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Synthesis of Fused and Linked Heterocyclic Ring Systems *via* Cyclization of Functionally Substituted Alkynes

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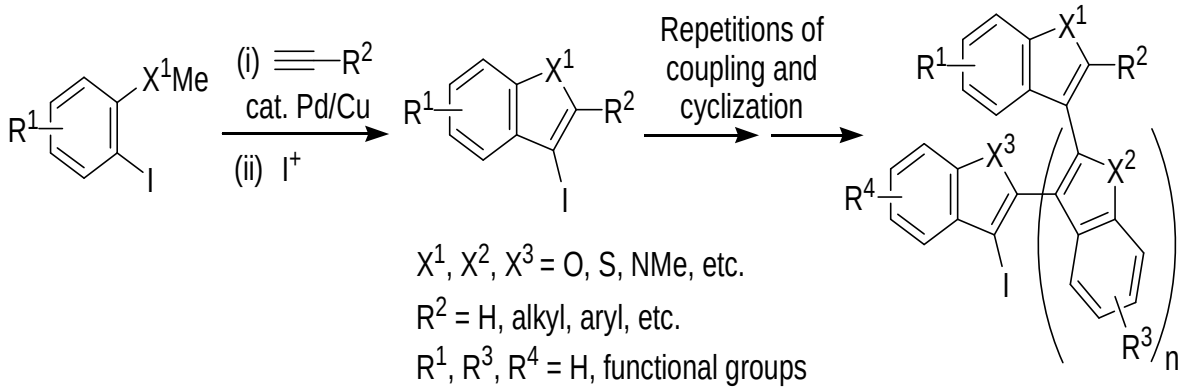
ABSTRACT



The recent progress for the synthesis of fused and linked heterocyclic ring systems through the cyclization of functionalized alkynes has been briefly reviewed in this paper. A variety of ring systems such as substituted azulenes, isocoumarins, benzothiophenes, benzofurans, benzimidazoles, pyranones, *etc*. have been conveniently assembled together using the metal-catalyzed as well as the electrophile-mediated reactions. Highly substituted novel heterocyclic compounds with potential applications in the areas of medicinal chemistry as well as materials chemistry have been synthesized using these versatile approaches.

INTRODUCTION

Alkynes are very important and versatile building blocks in organic synthesis of a wide variety of heterocyclic and carbocyclic compounds.[1] The cyclization of functional group containing alkynes has proven to be an efficient way for the synthesis of various important classes of compounds including indoles,[2,3] benzofurans,[4] quinoolines,[4] isoxazoles,[5,6] *etc*. Such cyclizations have been performed using various electrophiles such as iodine, bromine, *etc*. as well as metal-catalyzed annulations.[7–10] Such cyclization strategies have been extended for the synthesis of many linked as well as fused systems that contain more than one type of heterocyclic and/or carbocyclic moieties.[11] Such compounds are known to be important biologically[12] as well as in the area of materials chemistry.[13] In this paper we briefly review the recent progress made in this area, *i.e*. synthesis of linked and fused ring systems through the cyclization of alkyne substrates.

We have previously accomplished the iodine mediated synthesis of Polyheterocyclic compounds through the Palladium- and Iodine mediated annulations of functionally substituted alkynes (Scheme 1).[11]

Scheme 1. Synthesis of Polyheterocyclic Compounds through Pd/Iodine-mediated Reactions

