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HETEROCYCLES IN FOCUS

Synthesis and application of azacycloalk-1-ene-fused oxazol-3-ium salts (microreview)

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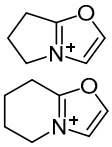


Synthesis and application of azacycloalk-1-ene-fused oxazol-3-ium salts are summarized. The microreview covers all synthetic methods for obtaining 6,7-dihydro-5*H*-pyrrolo[2,1-*b*]oxazol-4-ium and 5,6,7,8-tetrahydrooxazolo[3,2-*a*]-pyridin-4-ium derivatives that have been classified in two distinct categories: cyclization leading to the formation of azacycloalk-1-ene ring and cyclization leading to the formation of oxazole ring. Application of these azacycloalk-1-ene-fused oxazol-3-ium salts has been discussed.

Jiaxi Xu received his PhD degree in 1992 from Department of Chemistry at the Peking University in China. After a post-doctoral stay in the School of Pharmaceutical Sciences at Beijing Medical University, he was appointed as an associate professor at College of Chemistry and Molecular Engineering at the Peking University. He also worked as a visiting scholar in Department of Chemistry at the Chinese University of Hong Kong (1995–1996), Department of Chemistry at the Colorado State University (2000–2001), and the Medical School at Vanderbilt University (2001–2002). He was promoted a full professor in 2004. At the end of 2007, he started working at the Faculty of Science (College of Chemistry now) at the Beijing University of Chemical Technology. His research interests are synthetic methodologies and the related mechanisms, asymmetric synthesis and catalysis, synthesis of heterocyclic compounds, unnaturally occurring amino acids and peptides.

Eugene V. Babaev received his PhD degree in 1987 and his Doctor Habilitus degree in 2007 from the Lomonosov Moscow State University. Currently he serves as professor at this University. He is author of 200 papers and books. His research interests include general theory of rearrangements and ring transformations and chemistry of ring-fused systems, especially indolizines, oxazoles, pyridines, cyclazines.

