Synopsis

The thesis entitled **"Phenacyl azide: A Versatile Intermediate for the Synthesis of Imidazo[1,2-*a*]pyridines, Pyrrolo[1,2-*a*]imidazoles, β-Enaminones, Pyrrolidin-2-ones and Amides; Diastereoselective Synthesis of Spiro[cyclopropane-1,3'-indolin]-2'-ones as Potential Anticancer Agents"** has been divided into four chapters.

- **Chapter I:** Types of cancers, Types of Treatment, cancer chemotherapy, Classification of Chemotherapeutic Agents, This chapter gives the general introduction about azide structure, reactivity, 1,3 diplor cycloaddition, and the objectives of the present work.
- **Chapter II: (Section-A):** This chapter describes the "$Cu(OAc)_2$/Et_3N mediated oxidative coupling of α-azido ketones with pyridinium ylides: Utilizing in situ generated imines for regioselective synthesis of imidazo[1,2-a]pyridine".
- **Chapter II: (Section-B):** Deals with "Coupling of α-azido ketones with pyridinium ylides: Convenient synthesis of β-enamino-carbonyls and pyrrolidin-2-ones".
- **Chapter III (Section-A):** Deals with the "Phenacyl azides as efficient intermediates: One-pot synthesis of pyrrolidines and imidazoles".
- **Chapter III (Section-B):** This chapter deals with the "Synthesis of *N*-alkylated benzamides from phenacyl azides and methanamines via base promoted C-C bond cleavage between carbonyl carbon and α-carbon of α-azido ketones".
- **Chapter IV:** This chapter deals with the "Synthesis and biological evaluation of spiro[cyclopropane-1,3'-indolin]-2'-ones as potential anticancer agents".

Chapter I

Introduction of Cancer

Cancer is a group of diseases characterized by aberrant cell growth. It is one of the dangerous diseases that insidiously attack people of all ages and cultures. It is assumed to be incurable due to its property of metastasis by which tumor cells located at one part of the body are transported to the other parts through blood stream and

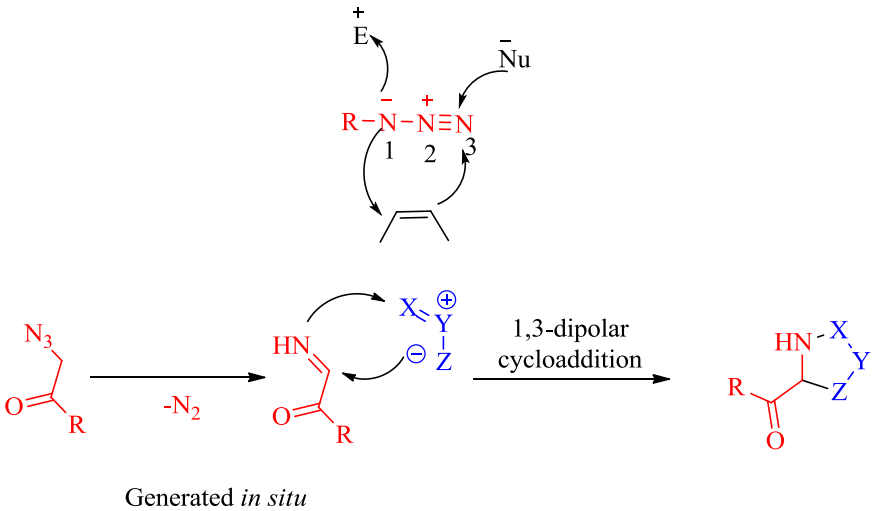
establish secondary tumors. The well–established techniques to combat cancer include surgery, radiation therapy and chemotherapy. However the type of treatment is decided based on the type and the stage of cancer.

Chemotherapy is one of the key techniques to combat cancer and it involves treatment of cancer using one or more anti–neoplastic agents. The improvement of survival rate and patient's health makes this technique of outmost importance in cancer treatment. The chemotherapy of cancer has evolved from highly empirical approaches, serendipitous findings and random testing of selected compounds to the more focussed testing of natural products, target oriented synthesis of chemical libraries and development of biological products. The chemotherapeutic agents are majorly classified according to their target of action. Several classes of chemotherapeutic agents include DNA interactive agents, enzyme inhibitors such as DHFRs, carbonic anhydrase, kinases, topoisomerases; growth factor inhibitors, mitotic inhibitors such as microtubule stabilizing and destabilizing agents etc.

