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Divergent ionic liquid supported synthesis of isolable guanidine linked quinoxalinone and benzodiamine

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ABSTRACT

Ionic liquid supported synthesis of guanidine linked piperazine, diazepane, and aminomethylpiperidine to difluoroquinoxalinones and difluoro benzodiamine was achieved by two regioisomeric products. They were isolated from one pot reduction and intramolecular cyclization to afford quinoxalinone ring system with traceless cleavage of ionic liquid support. Besides, the ionic-supported other isomer was further cleaved in methanol. All the reactions were carried out on an ionic liquid support under various conditions to deliver biologically relevant scaffolds with high purity and excellent yields.

Introduction

Diversity oriented synthesis (DOS) has significantly revolutionized the drug discovery process and also has an impact on material science, catalysts, polymers, and pesticides.[1] In recent years, the design and synthesis of pharmacologically relevant heterocyclic molecules by DOS techniques has proven to be a promising strategy in the preparation of privileged-substructure-based libraries.[2] Integration of advanced technologies such as microwave, ionic liquid (IL), and polymer supported synthesis in the combinatorial synthesis of numerous multi-functionalized molecules is the key to speed up initial drug discovery.[3] Microwave-assisted IL supported organic synthesis is more popular in recent years because of the advanced instrumentation to provide reproducible results in homogeneous conditions.[4] Focusing on the synthesis of drug-like molecules, substituted heterocyclic compounds with a high degree of structural diversity are useful as potentially therapeutic agents.[5] Furthermore, compounds that contain heterocyclic moieties often exhibit improved solubility and can facilitate salt formation properties, which are important for oral absorption and bioavailability.[6] In chemical genetics, development of synthetic libraries in privileged scaffolds is specifically utilized to explore biological pathway in cells or organisms. The design and synthesis of small molecules with structural, substituent, and chiral diversity from easily available building block through a short and efficient approach is important to access a wide variety of structurally complex small molecules.[7,8]

Our interest is to develop the regioselective nucleophilic method for IL-fluorinated nitrobenzene. We choose 2,3,4,5-tetrafluoronitrobenzene (TFNB) for our studies where two activated fluorine atoms (2 and 4 positions) for regioselective nucleophilic substitution and two non-active fluorine atoms (3 and 5 positions) could present in target compound to attempt to increase its potential pharmacodynamic utilities. In the solution phase synthesis, generally nucleophilic aromatic substitution follows the sequence of C-2 ≈ C-4 > C-5 > C-3 order according to MNDO semi-empirical calculation for nucleophilic reactivity on TFNB as shown in Figure 1. Based on these differences in calculations of reactivity in activated fluoro group as well as analysis of the nature of nucleophile, we contemplate that the modification in the reaction conditions could provide the selective nucleophilic substitution. According to our assumption, we designed a synthetic route that allowed sequential nucleophilic aromatic substitution and provide the controlled synthetic route for multi-substituted TFNB system. For a succession of two nucleophilic substitution steps, where N1 is the first nucleophile and N2 is the second nucleophile, the order of substitution presents the opportunity of obtaining heterocyclic scaffolds and was shown in Figure 1.[9]

Our approach based on sequential S_NAr reactions on TFNB was planned to apply for the synthesis of guanidine linked to quinoxalinone moiety by heterocyclic core such as piperazine, azepane, and aminomethylpiperidine. Quinoxalinones represent a privileged moiety in medicinal chemistry and are ubiquitous substructures in material science and pharmaceuticals.[9] Some of the quinoxalinone derivatives act as psychotropic, hypnotic, cardiotonic, antihistamine agents, and possess cardiovascular activity, antiinflammatory activity as well as are HIV-1 reverse transcriptase

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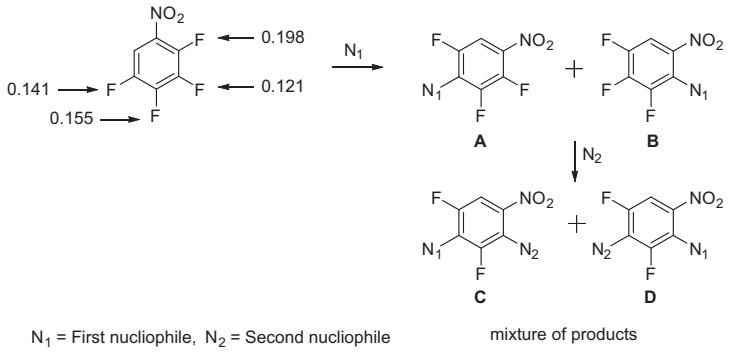

Figure 1. MNDO semi-empirical calculation for TFNB.

inhibitor (I).[10] The incorporation of piperazine or related heteroaromatic sub-units on the quinoxalinone ring system has been the focus of much attention which has exhibited a wide range of biological activities, for example, Carta et al. recently reported the synthesis and antimicrobial activities of over 150 quinoxalinones (II).[11] Moreover, the synthesis of such systems bearing bioactive guanidine unit that are attached to heterocyclic systems are of much interest due to the often unusual chemical, physical, and biological properties that such systems exhibit.[12] The introduction of a guanidyl type group improves the in vivo pharmacokinetic properties of thrombin and FXa inhibitors (III)[13] (Fig. 2).