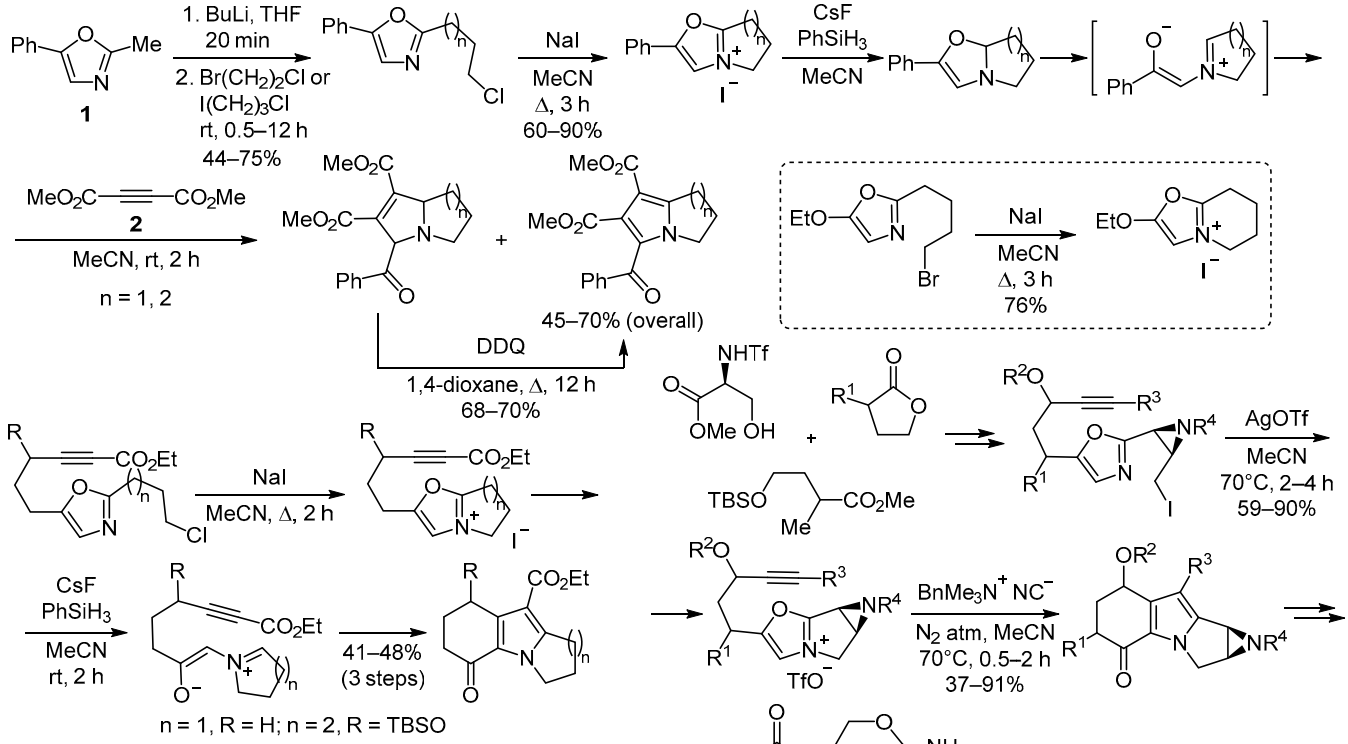
Introduction

Fused azaheterocycles are very important natural compounds and building blocks in organic synthesis.[1] Oxazol-3-ium derivatives are interesting and valuable organic salts that are widely used as synthetic intermediates.[2] 6,7-Dihydro-5*H*-pyrrolo[2,1-*b*]oxazol-4-ium and 5,6,7,8-tetrahydrooxazolo[3,2-*a*]pyridin-4-ium salts are a class of important bicyclic oxazol-3-ium derivatives. Their fused imidazolium and thiazolium[3] analogs are useful products in medicinal chemistry. Oxazol-3-ium salts can be prepared *via* the formation of either azacycloalk-1-ene or oxazole ring and applied as electrophiles in synthetic organic chemistry, especially in the total synthesis of natural products, such as aziridinomitosenes and pentacyclic quaternary indole alkaloids.

Cyclization toward azacycloalk-1-ene ring

2-Methyl-5-phenyloxazole (**1**) was first applied in the synthesis of azacycloalk-1-ene-fused oxazol-3-ium salts by Vedejs' group. It was treated with butyllithium followed by the addition of 1-bromo-2-chloroethane or 1-chloro-3-iodopropane to afford 2-chloroalkyl-5-phenyloxazoles, which were heated in MeCN in the presence of NaI leading to the formation of 2-substituted azacycloalk-1-ene-fused oxazolium iodides. The obtained oxazolium salts were further reduced and converted into oxazoline derivatives. Subsequent electrocyclic ring opening generated stabilized azomethine ylides, which served as 1,3-dipoles and were used in 1,3-dipolar cycloadditions with dimethyl but-2-ynedioate (**2**) affording fused dimethyl pyrrole-3,4-dicarboxylate derivatives. Similarly, azacycloalk-1-ene-fused oxazolium salts with substituent at C-2 atom that contains propynoate moiety were also prepared and underwent intramolecular 1,3-dipolar cycloaddition.[4]

Cyclization toward azacycloalk-1-ene ring (continued)

