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Review of the Progress for the Synthesis of *N*- and *O*-Heterocycles through Iodine-mediated Cyclizations

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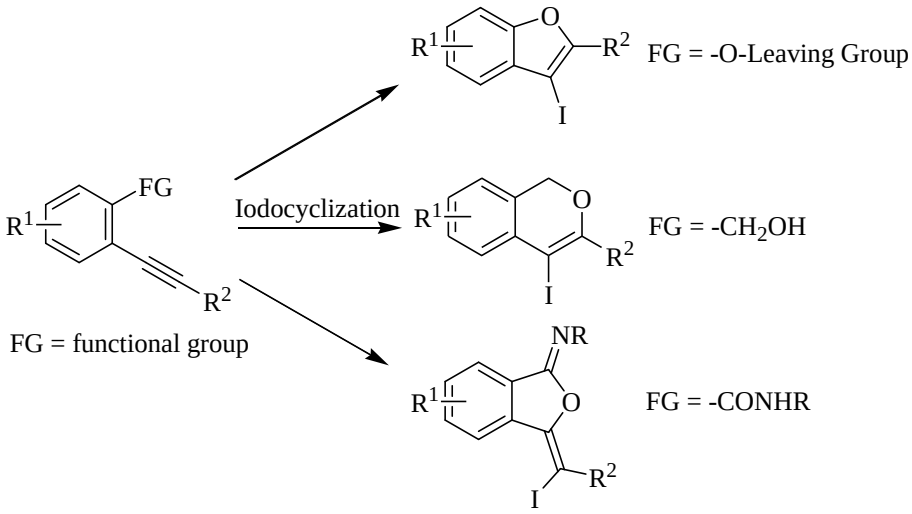
ABSTRACT



In this review, the recent progress with respect to synthesis of a few important nitrogen and oxygen heterocycles through the iodocyclization strategy has been briefly summarized. The alkyne substrates containing nucleophilic functional groups can be efficiently cyclized to afford important heterocycles with diverse substitution patterns. In general there is good control over the stereo- and regionselectivity of the cyclization products. The cyclization products can be diversified through metal-catalyzed coupling reactions.

INTRODUCTION

Heterocycles compounds are very important in the areas of pharmaceuticals, agrochemicals, materials research, etc. Several privileged heterocyclic cores such as benzofurans,[1,2] indolinones,[3–5] *etc*. are frequently observed in natural products as well as other biologically important compounds. Synthetic and medicinal chemists put great efforts for developing novel syntheses and compounds for various applications. In the recent past many research group around the world have developed interesting organic syntheses of important heterocyclic and carbocyclic ring systems. One of the popular ways for making these privileged scaffolds is through the electrophilic cyclization, particularly iodocyclization.[6,7] Here we present a review for the recent literature for the synthesis of a few important nitrogen and oxygen containing heterocycles such as Benzo[*b*]furans, Isochromenes,[8,9] Iminolactones,[10] and other fused compounds containing multiple heterocyclic rings.[11,12] It is notable that these scaffolds are very important and their importance is well established in the various areas including medicinal chemistry.

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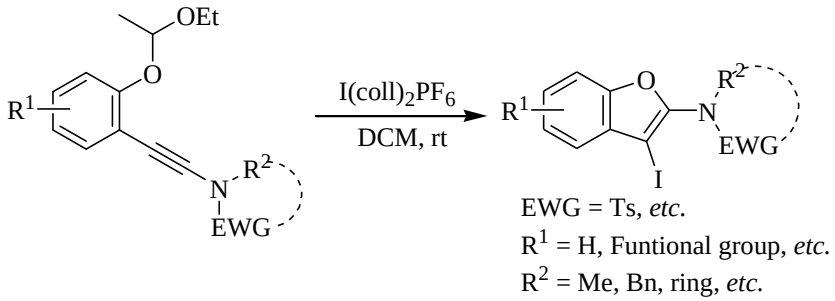
DISCUSSION