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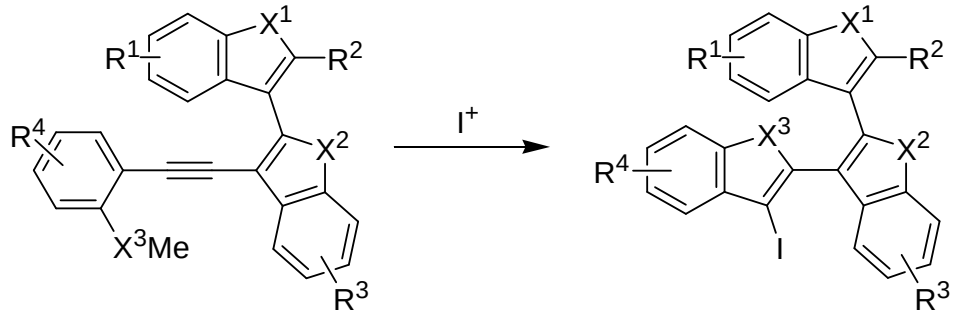
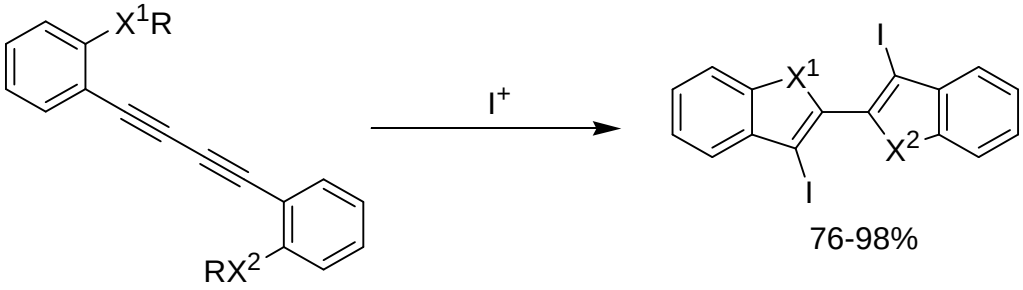


Using many variations of this general approach various fused as well as linked polyheterocyclic compounds were synthesized in good yields (Scheme 2).

Scheme 2. Iodocyclization of Di-ynes.

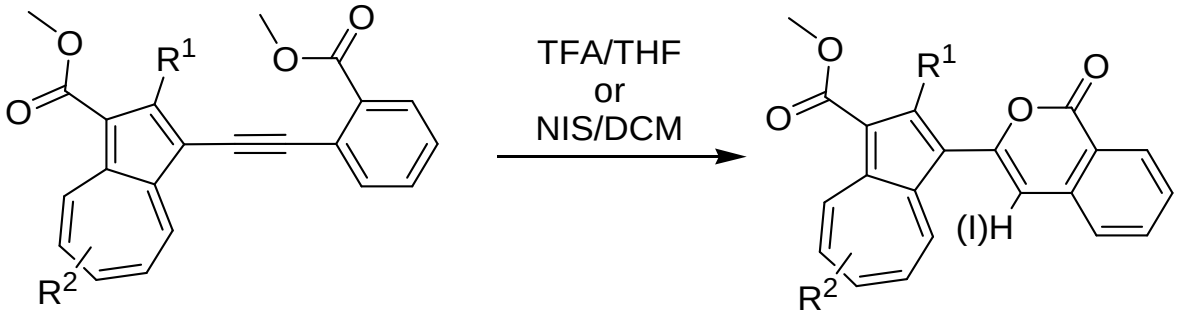


X^1R/X^2R = OMe, SMe

DISCUSSION

Shoji et al. recently reported the synthesis of various azulene-substituted benzofurans and isocoumarins.[14] The trifluoroacetic acid (TFA) mediated or *N*-iodosuccinimide (NIS)-mediated cyclization of 1-(phenylethynyl)azulenes bearing the ester group afforded the azulene-substituted isocoumarins and 4-iodoisocoumarins in good yields (Scheme 3).

Scheme 3. Synthesis of azulene-substituted isocoumarins



The synthesis of 2,3-bis(1-azulenyl)benzofurans was accomplished by the palladium-catalyzed cross-coupling reaction of 1-iodoazulenes with 2-ethynylphenol followed by the intramolecular nucleophilic addition of the oxygen nucleophile (Scheme 4).