Introdution of Organic Azides

Organic azides are attractive not only industrially, but also agriculturally, and pharmaceutically. For these reasons, organic azide chemistry has developed extensively. In especial, azide-mediated coupling reactions, which exhibit excellent chemo-selectivity, regioselectivity, stereoselectivity and high reactivity, have been employed in a wide range of applications.

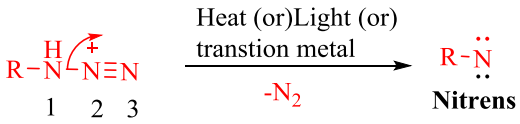
Reactivity of Organic Azides:



Generated *in situ*

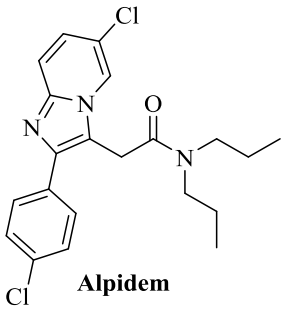
Organic azides show different chemical reactivities: the N1 atom can work as a electophile, and the N3 position nitrogen atom shows nuleophilic reactivity. The specific efficiency of organic azides is its character as 1,3-dipolar and this provides [3+2] cycloadditions with unsaturated bonds to give triazolines, triazoles and tetrazoles. Recently, the cyclization reactions of organic azides with alkynes (Huisgen reaction) have been a focus in the area of chemical biology and extensive reports have been published (Meldal-Sharpless click reaction or Copper-Catalyzed Azide-Alkyne Cycloaddition-CuAAC).

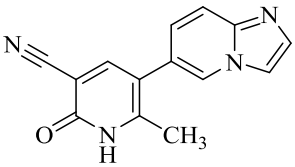
Azides can easily evolve nitrogen gas in many reactions. Especially, heating conditions or photoirradiations produce nitrenes from organic azides, which are highly reactive and give aziridinations and C-H aminations.

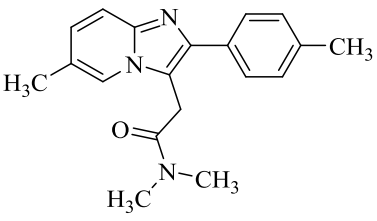


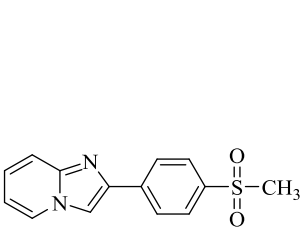
Chapter IIA: $Cu(OAc)_2/Et_3N$ mediated oxidative coupling of α-azido ketones with pyridinium ylides: Utilizing in situ generated imines for regioselective synthesis of imidazo[1,2-*a*]pyridine

The imidazopyridines are the very important nitrogen containing heterocyclic derivatives, exhibits promising biological activities like antifungal, antitumor, antiviral, anti-inflammatory, antibacterial, antipyretic, antiprotozoal, analgesic, anxioselective and antiapoptotic. Benzodiazepine, GABA receptor cardiotonic and agonists agents. There are some drugs alpidem used in the anxiolytic agent, olprinoneare used in the treatment for heart failure, zolpidem used in the treatment for insomnia, zolmidine used in the action of peptic