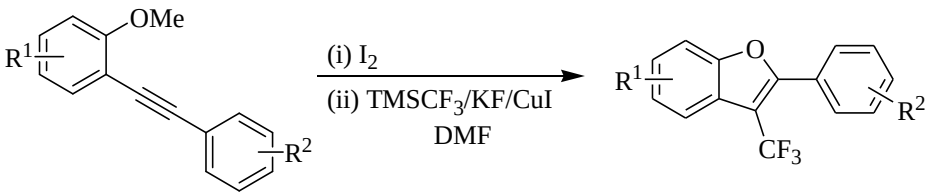
An efficient synthesis of Benzofurans *via* the iodocyclization of the ethoxyethyl ether-protected substrates was reported by Okitsu *et al.* (Scheme 1).[13] An interesting feature of the methodology was that the reactions are performed under mild conditions and get over within seconds affording high yields of the desired products. A similar synthesis was used for the preparation of an antiarrhythmic drug Dronedarone.[14]

Scheme 1.



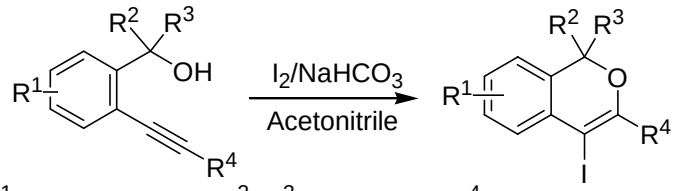
An interesting synthesis of 3-trifluoromethylbenzofurans was reported by Wang *et al.*[15] The one-pot tandem iodocyclization and trifluoromethylation results in the desired products in good yields (Scheme 2).

Scheme 2.



We also reported a mild synthesis of iodine containing isochromene derivatives via the iodocyclization of Alkynyl benzylic alcohol substrates (Scheme 3).[16]

Scheme 3. Preparation of Isochromenes *via* iodocyclization of Alkynyl benzylic alcohols.



R^1 = H, OMe, NO_2; R^2, R^3 = H or alkyl; R^4 = alkyl, aryl, heteroaryl

A similar iodocyclization strategy was reported by Kundu et al. (Scheme 4).[17] The alkynyl aldehyde substrates were first converted to the corresponding alcohols through the reaction with external nucleophile nitromethane, and the alcohols were eventually iodocyclized affording the Isochromenes.

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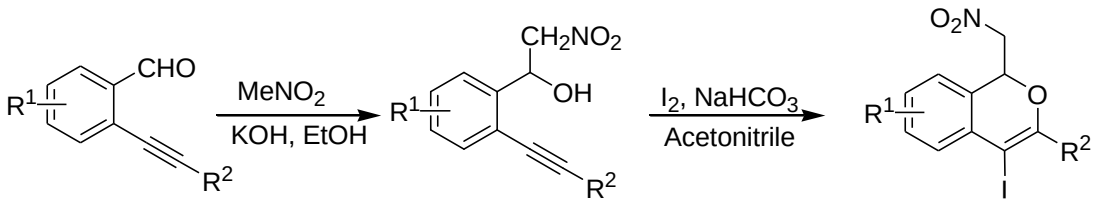
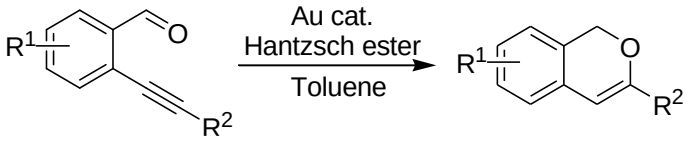
Scheme 4. 2-step synthesis of Isochromene derivatives from 2-Alkynyl benzaldehydes.



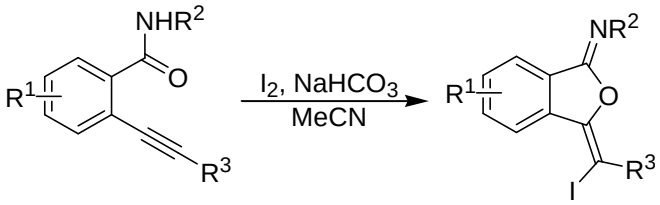
An interesting Synthesis of 1*H*-Isochromenes involving a Gold-catalyzed Domino Cycloisomerization/Reduction strategy was reported by Michelet et al. (Scheme 5).[18]

Scheme 5. Au-catalyzed Cycloisomerization/Reduction Methodology.



