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Original article

A facile method for building fused quinoxaline-quinolinones *via* an acidless post-Ugi cascade reaction

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ABSTRACT

A series of quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones have been synthesized using an Ugi/deprotection/cyclization (UDC) strategy, followed by a nucleophilic aromatic substitution reaction. This facile microwave-assisted method provided good yields and could potentially be used for the construction of a diverse library of quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones for high-throughput screening in medicinal chemistry.

1. Introduction

Nitrogen-containing heterocycles are important compounds that can be found in a wide range of drugs and biologically relevant molecules [1]. For this reason, research towards the development of novel and efficient strategies for the construction of these compounds represents one of the most active areas of present day synthetic organic chemistry [2]. Multicomponent reactions (MCRs) have become useful tools for the diversity-oriented synthesis of complex heterocyclic compounds [3]. One of the powerful multicomponent reactions is the Ugi reaction, which involves the effective multicomponent reaction of an aldehyde (or ketone), amine, isonitrile and carboxylic acid to afford an α-acylamino carboxamide adduct [4,5]. Tandem reaction sequences involving the use of an Ugi reaction, followed by various post-condensation transformations, represent extremely powerful synthetic methods for the construction of heterocyclic compounds with elaborate substitution patterns [6]. For example, Ugi/Buchwald–Hartwig/Michael [7], Ugi/Heck [8], Ugi/Aldo [9], Ugi/Bischler Napieralski [10] and Ugi/gold-catalyzed [11] reaction sequences have been reported to provide efficient access to a wide variety of cyclic scaffolds.

The quinoxaline skeleton is found in a wide range of biologically active natural products (**1**,**2**,**5**, Fig. 1) and synthetic compounds (**3**, **4**, Fig. 1) [12]. Notably, quinoxaline derivatives have been reported to display a wide range of biological properties, including anticancer [13], antitumor (*i.e.*, thymidylate synthase inhibitors) [14], antibacterial [15], antifungal [16], antihypertensive [17] and dopamine agonist [18] activities. In this study, we used a UDC, followed by an intermolecular nucleophilic substitution reaction to prepare a series of novel quinolino[3,4-*b*]quinoxalin-6(5*H*)-one compounds. It is noteworthy, however, these compounds were formed unexpectedly during our efforts to prepare a related scaffold and therefore represent a serendipitous discovery.

The synthesis of a series of fused piperazine-benzimidazoles *via* an UDC strategy was reported [19]. It was envisaged that we could expand the scope of this research to the construction of much more interesting and structurally complex compounds with a wide range of biological activities. During the last decade, G-quadruplexes have emerged as valid targets for the development of new anticancer drugs [20]. Numerous compounds have been reported to target these structures, and some of these compounds progressed into preclinical or clinical trials for the treatment of

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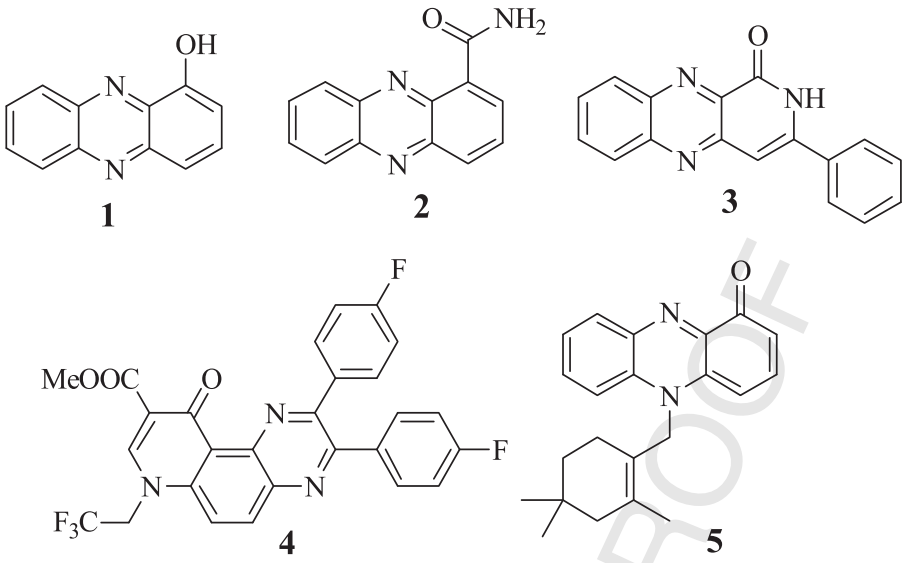


