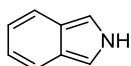


Pyrrole ring closure reactions in the synthesis of isoindoles (microreview)

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The microreview describes recent advances in the synthesis of isoindole derivatives *via* pyrrole ring closure reactions. We report the latest selected examples (2012–2018) on the synthesis of isoindoles: multicomponent reactions, [3+2] cycloaddition of azomethine ylides and münchnones, and transition metal-catalyzed C–H activation reactions.

Introduction

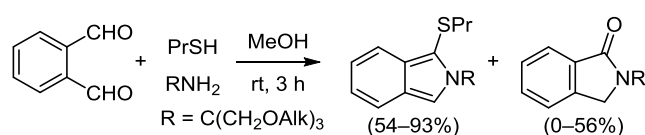
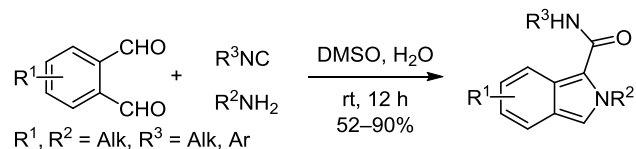
The isoindole skeleton has attracted scientists for decades and can be found in numerous natural and pharmaceutical compounds.^{1,2} These nitrogen heterocycles remain popular as far as they continue to find use in medicinal chemistry and drug discovery, natural product synthesis, and

materials chemistry.³ Wide number of isoindole derivatives has found to possess anti-inflammatory, analgetic, CNS depressant, antimicrobial, and many other biological activities.⁴ In addition, isoindole-containing dyes are used in various fields of science.⁵

Multicomponent reactions

In 2012, Li et al. reported a three-component reaction approach toward the synthesis of 1-carboxamidoisoindoles under mild conditions. Authors investigated the reaction scope and optimized conditions. It was shown that synthesized isoindoles can be used for the preparation of fused-ring heterocycles *via* Diels–Alder reaction.⁶

Nakao et al. have synthesized a series of novel 2-alkyl-1-propylsulfanyl-substituted isoindoles using multicomponent reactions of *o*-phthalaldehyde with *O*-protected tris-(hydroxyalkyl)aminomethanes in the presence of propane-1-thiol. It should be noted that isoindolin-1-ones as byproducts are also formed.⁷



Maxim A. Bastrakov was born in 1982 in Yoshkar-Ola, Russia. He graduated from the Mary State University in 2005. In 2008, he defended PhD theses under supervision of professor S. A. Shevelev. Currently, Dr. Bastrakov is a senior scientist of the Laboratory of Aromatic Nitrogen Compounds at the N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences. In 2014, he was awarded Gold medal of the Russian Academy of Sciences for young scientists. His research interests cover the chemistry of heterocyclic compounds and nitroarenes and synthesis of multipurpose compounds on its basis.



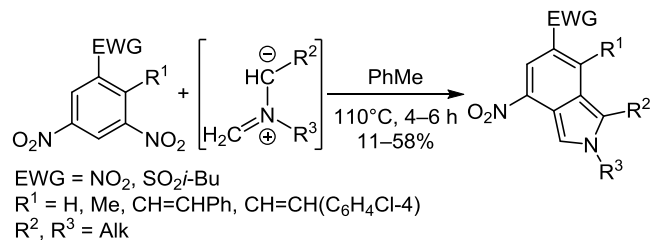
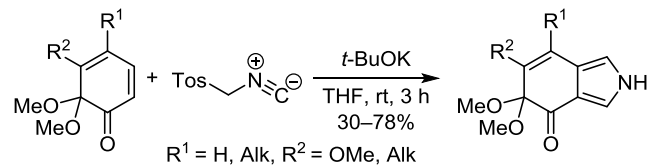
Alexey M. Starosotnikov was born in 1978 in Moscow, Russia. He graduated from the Higher Chemical College of Russian Academy of Sciences in 2000. He obtained his PhD (2003) and Doctor of Science degrees (2016) at the N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences. At present he is research group leader at this Institute. His research interests include chemistry of nitrogen heterocycles and aromatic nitro compounds, pericyclic reactivity of aromatic systems.