We also studied the iodocyclization of Alkynyl benzamide substrates and reported that the reaction under mildly basic conditions leads to the synthesis of iminolactones/Cyclic imidates (Scheme 2).[19] The stereochemistry of the products was confirmed NMR spectroscopy as well as single crystal X-ray crystallographic evidence.

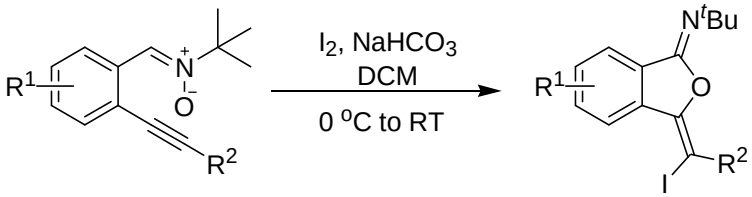
Scheme 6. Regio- and Stereoselective synthesis of Cyclic Imidates *via* Iodocyclization of Alkynylbenzamides



***E*-products**

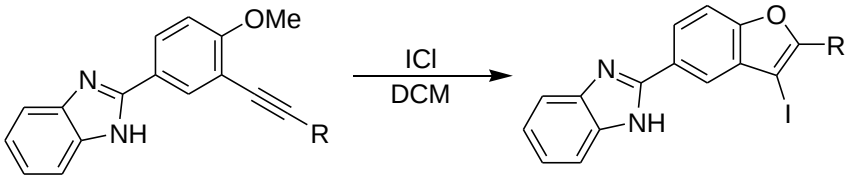
The cyclization of Nitrone-containing alkyne substrates also resulted in the the formation of corresponding iminolactones (Scheme 7).[20]

Scheme 7: Iodocyclization of Alkynyl Nitrones



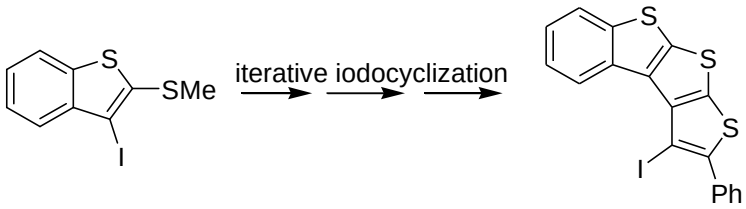
The synthesis of Polyheterocyclic compounds through the Palladium- and Iodine mediated cyclization reactions of appropriately substituted alkynes has been reported by us in the past.[21] It was observed that these reactions may be used to generate linked as well as fused systems very conveniently. Soodamani et al. Recently reported an interesting synthesis of novel compounds containing benzofuranyl and benzimidazole scaffolds linked together (Scheme 8).[22]

Scheme 8. Synthesis of benzofuranyl benzimidazoles



Flynn et al. also reported an interesting synthesis of fused thiophenes through iterative iodocyclizations (Scheme 9).[23]

Scheme 9. Access to Polyfused thiophenes



Pal et al. used an interesting iodocyclization strategy for the synthesis of novel thieno[3,2-c]pyran-4-one derivatives (Scheme 10),[24] and also evaluated their anticancer activities. A few of these derivatives showed the Inhibitory activity in a some cancer cell lines.

Scheme 10. Synthesis of fused hetrocycles such as thieno[3,2-c]pyran-4-ones.

CONCLUSIONS

Thus, various important heterocyclic scaffolds such as benzofurans, iminolactones, ishoochromenes, such as can be efficiently synthesized through the iodocyclization (using I_2/ICl) of alkyne substrates. The reactions can be performed under mild conditions in general and the yields are also good. It has also been demonstrated that these reactions can be futher designed to afford interesting linked and fused heterocyclic ring systems.

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