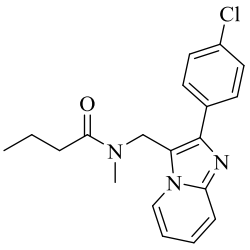

Alpidem


Olprinone

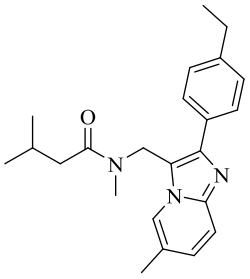

Zolpidem



Zolimidine

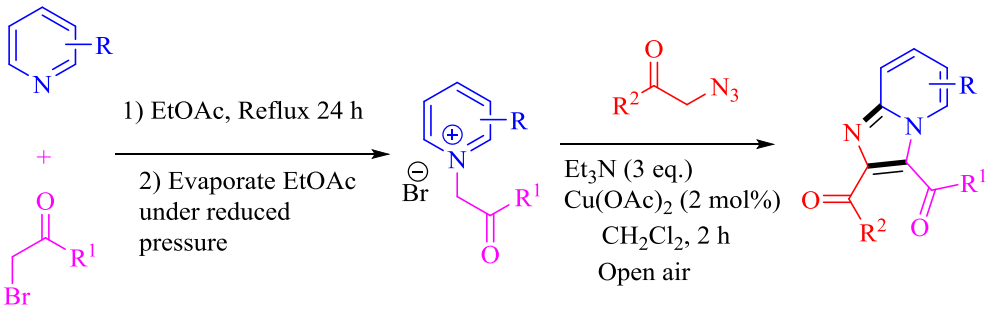


Saripidem

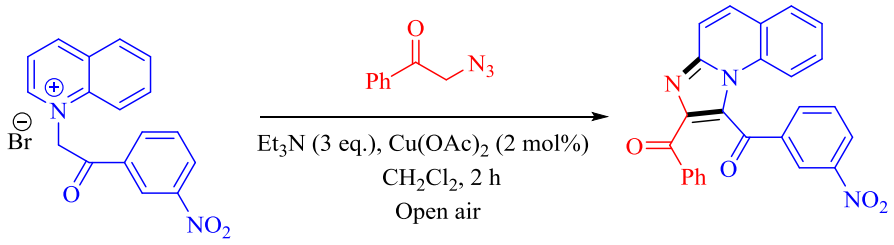


Necopidem

ulcer, saripidem and necopidem and together used for the anxiolytic agent, GSK812397 is a drug used for the treatment HIV virus, econazole shows antifungal activity. Therefore, the synthesis of these imidazopyridines is significantly important both in synthetic as well as medicinal chemistry. Most of these methods rely on the annulations of 2-aminopyridines with various reagents, therefore both nitrogen atoms of the imidazo[1,2-*a*]pyridine come from 2-aminopyridines. Whereas our synthetic route described herein utilizes coupling of pyridines and phenacyl azides to yield imidazo[1,2-*a*]pyridines, hence the nitrogen atoms of the product come from two different coupling partners.



Pyridinium ylides were taken as typical 1,3-dipoles. Herein, we disclose the results of $Cu(OAc)_2$/base mediated coupling of pyridinium ylides, generated from pyridine and phenacyl bromides, with phenacyl azides. Imines were generated in situ and reacted with pyridinium ylides to form cycloadducts which underwent facile air oxidation yielding pharmaceutically valuable imidazo[1,2-a]pyridines.



In conclusion, the reactivity of a class of α-azido ketones towards pyridinium ylides for the formation of pharmaceutically important fused heterocycles has been explored for the first time. $Et_3N/Cu(OAc)_2$ mediated one-pot strategy for the synthesis of valuable imidazo[1,2-*a*]pyridines was developed and 28 different chemical entities were synthesized in high yields (71-92%). The experimental results revealed that copper salt plays an important role for controlling the reactivity of in situ generated imines towards pyridinium ylides. The reaction and the one-pot protocol we developed has the potential for scale-up production of imidazo[1,2-*a*]pyridines.

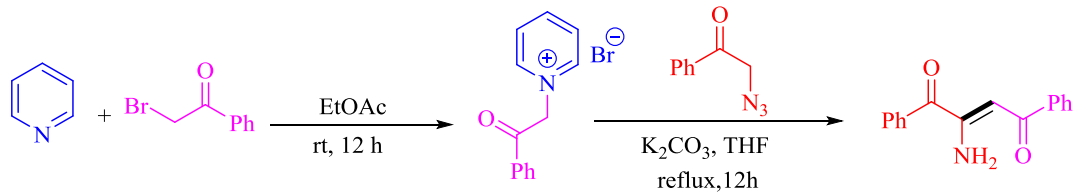
(Chem. Commun., **2015,** *51*, 10475)

Chapter IIB: Coupling of α-azido ketones with pyridinium ylides: Convenient synthesis of β-enamino-carbonyls and pyrrolidin-2-ones