Scheme 4. Synthesis of 2,3-bis(1-azulenyl)benzofurans

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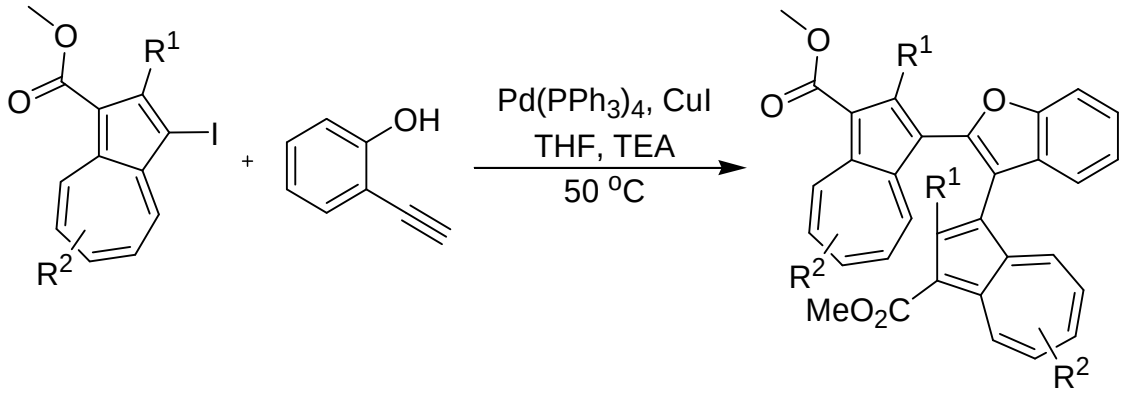
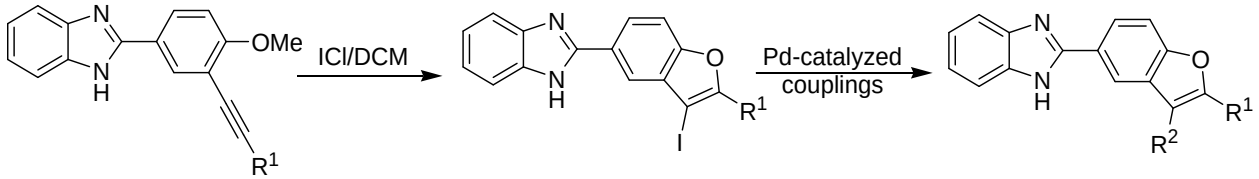


Using the variations of these methods, several substituted azulene derivatives were synthesized. The structures of the complex compounds were also confirmed through the single crystal X-ray crystallography, and their optical properties were studied using UV-Vis spectroscopy and also through theoretical calculations.

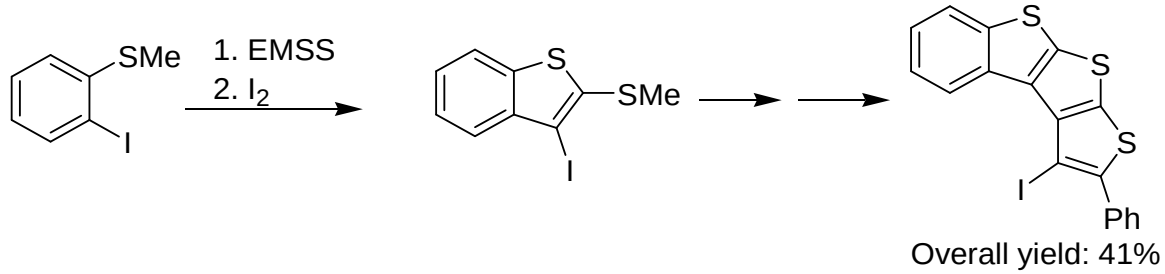
Soodamani et al. reported a facile strategy for the synthesis of novel benzofuranyl benzimidazole compounds (Scheme 5).[15] A significant molecular diversity was incorporated using Palladium-catalyzed coupling reactions such as Sonogashira, Heck etc.

Scheme 5. Synthesis of benzofuranyl benzimidazoles



Flynn and co-workers have exploited this approach for the synthesis of polyfused thiophenes (Scheme 6).[16] They used the Ethynyl methyl sulfide synthesis (EMSS) and iodocyclization iteratively and achieved the efficient synthesis of an extended oligomer in 41% overall yield from the commercially available 2-iodothioanisole.

Scheme 6. Synthesis of Polyfused thiophenes



Pal and coworkers synthesized novel pyrano[4,3-b]pyran-5(4H)-ones (Scheme 7) and performed biological evaluation of these compounds.[17] A few derivatives were found to have inhibitory activity against yeast sirtuins sir2.

