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Review Article

PEG-Supported Ketoacid Functionalization of Quinazolines: A Rapid Efficient Entry into Synthesis of Pyrrolo-/, Isoindolo Quinazolin-Ones under Microwave Irradiation

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ABSTRACT

The synthesis of polyethylene-glycol supporting arms and to demonstrate the utility of the polyethylene glycol as the multistep supported synthesis by designing the quinazolin based library studied. The rapid condensation of PEG-immobolized substituted diamine with various ketoacids and subsequent *in situ* intramolecular cyclization under microwave irradiation resulting one pot synthesis of quinazoline fused heterocyclic motifs. This facilitates rapid assembly of chemical diversity in short reaction time, simple purification, reduced environmental impact and convenient procedure.

Keywords: Isoindolofused quinazolines; Indole fragment analogues; Ionic liquid; Microwave

INTRODUCTION

The substantial efforts by taking the advantage of the soluble polymer supports and the benzimidazole scaffolds there by constructing and various heterocycles whereas the benzimidazole as the constituent or the one of the heterocycle in the bis-heterocoyels as the characterized bis-heterocyclic scaffolds. the researches has contributed in this scenario. Tandem reaction procedures led polyheterocycles are rich in synthetic diversity; the ubiquity of quinazoline based polyheterocycles system in biomedical relavence molecules and natural products has stimulated many efforts for their synthesis [1].

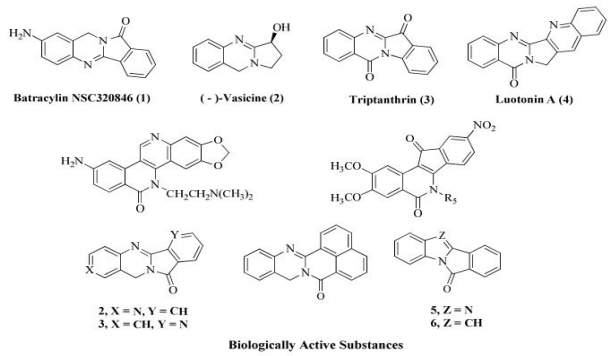


Figure 1: Quinazoline fused pharmacologically active substances.

LITERATURE REVIEW

Generating efficient interface between the ionic liquid supported microwaves assisted synergic synthetic application to synthesis the large collection of compound libraries are receiving ever increasing attention in research laboratories. The synergic synthetic assisted multi step ionic liquid supported intermediates are organic salts that are liquid at ambient temperatures (Figure 1) [2].

The synergetic rapid synthesis of diverse chemical entities enhanced where it serves the need to purify synthetic intermediates is minimized or eliminated. Each intermediate compound is purified and characterized for identity and purity with techniques such as 1H Nuclear Magnetic Resonance spectroscopy (NMR) before detaching the desired synthetic compound facilitate on support molecular confirmation. Quinazolin that share a common scaffold but differ only in their substituent patterns may display a range of well-defined

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biological activities. Quinazolin fused heterocyclics remain a major source of inspiration for the development of new drugs. The represented quinazolin isosteric conformational structures have been shown to be topoisomerase II inhibitors serving as antitumor agents. They define "privileged structures" that is, molecular scaffolds that confer the ability to interact with multiple protein targets to the entire compound class and that, therefore, are capable of interacting with a variety of cellular targets. Quinazoline constituted heterocyclics batracylin has advanced through the NCI drug development pipeline based on its activity against colon carcinomas as well as cisplatin- and doxorubicin-resistant tumors. Batracylin (8-aminoisoindolo [1,2-b]quinazolin-10(12H)-one; NSC320846) is an investigational clinical anticancer agent. Structural modifications effected to retain the ability to inhibit topoisomerase II, reducing toxicity and increasing water solubility by the introduction of diverse substituents on the isoindoloquinazolinone core. The enormous structurally isoindolone fused diversity presented by this class of quinazolines ensures a broad range of biological properties ranging from anti-cancer and anti-malarial activities to tumor promotion and ion-channel binding. Similar structures are present in many natural products of great pharmacological interest, including vasicine and tryptanthrin, which have anti-inflammatory activity and luotonin A, which has antitumoural activity [3].