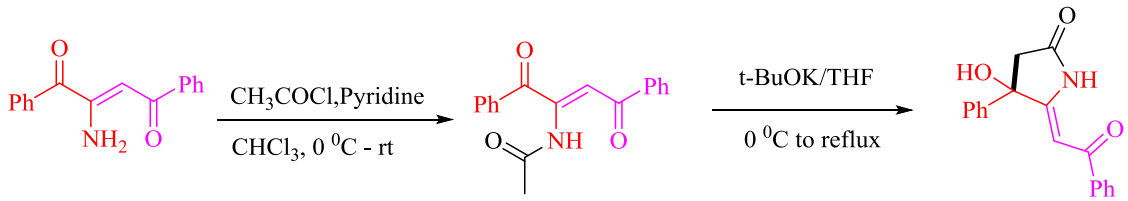
β-Enamino carbonyls are very attractive building blocks for the construtio of numerous biologically important heterocycles such as quinolines, oxazoles, pyrazoles, pyridinones, tetrahydrobenzoxazines,dibenzodiazepines, tetrahydro phenanthridines, and natural products. Furthermore they have been utilized for the synthesis of numerous anticancer, anticonvulsant, antibacterial and anti-inflammatory agents. Owing to their importance and utility, numerous synthetic procedures for β-enamino carbonyls have been developed. Most of these methods rely on the condensation of 1,3-dicarbonyls with amines using various catalysts.

We found that base mediated coupling of α-azido ketones with pyridinium ylides leads to the formation of a class of β-enamino carbonyl derivatives and we disclose the results of the same in some more detail along with the application of β-enmino carbonyl derivatives for the application β-enamino carbonyl derivatives for the synthesis of pyrrolidin-2-ones.

In order to optimize the reaction condensation for the formation of β-enamino carbonyl derivatives, the reaction of pyridinium salt with was t taken as a model reaction (Table 1). The pyridinium salt was prepared by stirring an equimolar mixture pyridine and phenacyl bromides in EtOAc at ambient for 12h. The crude pyridinium salt was sufficiently pure for further transformations hence after the formation of was complete the same reaction vessel was changed with phenacyl azide and base. For studying solvent effects, firstly EtOAc was removed under reduced presence and then same reaction vessel was changed with azide, base and other solvents (THF, CH_3CN and DCE).



In order to demonstrate synthetic utility of β-enamino carbonyls, acetylation of the amino group of followed by base mediated condensation of the acetylated amine was planned. Acetylation of was carried out using acetyl chloride as the acetylating agent and condensation was carried out using *t*-BuOK as a base. Though there are two carbonyls in compound which could react with the active methyl to yield a five or six member ring system, the five membered heterocycles was obtained exclusively. Exclusive formation of the five membered ring. Next several β-enamino carbonyls were subjected to acetylation/intramolecular condensation to yield pyrrolidin-2-ones in good yields.



In conclusion, a base promoted construction of β-enamino carbonyls using phenacylazides and pyridiniumphenacyl bromide was performed as a synthetically efficient protocol. Moreover, the resulting products were valuable intermediates in the synthesis of 4-hydroxypyrrolidin-2-ones in good yields.

(To be communicated)

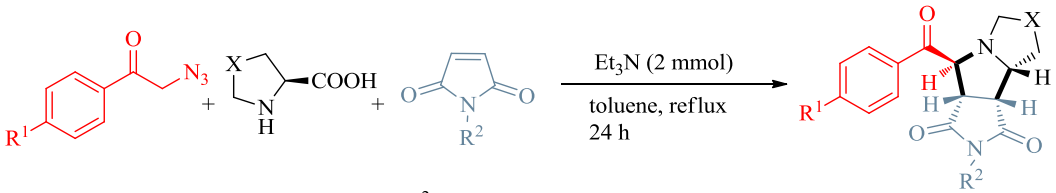
Chapter IIIA: Phenacyl azides as efficient intermediates: One-pot synthesis of pyrrolidines and imidazoles

Nitrogen-containing heterocyclic compounds play a vital role in the pharmaceuticals as well as medicinal chemistry. Particularly, five-membered saturated/unsaturated *N*-heterocycles appears frequently in natural and unnatural products. Moreover, fused imidazole and pyrrolidine derivatives gain tremendous importance as they have numerous biological activities such as antifungal, antimalarial, antituberculosis and antitumor activities. Due to the significant importance, development of mild, alternative and efficient protocols for the construction of five-membered *N*-heterocycles from inexpensive substrates is of highly enviable.