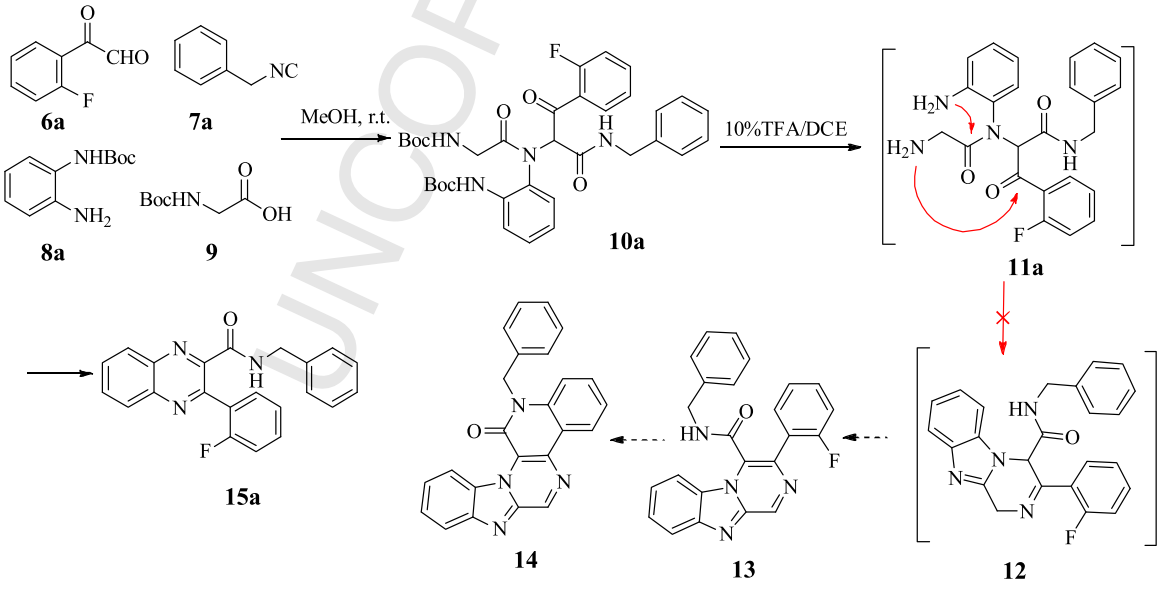
Fig. 1. Quinoxaline natural and prepared products.

cancer. It is noteworthy that most of the compounds designed against G-quadruplexes are based on polycyclic heteroaromatic scaffolds, which could be constructed from Ugi products following a series of nucleophilic substitution reactions to provide access to additional aromatic ring structures. It was therefore envisioned that the reaction of 2-*oxo*-2-phenylacetaldehyde **6a** with isonitrile **7a**, *N*-Boc-protected-phenylenediamine **8a** and *N*-Boc amino acetic acid **9** under the tandem UDC conditions would provide access to the corresponding benzo[4,5]imidazo[1,2-*a*]pyrazine derivative **14**, as shown in Scheme 1.

2. Results and discussion

The Ugi product **10a** was obtained in good yield and subjected to a Boc-deprotection step to afford intermediate **11a**. It was anticipated that compound **11a** would react as indicated by the arrows shown in Scheme 1 to give compound **12**. This material would then undergo a dehydrogenation reaction to give intermediate **13**, followed by a nucleophilic aromatic substitution reaction to provide the target compound **14** in the presence of an inorganic base catalyst, such as Cs_2CO_3 or Na_2CO_3. In practice, however, the UDC product resulting from the reaction of **11a** was determined to be the quinoxaline derivative **15a** instead of the expected product **12**. Notably, the formation of **15a** involved the cleavage of the amino acid group from **11a** during the UDC strategy when the cyclization was conducted under acidic condition. To develop a detailed understanding and further expand the scope of this process, we investigated the application of these reaction conditions to a series of different starting materials (Scheme 2). The results of these reactions revealed that they gave rise to the corresponding quinoxaline products.

The Ugi product **10** was obtained following the reaction of the *N*-Boc amino acetic acid **9** with *N*-Boc-protected-phenylenediamine **8**, 2-*oxo*-2-phenylacetaldehyde **6** and isonitrile **7** in methanol at room temperature overnight, and used in the next reaction without purification. The methanol solvent was removed under a gentle stream of nitrogen to give a residue, which was dissolved in 10% TFA/DCE and heated under microwave irradiation



Scheme 1. Ugi/deprotection/cyclization (UDC) strategy.

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