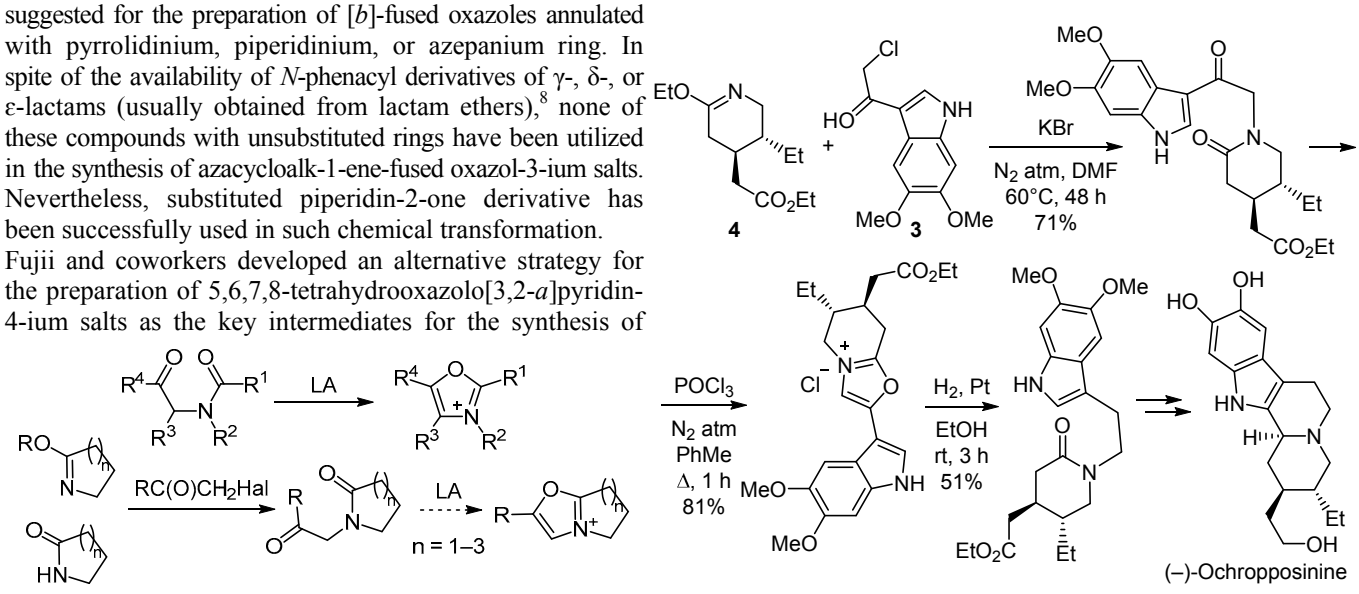


Similar strategy was used to synthesize fused tricyclic pyrrolo[2,1-*b*]oxazol-4-ium derivatives as key intermediates that were further transformed into aziridinomitosenes – analogs of natural products mitomycins exhibiting antitumor activity.[4,5]

Cyclization toward oxazole ring

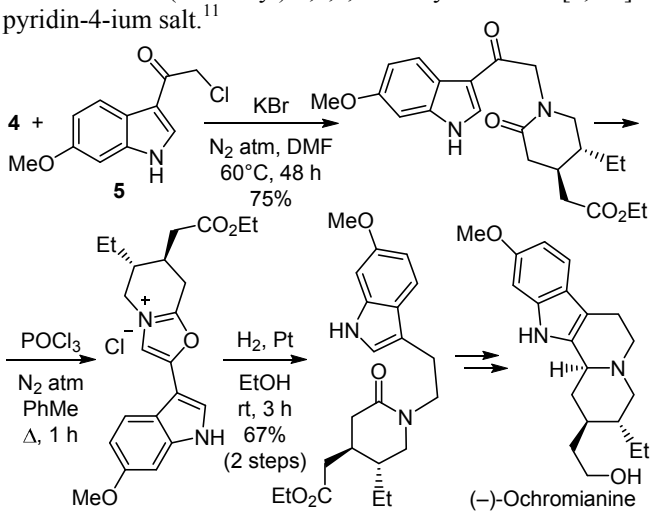
An alternative strategy for building azacycloalkene-fused azolium salts is to attach an azole to a saturated azacycle. Such approach was used for the preparation of biologically active [*a*]-fused imidazoles and thiazoles *via* Hantzsch-like synthesis.[3] Oxazol-3-ium salts may be directly obtained by Robinson–Gabriel synthesis[6] using *N*-substituted α-(acylamino) ketones and Lewis acids (Tf_2O, Ac_2O, P_2O_5, PCl_3) or Brønsted acids ($HClO_4$).[7] Similar strategy could be suggested for the preparation of [*b*]-fused oxazoles annulated with pyrrolidinium, piperidinium, or azepanium ring. In spite of the availability of *N*-phenacyl derivatives of γ-, δ-, or ε-lactams (usually obtained from lactam ethers),[8] none of these compounds with unsubstituted rings have been utilized in the synthesis of azacycloalk-1-ene-fused oxazol-3-ium salts. Nevertheless, substituted piperidin-2-one derivative has been successfully used in such chemical transformation.

