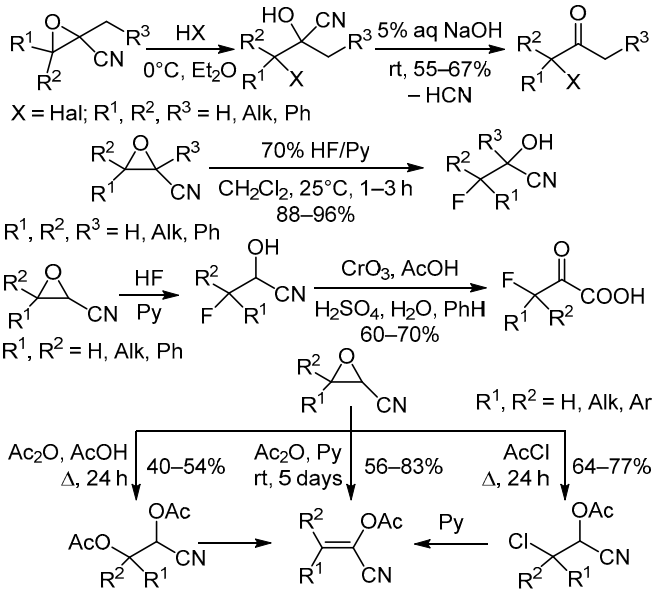
Introduction

Oxiranecarbonitriles are important oxirane derivatives and bifunctional compounds comprising both oxirane ring and cyano group. They can be readily prepared by the Darzens reaction of carbonyl compounds and haloacetonitriles in the presence of a base.[1,2] Both oxiranes and nitriles are important and versatile building blocks and have been widely applied in synthetic organic chemistry.[3] Thus, bifunctional oxiranecarbonitriles are important synthetic intermediates and have versatile applications in organic synthesis.

Ring opening

Oxiranecarbonitriles underwent an acid-catalyzed nucleophilic ring opening in the presence of hydrogen halides to generate vicinal halocyanohydrins, which further were transformed into α-halo ketones by elimination of HCN.[4] Similarly, oxiranecarbonitriles produced vicinal fluorocyanohydrins in excellent yields through the reaction with HF in the presence of pyridine in CH_2Cl_2.[5] The cyanohydrins could be further converted to 3-fluoro-2-oxoalkanoic acids in good yields after the oxidation with CrO_3 under acidic conditions.[5b] This two-step reaction was an efficient method to prepare 2-oxoalkanoic acids.

Reactions of oxiranecarbonitriles with Ac_2O resulted in different products under acidic or basic conditions, giving 1-cyanoalkane-1,2-diyl diacetates in AcOH *via* acidic ring opening with AcOH followed by acetylation of the formed cyanohydrin hydroxyl group, but giving 1-cyanoalk-1-en-1-yl acetates as the main products in pyridine *via* tandem pyridine-catalyzed ring opening, acetylation of cyanohydrins, and pyridinium elimination. The reaction of oxiranecarbonitriles and AcCl gave 2-chloro-1-cyanoalkyl acetates through the ring opening followed by the acetylation of 2-chloro-1-cyanoalkoxides. Both 1-cyanoalkane-1,2-diyl diacetates and 2-chloro-1-cyanoalkyl acetates underwent further elimination to afford final products 1-cyanoalk-1-en-1-yl acetates.[6] Treatment of oxiranecarbonitriles with Ac_2O and pyridine was the direct way to prepare 1-cyanoalk-1-en-1-yl acetates in satisfactory to good yields.



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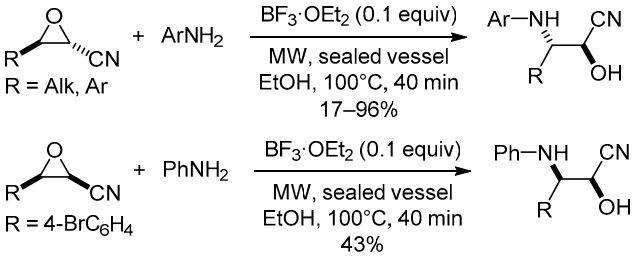
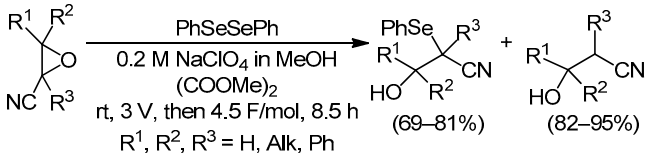
Ring opening (continued)

Under the $BF_3 \cdot OEt_2$ catalysis, oxiranecarbonitriles participated in a nucleophilic ring opening with arylamines stereospecifically to give the corresponding 3-arylamino-2-hydroxyalkanenitriles in low to excellent yields depending on the nucleophilicity of the arylamines in EtOH under microwave irradiation. *Cis*- and *trans*-2-aryloxiranecarbonitriles generated stereospecifically *syn*- and *anti*-3-arylamino-2-hydroxyalkanenitriles, respectively.[2]



The reaction of oxiranecarbonitriles and phenyl diselenide produced β-hydroxy-β-phenylselenoalkanenitriles and β-hydroxyalkanenitriles under electrochemical conditions. During the reaction, phenyl diselenide was first reduced to phenyl selenide, which nucleophilically attacked the oxiranes to generate ring-opened products followed by further reduction.[7] Differently from the conventional acid-catalyzed ring opening of oxiranecarbonitriles, the electrochemical method gave β-hydroxyalkanenitriles rather than α-hydroxyalkanenitriles obtained in the conventional acidic ring opening.[7] The electrochemical method showed different regioselectivity from the conventional nucleophilic ring opening.