[3+2] Cycloaddition of azomethine ylides and münchnones

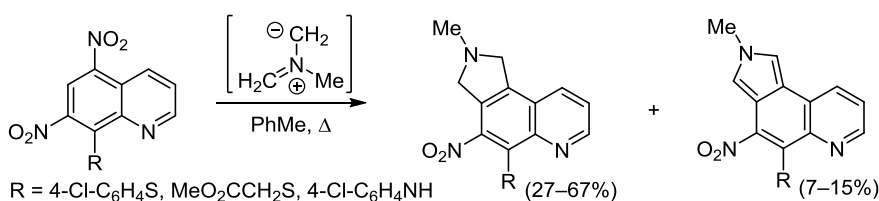
In 2012, Chittimalla et al. reported a simple and efficient approach to highly functionalized isoindolones *via* 1,3-dipolar cycloaddition of *in situ* generated azomethine ylides to stable masked *o*-benzoquinones. This method represents a rapid and general access to isoindolones with high synthetic potential.⁸

[3+2] Cycloaddition of unstabilized *N*-alkylazomethine ylides (generated *in situ*) to polynitrobenzenes was studied by Shevelev et al.⁹ The authors developed a new simple one-step method for the annulation of a pyrrole ring to polynitrobenzenes providing a pathway to the previously unknown functionalized nitroisoindoles unavailable by other methods. All reactions proceed with excellent site selectivity.⁹

Later the same authors described synthesis of isoindole derivatives annulated to pyridine core. These compounds were

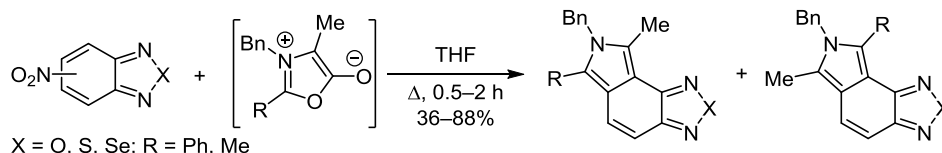


isolated as minor products in [3+2] cycloaddition of *N*-methylazomethine ylide to 8-substituted 5,7-dinitroquinolines.¹⁰



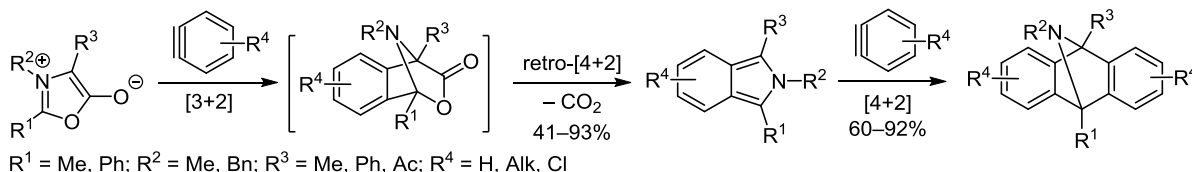
In 2012, a new method for the annulation of pyrrole to benzene ring was reported by Shevelev et al. The authors studied 1,3-dipolar cycloaddition of *in situ* generated 1,3-oxazolium-5-olates (münchnones) to 4- and 5-nitrobenzazoles. Heating

of unsymmetrical münchnone in the presence of nitrobenzazoles resulted in a formation of the mixtures of regioisomeric isoindoles. In case of symmetrical münchnone containing two methyl groups, only one isomer was formed.¹¹