As continuation of our research devoted to the development of multidisciplinary synergetic approaches for the rapid access to biologically active small heterocyclic molecules, we herein demonstrated the derivatization of quinazoline fused activity model heterocyclic libraries. Several compounds aiming on the structural modification of quinazoline moiety prepared by the condensation of the appropriate aliphatic ketoacids and aromatic ketoacids to prepare various structural conformations represents pyrrolo, Isoindolo quinazolinones under synergistic microwave assisted ionic liquid support [4].

DISCUSSION

The efficient preparation of functionalized quinazoline fused heterocyclics using the 4-bromomethyl-3-nitrobenzoicacid building block and the sequence of chemical transformations. This building block has been attached to the ionic liquid which acts as the anchor to the substrate throughout the sequence of reaction transformations. The aliphatic quarternary ammonium salts based ionic liquid chosen from the published literature. The appropriate amounts of the building block molecule 4-bromomethyl-3-nitrobenzoicacid and the ionic liquid in the microwave vessel presence of coupling reagent DCC and the catalytic amount of DMAP in acetonitrile for about 15 min of reaction time at 100°C leads to the formation of Ionic liquid supported 4-bromomethyl-3-nitrobenzoicacid has been occur [5]. Whereas the same reaction took place the 10 hr of room temperature and the 5 hr at the reflux conditions led the formation of attached compound. After carried out the reaction the insoluble DCU has been filtered and product washed with several times with ether solvent. The use of microwave irradiation was observed that the dramatic reduction of reaction time and effect the product ratio and the reaction yield. Further, this substrate treated with various aliphatic and aromatic primary amines to create the diversity point through the nucleophilic substitution reactions. This reaction carried out in the presence of microwave irradiation for about 10 min of reaction time at the 100°C of temperature to offer the amine substituted ionic liquid conjugate. Whereas the same reaction took place 5 hr of room temperature and 3 hr of reflux reaction conditions [6]. The substrate has been washed several times with the ether solvent. Further this substrate has been taken for reduce the nitro functional group and create the ionic liquid conjugate scaffold to generate various structural frame works. The reduction of nitro functional group has been done in the presence of Zn and the ammoniumformate using the microwave irradiation for about 80°C of reaction temperature and 5 min of reaction time in methanol. The reduction of the nitro functional group leads to the formation of ionic liquid supported diamine. This conjugate diamine has been used as a scaffold to generate various quinazoline based heterocycles. This conjugate diamine has been used as a scaffold to generate various quinazoline based heterocycles. By taking the conjugate diamine and treated with the ketoacids in the presence of 20 mol % of trifluoroaceticacid and anhydrous megnisiumsulfate under microwave irradiation for about 130°C of reaction temperature and the 10 min of reaction time leads to the formation of the pyrrol fused quinazolins. Whereas the same reaction took place 10 hr under reflux conditions (Figure 2) [7].

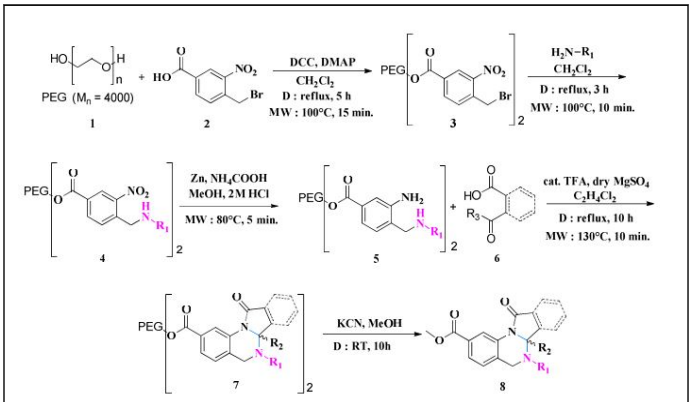


Figure 2: PEG-supported synthesis of quinazoline fused pyrrol and isoindol fused compounds.