Ring expansion

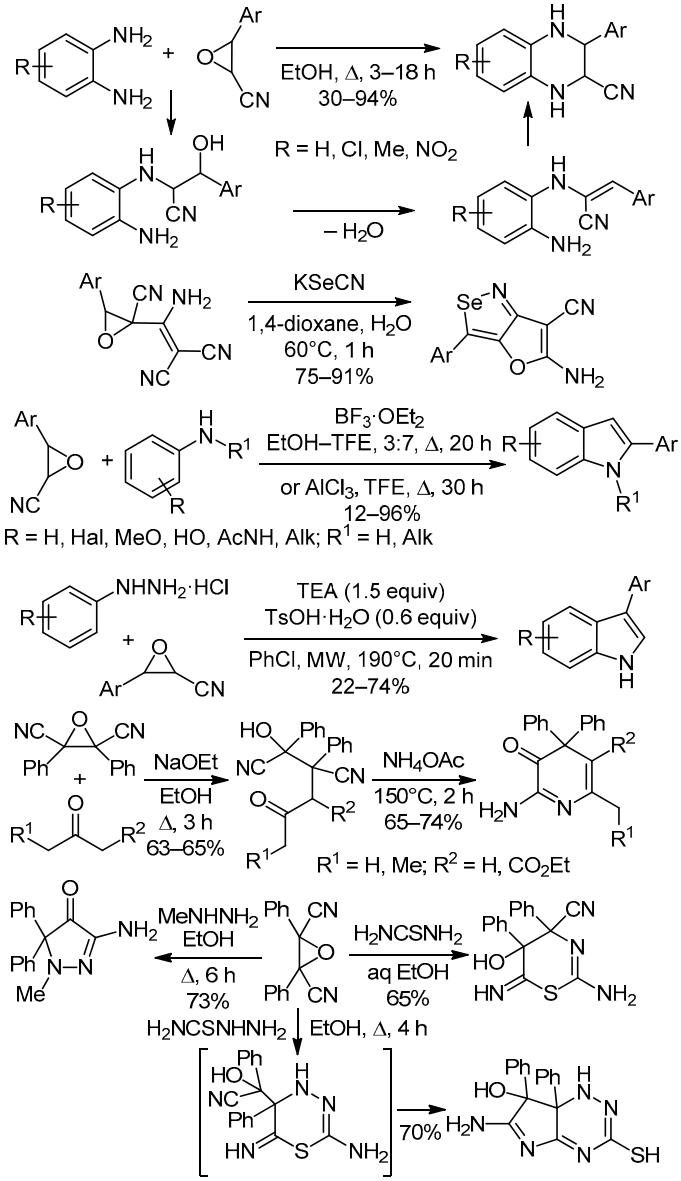
Oxiranecarbonitriles and phenylenediamine underwent ring expansion, generating 1,2,3,4-tetrahydroquinoxaline-2-carbonitriles in low to excellent yields. The reaction was a tandem process with the nucleophilic ring opening, H_2O elimination, and the intramolecular Michael addition.[8]

Potassium selenocyanate and 2-[amino(3-aryl-2-cyanooxiran-2-yl)methylidene]malononitriles generated fused furo[3,2-*c*]isoselenazole derivatives in good yields through tandem ring opening, elimination, tautomerization, and double cyclization.[9]

Differently, the reaction of oxiranecarbonitriles and anilines under the catalysis of Lewis acids, such as $BF_3 \cdot OEt_2$ in EtOH–TFE and $AlCl_3$ in TFE, yielded indole derivatives. Vicinal aryloxiranecarbonitriles generated 2-arylindoles regiospecifically. The reaction includes acid-catalyzed ring opening of oxiranes with anilines, the elimination of HCN, the intramolecular Fridel–Crafts alkylation, and the acid-catalyzed elimination of H_2O.[10] The anti-oestrogen medicine zindoxifene was efficiently prepared using this strategy.[10]

The reaction of oxiranecarbonitriles and arylhydrazines gave 3-arylindoles regiospecifically under the cocatalysis of TEA and TsOH in chlorobenzene under microwave irradiation.[11]