Azomethine ylides are powerful 1,3-dipoles for the construction of five-membered *N*-heterocycles. They are usually generated *via* thermal or photochemical ring-opening of aziridines, catalytic/photoredox oxidation of suitably substituted amines, condensation of carbonyls and amines, and decarboxylative coupling of carbonyls with amino acids. We envisioned that the imines could react with L-proline to generate an azomethine ylide, that should react with activated alkenes like *N*-alkyl/H maleimides or with *N*-unsubstituted imines itself to generate valuable *N*-heterocycle like hexahydropyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,8*bH*)-diones or 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazoles respectively.

To test the feasibility of this new method, a one-pot reaction using 4-chlorophenacyl azide (**1b**) with L-proline (**2a)** and *N*-methylmaleimide (**3a**) as a model reaction in EtOH and Et_3N (2 equiv.) as an additive under reflux condition was attempted. A clean product was observed which was isolated in good yield. Additionally, the effect of other solvents such as CH_2Cl_2, THF, CH_3CN, toluene, MeOH and with/without additive was investigated. After careful screening of all reactions, we found toluene as suitable solvent and Et_3N as additive in refluxing reaction condition.

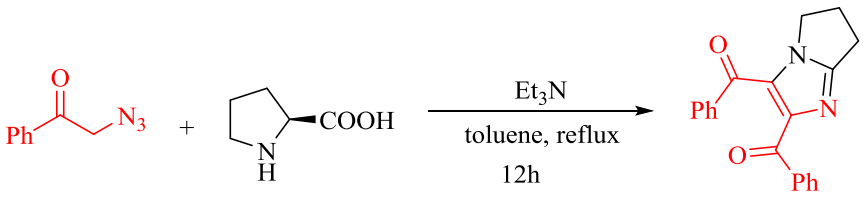
Having optimized reaction conditions in hand, we have successfully explored the scope of this one-pot reaction to produce a new series of fused heterocycles using various phenacyl azides, L-proline, and maleimides. A number of phenacyl azides bearing substitutions such as *p*-Cl, *p*-OMe and -H groups went well and provided good yields. Surprisingly, this reaction with L-thioproline gave good yield however; the yields were low with pipecolic acid.



R^1 = Cl, OMe, H X = CH_2, S, $(CH_2)_2$ R^2 = H, CH_3, Bn

Next, we attempted to explore the applicability of phenacyl azides, we successfully investigated this protocol without maleimides. A number of phenacyl azides bearing halogen, electron with-drawing or releasing functional group in their aromatic ring reacted under optimized conditions and expected to produce imidazoline derivatives. Surprisingly, the aromatized 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazoles

were observed with good to moderate yields (78–90%). It was probably due to the unfavourable [3+2] cycloaddition of imine with ylide (generated from other amino acids except proline) or inefficient air oxidation of the resulting cycloadduct. In this reaction the *in situ* generated azomethine ylide reacts with another molecule *N*-unsubstituted imine as a third component, therefore the products 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazoles were produced in one-pot three component process as shown in Scheme 1 which finally undergo aromatization using aerobic oxygen.



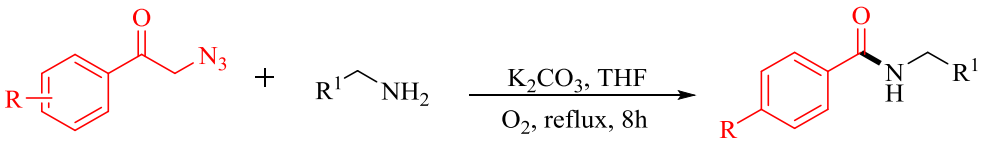
In conclusion, the reactivity of α-azido ketones for the construction of structurally diverse *N*-heterocyclics was explored. Phenacyl azides were decomposed under basic medium to produce N-unsubstituted imino ketones that subsequently reacted with L-proline and maleimides in one-pot three component manner to yield *N*-hetero tricyclic compounds hexahydropyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,8*bH*)-diones with excellent stereoselectivity via [3+2] cycloaddition reaction. Besides, the protocol used to produce a series of 6,7-dihydro-5H-pyrrolo[1,2-*a*]imidazoles by reacting phenacyl azides with L-proline. These products were isolated in good yields via [3+2] cycloaddition/oxidative aromatization reaction cascade. The successful demonstration of the reaction of α-azido ketones with various substrates opens the possibility of exploring readily available phenacyl azides for the synthesis of valuable heterocycles in an operationally simple and atom economical protocol.