Here we report the efficient traceless synthesis of guanidine linked piperazinyl, azepanyl, and aminomethylpiperidinyl quinoxalinones with substitutional diversity from versatile building blocks which include chiral amino acids, secondary amine derivatives such as piperidines, piperazines, and homopiperazines, and their stepwise regio-selective reaction with TFNB. The method describe in this Letter is a part of our continuing effort to explore traceless synthetic methodology to construct new heterocycles libraries. An IL-supported approach gives the advantage to employ the inexpensive asymmetric scaffold TFNB for the straightforward construction of complicated, fused heterocycles.

The synthetic strategy commenced with anchoring of amino acids to IL by the esterification method developed by our group.[8] Various aliphatic, aromatic, and hetero-aromatic chiral amino acids were immobilized on an ionic liquid support to produce the IL-supported amino acid conjugates **1** with built-in structural diversity. The main task of this synthetic pathway was the regioselective nucleophilic aromatic substitution reaction with tetra-fluoro-nitrobenzene (TFNB) by IL anchored chiral amino acid **1**. The TFNB has two active sites (2-fluoro and 4-fluoro) for nucleophilic substitution. Previously, Hardcastle and co-workers tried the similar nucleophilic substitution with penta-fluoro-nitrobenzene and ended up with the mixture of 2-substituted and 4-substituted nitrobenzene products.[9] Similarly, Ji et al also obtained the mixture of *ortho* and *para* substituted compounds in a similar substitution in dimethyl formamide at room temperature.

We reported here the efficient traceless synthesis of 5,7-difluoro-2-oxo-1,2,3,4-tetrahydro-quinoxalin-piperazines with three points of diversity. These versatile building blocks which include chiral amino acids, secondary amine derivatives such as piperidines, piperazines, and homopiperazines, and their regio-selective reaction appear to occur at either 2- or 4-position of 2,3,4,5-tetrafluoronitrobenzene (TFNB) to provide two isomeric products. For the purpose of library generation, the multi-step synthesis is conveniently carried out on the ionic liquid support to facilitate purification by precipitation. The fluoro displacement reaction of **1** with an excess of TFNB inside the microwave cavity proceeds to completion in 30 min with the formation of IL-bound tri-fluoronitrobenzoamines **3** and **4**. It takes 10 h to finish the same coupling reaction by conventional reflux heating or 1 h by sealed tube or 24 h to complete the coupling reaction at room temperature (Scheme 1).

When IL-bound amines **1** react with TFNB **2** in acetonitrile, two IL-bound region-isomers **3** and **4** are formed to display a 'one-bead-two-compound' feature. Just as expected, the reaction appears to occur at either 2- or 4-position to provide two isomeric products from each IL support. This was theoretically predicted by the MNDO semi-empirical calculation method and other organic synthesis reports.[9] So in a subsequent step, the displacement of the second active fluorine at 2- or 4-position with piperazines, homopiperazines, and 4-(aminomethyl)piperidines in the presence of triethylamine was introduced to this basic structure to give the products **5** and **6**, though there is a primary amine group in the 4-(aminomethyl)piperidine. Next we tried to introduce the guanidinyl group into **5** and **6** with *N,N′*-di-*tert*-butoxycarbonyl 1*H*-benzotriazole-1-carboxamidine derivatives **7** in ACN in the presence of TEA which took place for 18 h to give products **8** and **9**. All the IL bound intermediates and final compounds are purified by precipitation with the addition of ether (Scheme 2).

Reduction mixtures of IL bound intermediates **8** and **9** with Zn/$HCOONH_4$ gave the anticipated compounds **10** because the cyclization had taken place at the same time. The reduction and cyclization of **8** were operated simultaneously in situ, this is also accompanied by the cleavage of the ionic liquid support by an

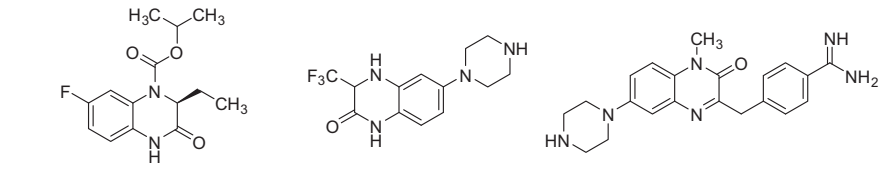

Figure 2. Biologically active relevant heterocyclic scaffolds.