Scheme 7. Synthesis of pyrano[4,3-b]pyran-5(4H)-ones

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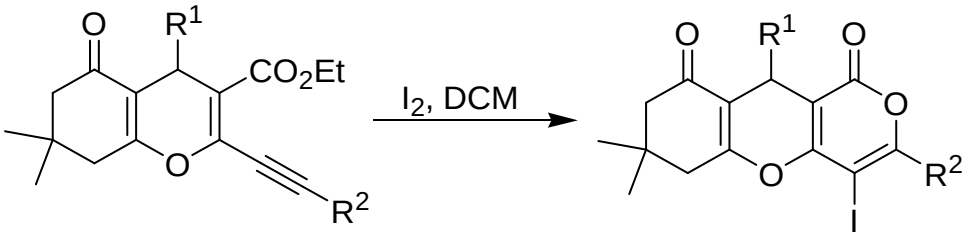
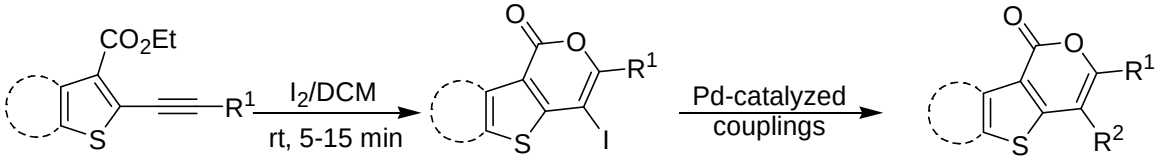


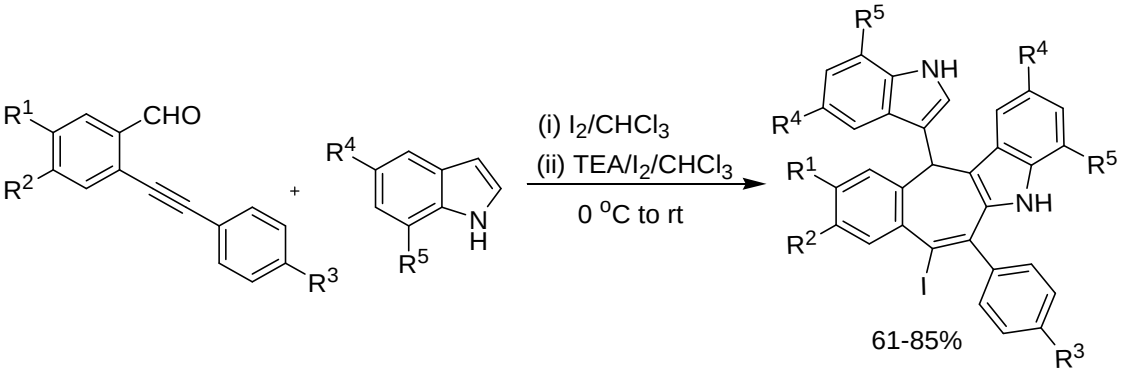
The same research group used a similar strategy for synthesizing novel thieno[3,2-c]pyran-4-ones (Scheme 8).[18] The compounds were also evaluated for their in vitro activities as potential anticancer agents. Several compounds exhibited the IC_{50} values in the range of 2.0–2.5 □M in the in vitro assay using three cancer cell lines, K562, MDA-MB 231 and HepG2.

Scheme 8. Synthesis of thieno[3,2-c]pyran-4-ones



Gawande et al. reported Iodine-Mediated Cascade Reaction of 2-Alkynylbenzaldehyde and Indole for the synthesis of Tetracyclic Indoloazulene Derivatives (Scheme 9).[19] The structure of the synthesized compounds were confirmed by NMR spectroscopy and X-ray crystallography. The authors took advantage of various Pd-catalyzed reactions for synthesizing highly diverse tetracyclic indole fused azulene compounds.

Scheme 9. Synthesis of Tetracyclic Indoloazulenes



Similarly many other groups have reported the synthesis of various other fused ring systems.[20–22]

CONCLUSIONS

Thus, various alkyne substrates have been cyclized using halogen electrophiles and/or metal-catalyzed reactions to afford various important linked and fused heterocyclic ring systems. In some cases the halogen-bearing cyclized products have been further elaborated using known metal-catalyzed reactions. This synthetic strategy is useful for the synthesis of medicinally important compounds.

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