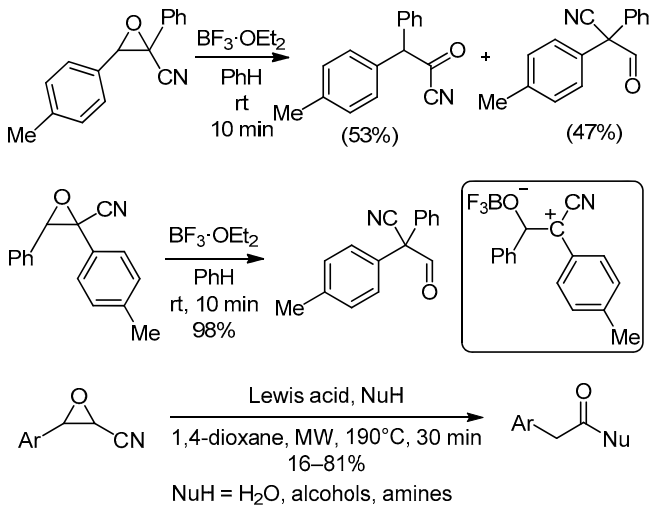
The reaction of 2,3-diphenyloxirane-2,3-dicarbonitrile and ketones in the presence of NaOEt produced ring-opening products, which were further treated with NH_4OAc to give 2-amino-4,4-diphenylpyridin-3(4*H*)-one derivatives *via* rearrangement and condensation. The reactions of the dinitrile with methylhydrazine, thiourea, and thiosemicarbazide generated dihydropyrazole, 5,6-dihydro-4*H*-1,3-thiazine-4-carbonitrile, and 7,7a-dihydro-1*H*-pyrrolo-[2,3-*e*][1,2,4]triazin-7-ol derivatives, respectively. Some of the synthesized compounds showed *in vitro* cytotoxic effects and inhibited cell proliferation.[12]



Meinwald rearrangement

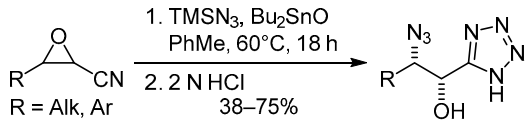
Although the Meinwald rearrangement of oxiranes has been widely investigated, less attention has been paid to oxiranecarbonitriles. 3-(4-Methylphenyl)-2-phenyloxiranecarbonitrile generated both 2-(4-methylphenyl)-2-phenylacetyl cyanide and 3-oxo-2-phenyl-2-(*p*-tolyl)propanenitrile. However, its isomeric 2-(4-methylphenyl)-3-phenyloxiranecarbonitrile gave 3-oxo-2-phenyl-2-(*p*-tolyl)propanenitrile only under the $BF_3 \cdot OEt_2$ catalysis.[13] It was assumed that cyano and tolyl groups stabilized the intermediate cation more than the phenyl group only.[13] Compared with other oxirane derivatives, oxiranecarbonitriles were relatively inert to the Meinwald rearrangement.

Recently, a novel and convenient strategy including tandem Meinwald rearrangement of oxiranecarbonitriles and subsequent nucleophilic substitution was developed for the synthesis of arylacetic acids and their derivatives, including acids, esters, and amides.[14]



Cycloaddition

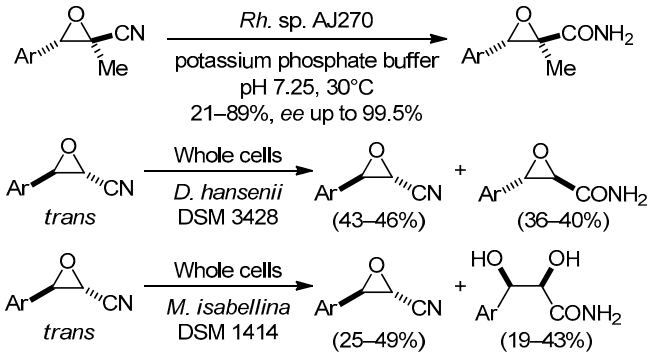
The dibutylstannanone-catalyzed reaction of oxiranecarbonitriles and $TMSN_3$ produced 5-(oxiran-2-yl)-1*H*-tetrazoles, which further underwent an oxirane ring opening with azide to afford *syn*-2-azido-1-(1*H*-tetrazol-5-yl)alkan-1-ols.[1]



Enzyme hydrolysis

The enzyme hydrolysis of oxiranecarbonitriles is an efficient method to convert oxiranecarbonitriles into the corresponding oxiranecarboxamides enantioselectively. 3-Aryl-2-methyloxiranecarbonitriles generated the corresponding carboxamides under the catalysis by enzyme *Rh.* sp. AJ270.[15]

Among *trans*-3-aryloxirane-2-carbonitriles, only (2*S*,3*S*)-3-aryloxirane-2-carbonitriles were selectively converted into (2*R*,3*S*)-3-aryloxirane-2-carboxamides when enzyme *D. hansenii* DSM 3428 was used, while enzyme *M. isabellina* DSM 1414 transformed (2*S*,3*S*)-3-aryloxirane-2-carbonitriles to (2*R*,3*R*)-3-aryl-2,3-dihydroxypropanamides selectively.[16]



Conclusions

In conclusion, oxiranecarbonitriles have been widely used in synthetic chemistry – in the preparation of ketones, hydroxynitriles and -amides, tetrazoles, indoles, quinoxaline-2-carbonitriles. As bifunctional starting compounds they have abundant application in the synthesis of various heterocycles.

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