Fujii and coworkers developed an alternative strategy for the preparation of 5,6,7,8-tetrahydrooxazolo[3,2-*a*]pyridin-4-ium salts as the key intermediates for the synthesis of indole-based quinolizidine alkaloids. First, they prepared *N*-[2-(indol-3-yl)-2-oxoethyl]piperidin-2-one from 3-(chloroacetyl)-5,6-dimethoxyindole (**3**) and 2,3,4,5-tetrahydropyridine **4** and treated it with $POCl_3$ in PhMe to afford the corresponding 2-(indol-3-yl)-5,6,7,8-tetrahydrooxazolo[3,2-*a*]-pyridin-4-ium salt.[9] When subjected to reduction, it produced *N*-[2-(indol-3-yl)ethyl]piperidin-2-one derivative, which was further converted into natural product (–)-ochropposinine.[10]



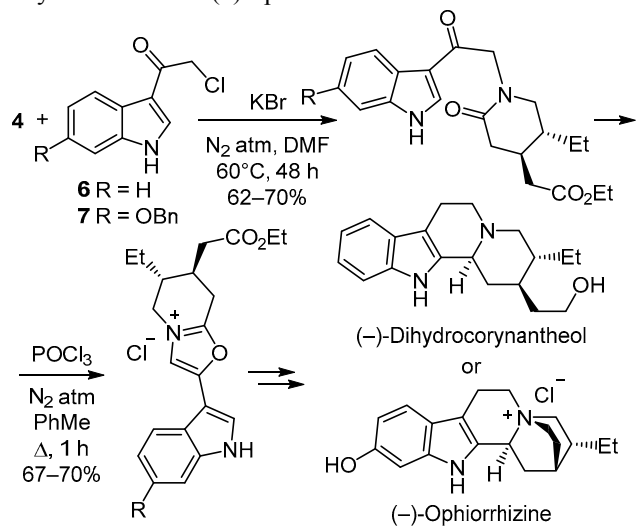
Cyclization toward oxazole ring (continued)

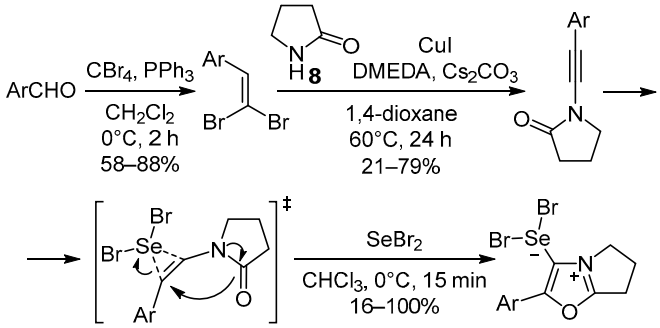
When 3-(chloroacetyl)-6-methoxyindole (**5**) was utilized, the desired *N*-[2-(indol-3-yl)-2-oxoethyl]piperidin-2-one derivative was synthesized and subsequently transformed into natural product (–)-ochromianine *via* the formation of intermediate 2-(indol-3-yl)-5,6,7,8-tetrahydrooxazolo[3,2-*a*]-pyridin-4-ium salt.[11]



Arsenyan and coworkers achieved the synthesis of dibromo-(2-aryl-6,7-dihydro-5*H*-pyrrolo[2,1-*b*]oxazol-4-ium-3-yl)-selenates(II). First, aromatic aldehydes were treated with CBr_4 in the presence of PPh_3. Subsequent reaction of the intermediate dibromoalkenes and pyrrolidin-2-one (**8**) under the catalysis of CuI allowed to obtain *N*-(aryl-ethynyl)pyrrolidin-2-ones, which were transformed into the corresponding dibromo(2-aryl-6,7-dihydro-5*H*-pyrrolo[2,1-*b*]-oxazol-4-ium-3-yl)selenates(II) *via* the reaction with $SeBr_2$. The possible mechanism of the last step encompasses electrophilic addition of $SeBr_2$ to the triple bond of *N*-(aryl-ethynyl)pyrrolidin-2-one followed by nucleophilic ring opening, which leads to the formation of target products.[14]

Similarly, when 3-(chloroacetyl)indole (**6**) and 6-benzyloxy-3-(chloroacetyl)indole (**7**) were applied as starting materials, the corresponding 2-(indol-3-yl)-5,6,7,8-tetra-hydrooxazolo[3,2-*a*]pyridin-4-ium salts were obtained and further transformed into natural products (–)-dihydro-corynantheol[12] and (–)-ophiorrhizine.[13]





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