The same reaction instead of using aliphatic ketoacids, aromatic ketoacids has been replaced to carry out the reaction under same reaction conditions leaves the isoindol fused quinazolin substrates. After the completion of the reaction the ionic liquid conjugate substrates has been washed several times with the ether solvent. The mechanistic formation of the products was understood that the under the strong acidic conditions the keto functional group was activated to generate the carbonyl electrophilic centre there by the ionic liquid conjugate primary amine functional group attaches the carbonyle electrophilic centre and forms the enamine by the expense of water molecule in the presence of anhydrous megnisumsulphate. The enamine substrate having under acidic conditions the conjugate secondary diamine attacks the enamine electrophilic carbon center forms the C-N bond leaves quinazoline secondary amines there by the tethered carboxylic functional group forms the amide bond by the expulsion of another water molecule. The

sequence of transformations carried out in the same reaction condition called the tandem reactions led quinazolin fused heterocycles (Figure 3) [8].

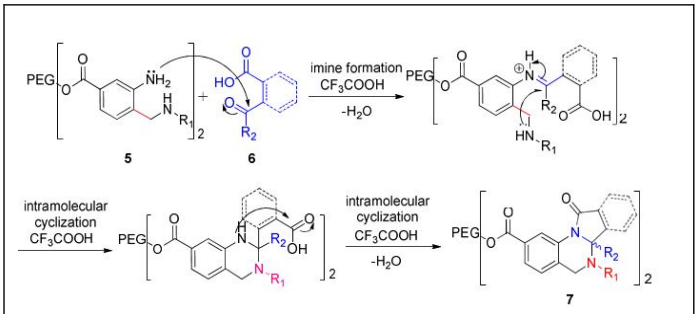


Figure 3: Possible mechanistic pathway of the targeted library of analogues.

The quinazoline fused heterocycles further cleaved from the ionic liquid support in the presence sodiummethaxoide in methanol. This reaction has been carried out under microwave irradiation in the presence of 120°C of reaction temperature and for about 15 min of reaction time leaves the products from the ionic liquid support. In contrast the same reaction under reflux conditions took place 10 hr of reaction time to cleave the products from the ionic liquid support. The synthetic utility of the efficient applicability of functionalized ionic liquid supported synthesis offers easy access to compound collections containing these crucial heterocyclic [9].

CONCLUSION

In conclusion, we have demonstrated an efficient procedure the use of homogeneous ionic liquids as soluble supports in the liquid phase synthesis of pyrrolo-/, Isoindolo quinazolin-ones. This microwave assisted ionic liquid supported synergistic synthetic methodology exemplifies the importance of functionalized ionic liquid phase synthesis offers easy access to compound collections containing this crucial quinazolinones fused heterocyclics. The ionic liquid anchored substrate throughout synthetic steps was stable in various ranges of temperatures. The synthesis of desired heterocycles with various aliphatic ketoacids and the extended aromatic ketoacids accomplished very short reaction times under microwave irradiation compared to the conventional reactions methods. The reactions accomplished in the homogeneous model, isolation of the desired products achieved *via* a simple filtration, and the characterization of the formation of product was monitored by the ^{1}H, ^{13}C and mass spectroscopic methods without detachment of the product from the ionic liquid. The rapid cyclocondensation and cleavage completed in only about 15 min under microwave irradiation, the effective methodology associated benefits derived from both tandem transformation and ionic liquid phase synthesis under microwave irradiation. The high loading capacity and lower molecular weight of the functionalized ionic liquid methodology offers significant improvements in regard to the yield of products avoiding toxic solvents to the green chemistry aspects.

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