(Org. Biomol. Chem., **2017,** *15,* 2730)

Chapter IIIB: Synthesis of *N*-alkylated benzamides from phenacyl azides and methanamines via base promoted C-C bond cleavage between carbonyl carbon and α-carbon of α-azido ketones

The amide functional group is a fundamental structural and functional motif of an array of biologically important proteins, natural products, pharmaceuticals, polymers and materials. Consequently, construction of amide bonds is of paramount interest in various subjects of study that include organic chemistry, polymers, bio-conjugation, plastic engineering, lubricants and detergents. Traditionally amides can be synthesised by coupling carboxylic acids with amines using either a coupling reagent or by direct

amidation of pre-activated carboxylic acid derivatives, such as acids, acyl halides, anhydrides, esters and aldehydes with amines or acyl azides and hydrazides with reducing agents. Other alternative methods include Staudinger ligation, Staudinger-vilarrasa reaction, aminocarbonylation of aryl halides, hydration of nitriles, rearrangement of aldoximes, dehydrogenative coupling of primary alcohols with amines and hydration of organonitriles to amides. However, most of these methodologies are associated with limitations such as usage of stoichiometric amounts of corrosive couplings reagents that lead to generation of equimolar amounts of toxic byproducts, high refluxing temperatures. Moreover, catalyst employed in catalytic procedures would limit the substrate scope for legion of simple to complex substrates having sensitive functionalities. Therefore, to develop an efficient method, a metal free approach has been achieved for the synthesis of *N*-alkylated benzamides from phenacyl azides via cleavage of C-C bond and formation of new C-N bondin the presence of K_2CO_3. Differentially substituted phenacyl azides could be readily cleaved to access a variety of *N*-alkylated benzamides utilising the present protocol, which is a viable alternative for the construction of amide bond. This metal-free reaction allows formation of amide bond in excellent yields with minimum waste generation. The high functional group tolerance and diverse substrate scope renders this reaction to be useful in organic synthesis.

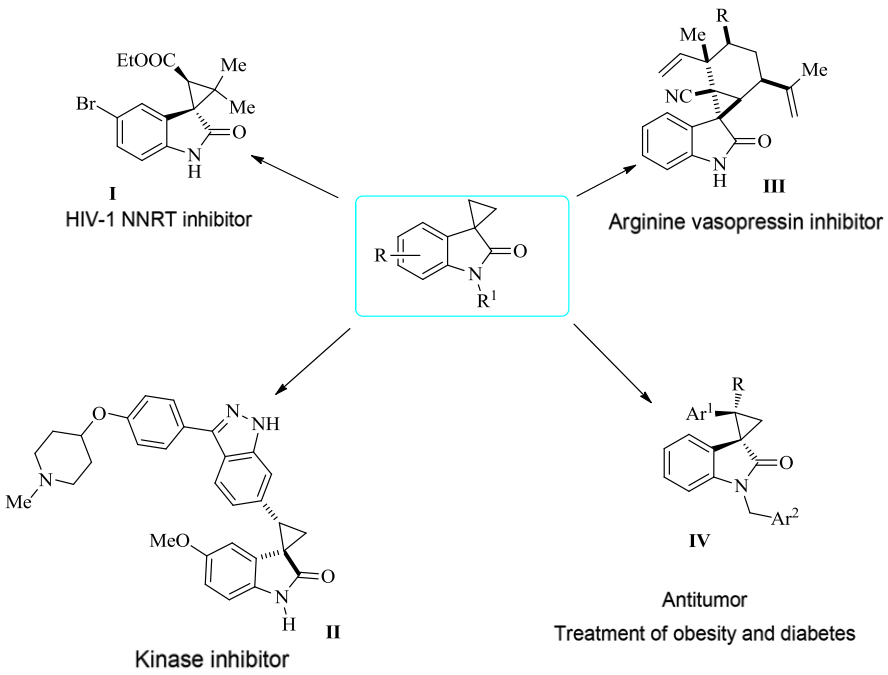


In conclusion a conceptually newer approach for the facile construction of amides using substituted α-azido ketones and benzyl amines in presence of base via C-C cleavage for the formation of new C-N bondis achieved. A wide range of substituted phenacyl azides can be cleaved and converted to the corresponding amides under the optimized reaction conditions. Absence of metal catalyst and usage of simple base are the promising features of this protocol which expand its synthetic applications.