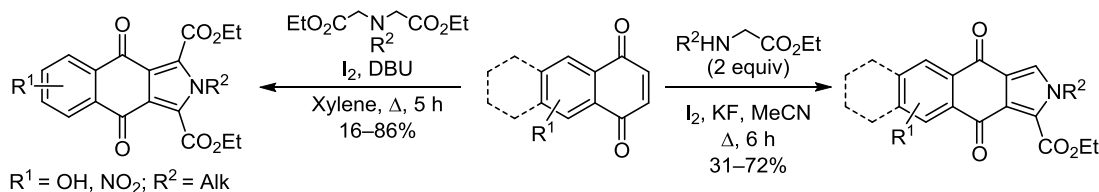
In 2014, two groups of researchers independently have shown that münchnones react with arynes under mild conditions in a [3+2] cycloaddition/[4+2] cycloreversion sequence to afford isoindoles. However, in most cases the reactions are difficult to be stopped at this stage and the

isoindole intermediates readily react with a second molecule of aryne in a [4+2] cycloaddition fashion to afford benzanthracenimine derivatives.^{12,13} An excess of münchnone allowed the selective formation of the labile isoindoles.



Unexpected I₂-mediated 1,3-dipolar cycloaddition/oxidative aromatization reaction between naphtha- or anthraquinones and substituted aminoesters was revealed by Li et al.^{14,15} As a result, an efficient method for the synthesis of benzo[*f*]-

isoindole derivatives was developed. This protocol provides a rapid and efficient strategy for the construction of biologically important compounds containing quinone structural fragment.

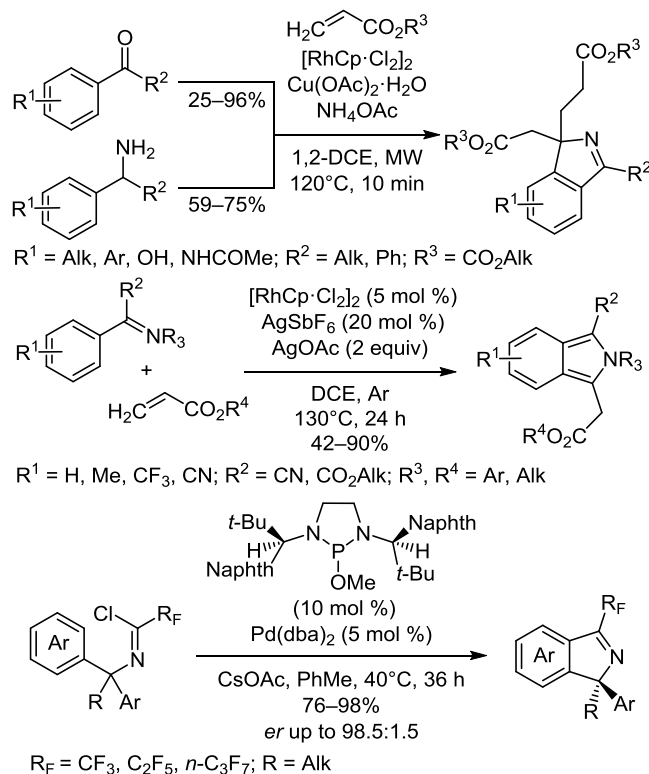


Transition metal-catalyzed C–H activation reactions

Yi et al. proposed novel one-pot 3-component microwave-assisted reaction of aryl ketones with acrylates in the presence of ammonium acetate or benzylamine that produced 1*H*-isoindoles. The process tolerates wide scope of ketone and acrylate substrates and efficiently generates various 1*H*-isoindoles containing quaternary carbon center.¹⁶

An efficient synthetic route to 2*H*-isoindole derivatives via Rh(III)-catalyzed reaction of α -iminonitriles or α -imino esters with acrylates and further cyclization have been developed by Li et al.¹⁷ This study provides novel opportunities to enrich isoindole chemistry and can be applied in the synthesis of pharmaceutically important 2*H*-isoindole derivatives.

In 2018, Cramer et al. described a catalytic enantioselective method for the synthesis of chiral 1*H*-isoindoles bearing quaternary stereogenic center.¹⁸ Pd(0)-catalyzed intramolecular cyclization of perfluoroalkylated imidoyl chlorides in the presence of phosphordiamidite ligands leads to previously inaccessible 3-perfluoroalkyl-1*H*-isoindoles in high yield and enantioselectivity.



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