

Tandem azaisobenzofurans formation – Diels-Alder reactions: Applications to the synthesis of biologically active aromatic heterocycles

Funding Agency	CSIR, New Delhi
Sanctioned Amount	Rs. 12.67 Lakhs
Project Duration	4 years
Project Status	Completed

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Brief Description of the Project:

Reactions involving Fischer carbene-chromium complexes and alkynes have emerged as a powerful tool for synthetic organic chemistry, allowing for the direct synthesis of a variety of structural types including aromatic rings and various bicyclic structures. The o-quinoid 10 π -electron isobenzofuran system has remained the subject of intense theoretical, structural and reactivity studies, but little work has been done with the analogous azaisobenzofuran systems. The primary objectives of the project were as follows:

1. Study of the scope and limit of the tandem furo[3,4-*c*]isoquinoline intermediate formation by the coupling of appropriate alkynyl carbonyl derivatives with Fischer carbene complex and trapping with Diels-Alder dienophiles: an approach to nitrogen containing heterocyclic analogs of 1-arylisoquinoline lignans.
2. To examine the generation of furo[3,4-*d*]pyrimidine intermediate by the coupling of appropriate alkynyl carbonyl derivatives with Fischer carbene complex: an approach to nitrogen containing heterolignans.
3. Studies on the generation of furo[3,4-*b*]quinoxaline intermediate by the coupling of appropriate alkynyl carbonyl derivatives with Fischer carbene complex: an application to the synthesis of phenazine derivatives.
4. Synthesis of heteroatom containing furanophane derivatives through [8+2]- cycloaddition of dienylisobenzofurans and alkynes.
5. Synthesis of heteroatom containing steroid ring systems by coupling of alkynyl carbonyl derivatives with suitably substituted Fischer carbene complex.

Keywords: Aromatic heterocycles, Fischer Carbene complexes, Azaisobenzofurans, Diels Alder Reaction

Methodologies/ Approaches Adopted

One-pot three-component coupling of *o*-alkynylheteroaryl carbonyl derivatives and simple Fischer carbene complexes/ α,β -unsaturated Fischer carbene complexes with suitable dienophiles were carried out which leads to the synthesis of varieties of nitrogen heterocycles

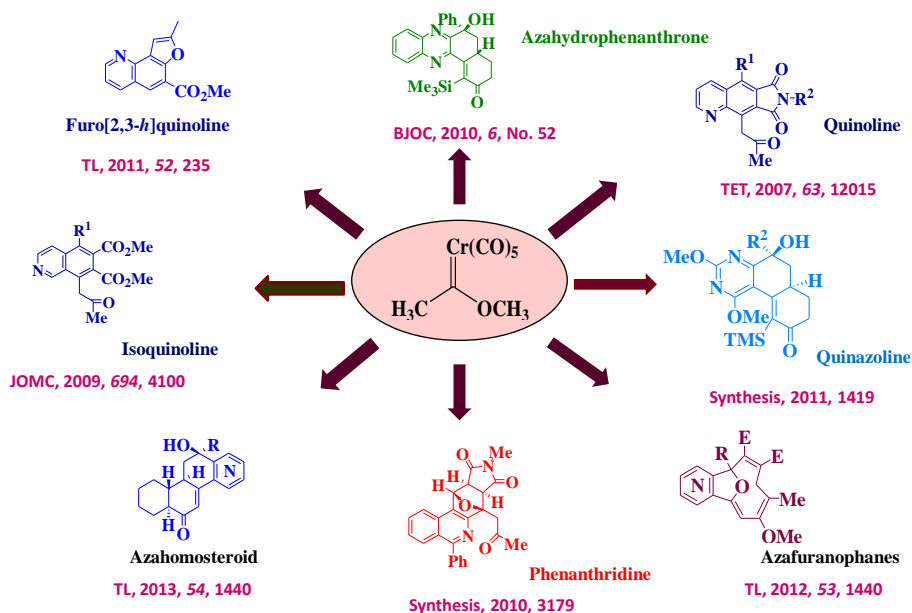
Project Highlights

The use of Fischer's carbene chemistry for the synthesis of varieties of nitrogen heterocycles such as quinolines, isoquinolines, quinoxaline, furo[2,3-*h*]quinoline, furo[2,3-*h*]isoquinoline, nitrogen containing heterolignans, phenazines, nitrogen analogs of furanophane derivatives and azahomosteroids was demonstrated in our work. It is very likely that other Scientist's in the country

may use this chemistry for further research work. The PI has presented the results of this investigation at various symposia/ lectures in the country.

Project Achievements

Synthesis of Nitrogen Heterocycles



1. A novel one-pot synthetic route to isoquinolines, phenanthridines, acridines, quinoxalines, phenazines, furo[2,3-*h*]quinolines, furo[2,3-*h*]isoquinolines through the coupling of appropriate *o*-alkynylpyridine carbonyl derivatives with carbene complex and subsequent Diels-Alder trapping with suitable dienophiles. An intramolecular variant of this protocol is also feasible with use of unactivated alkenyl tethers.
2. A new regioselective one-pot synthesis of pyranoquinolinones from readily available 2-alkynyl 3-formylquinolines under mild $\text{NaClO}_2/\text{H}_2\text{O}_2$ conditions involving oxidation followed by regioselective electrophilic 6-*endo-dig* cyclization has been found to be more efficient over the traditional Pd(0)-mediated synthesis. Chlorinated 3-substituted furo[3,4-*b*]quinolinone derivatives were also obtained under scavenger free conditions.
3. Direct metalation of 2,4-dialkoxy-5-bromopyrimidine with lithium diisopropylamide and consequent trapping by dimethylformamide resulted unexpected formation of 2,6-dialkoxy-5-dimethylaminopyrimidine-4-carboxaldehyde via displacement of bromine by dimethylamine moiety of dimethylformamide.
4. One-pot three-component coupling of *o*-alkynylheteroaryl carbonyl derivatives with α,β -unsaturated Fischer carbene complexes and dimethyl acetylenedicarboxylate, involves the generation of conformationally flexible dienylazaisobenzofuran intermediate as transient intermediates, which undergo [8+2] cycloaddition reaction with dienophile, leading to the synthesis of heterocyclic analogues of furanophane derivatives. In some cases, this intermediate undergoes twofold Diels-Alder reaction to afford heterolignan derivatives in a single step.
5. The coupling of carbene complex with *o*-alkynylheteroaryl carbonyl derivatives, involving tandem azaisobenzofuran formation–intramolecular Diels–Alder reactions, shows high region- and stereoselectivity and leads to one-step construction of azahomosteroid skeleton.

Publications

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10. P. Roy and **B. K. Ghorai**, "One-pot synthesis of azahomosteroid ring system through intramolecular [4+2] cycloaddition of azaisobenzofuran intermediates", *Tetrahedron Lett.* **2013**, *54*, 1440–1443

Facilities Developed

1. Ultrasonic bath
2. High vacuum pump (Precivac), dimmerstat
3. Hot air oven, Magnetic stirrers
4. Solvent still apparatus
5. Vacuum Dessicators, Heating mantles

Project Staff

1. Research fellows associated with scheme :
2. Gouranga Prasad Jana (SRF)
3. Mrinal Kanti Das (JRF)
4. Aniruddha Bandyopadhyay (JRF)
5. Debasish Dhenki (JRF)

Plan of Future Project Proposal based on the Current Project:

Further investigation on the generation, stability studies of the intermediate and its application to the synthesis of biologically active complex natural product will be carry out in this laboratory.