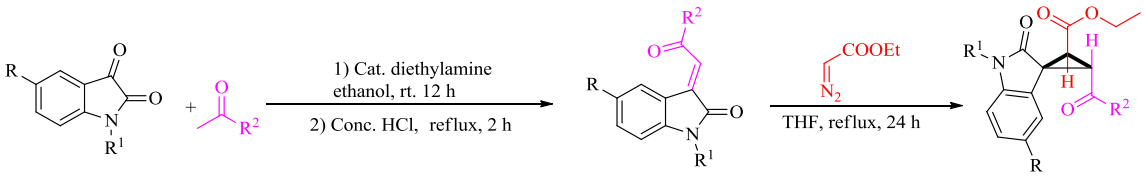
(To be communicated)

Chapter IV: Synthesis and biological evaluation of spiro[cyclopropane-1,3'-indolin]-2'-ones as potential anticancer agents

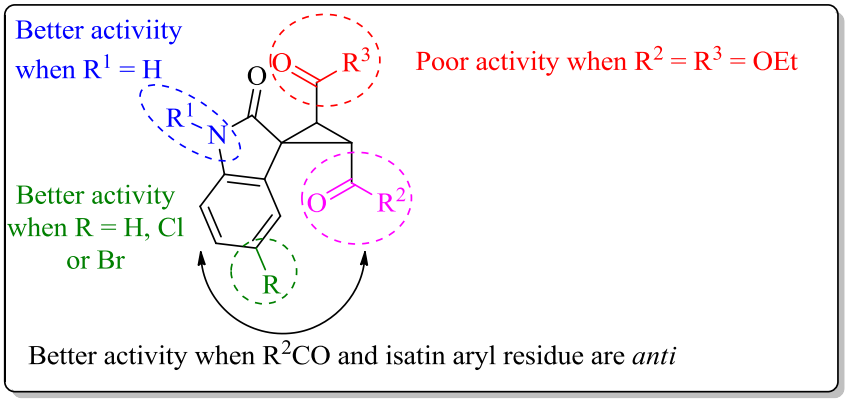
Spirocyclic compounds are notable for their molecular architecture as well as the prominent biological activities. Especially, spirocyclopropyl oxindoles are attractive synthetic targets because of their widespread occurrence in various natural products and biologically active molecules. The structural rigidity imparted by the spiro-carbon causes conformational restrictions and this may influence the binding of such compounds to the biological targets favourably. The spirocyclopropyl oxindoles with the smallest number of three-membered ring combined at the C_3 position of oxindoles, is an good-looking framework for both medicinal investigate as well as synthetic chemistry. First, during spiro-ring synthesis, spirocyclopropyl oxindoles combine two significant pharmacophores, cyclopropanes, quaternary oxindoles and together of which happen in several bioactive compounds showing a broad spectrum of biological activities. For example, compound **I** exhibited nanomolar activities as a HIV-1 non-nucleoside reverse transcriptase inhibitor. Compound **II** showed kinase inhibitor, compound **III** was found as arginine vasopressin inhibitor, whereas compounds of formula **IV** showed antitumor activity and and diabetes also helpful in treating obesity.



However, a careful survey of literature revealed that a few methods are available for the synthesis of spiro[cyclopropane-1,3'-indolin]-2'-ones. In this regard, most of these protocols involve expensive metal catalytic systems as well as low yields, limited diversification points in the product, and of environmental concerns. Moreover, in some method led to the access of highly diverse spirocyclic cyclopropanes, the competing formation of byproducts remains their major drawback. Therefore, to develop an efficient method, we have constructed a catalyst-free highly diastereoselective cyclopropanation of electron deficient alkenes using EDA.



Tetrahedron, **2014,** *70*, 4709



Bioorganic Med. Chem. Lett., **2015**, *25*, 4580

In summary, the synthesis and cytotoxic activity of a series of spiro[cyclopropane-1,3'-indolin]-2'-ones against five human cancer cell lines, namely HT-29 (colon), DU-145 (prostate), Hela (cervical), A549 (lung) and MCF-7 (breast) was investigated. Among them compounds showed significant anticancer activity against human prostate cancer cell line, DU-145. Detailed biological studies like, cell cycle analysis showed that these compounds arrest the cell cycle at G_0/G_1 phase and induced cell death by apoptosis. It was further confirmed by mitochondrial membrane potential, Annexin V-FITC analysis and Caspase-3 activity.