Route to Benzimidazol-2-ones via Decarbonylative Ring Contraction of Quinoxalinediones: Application to the Synthesis of Flibanserin, A Drug for Treating Hypoactive Sexual Desire Disorder in Women and Marine Natural Product Hunanamycin Analogue

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Supporting Information

ABSTRACT: A simple and practical method to access a variety of benzimidazol-2-ones is reported here. A series of N-alkyl-substituted benzimidazol-2-ones were synthesized by decarbonylative ring contraction starting from corresponding quinoxalinediones for the first time. The utility of the method has been demonstrated by synthesizing recently approved controversial drug fibanserin (Addyi) and a urea analogue of marine antibiotic natural product hunanamycin-A.

INTRODUCTION

Benzimidazol-2-ones 1 are an important class of heterocycles and a privileged scaffold in medicinal chemistry. They consist of cyclic urea fused with the aromatic backbone, which can potentially interact in a biological system by various non-covalent interactions such as hydrogen bonding and π stacking. Benzimidazolone derivatives exhibit a wide range of biological activities, and they are useful in treating various diseases including cancer, type II diabetes, central nervous system disorders, pain management, and infectious disease.1 Selected compounds embedded with a benzimidazol-2-one moiety along with their use are captured in Figure 1. It is worth mentioning that oxatomide drug with a benzimidazol-2-one core was approved for marketing a few years ago.2 Very recently, US Food and Drug Administration approved a new drug called fibanserin for the treatment of hypoactive sexual desire disorder (HSDD) in females, which contains benzimidazol-2-one motif.2b

RESULTS AND DISCUSSION

Considering interesting biological activity and the importance of this scaffold, we sought to develop a new and efficient method for the preparation of benzimidazolones. Literature search revealed that most of the methods for the synthesis of a benzimidazol-2-one core rely on carbonylation of benzene-1,2-diamines 2 or cyclization of appropriately substituted phenyl urea 3. The carbonylation reaction of benzene-1,2-diamines requires the use of phosgene, triphosgene, or carbonyl diimidazole.1 To avoid the use of such hazardous chemicals, alternative procedures using transition metals (palladium4 and copper5)-catalyzed intramolecular 3 or intermolecular 4 cyclization or C–H oxidation6 reactions were developed. Some of the interesting interconversions of heterocyclic rings for the synthesis of benzimidazol-2-ones are also reported. According to Zhou’s work, aminomethylene benzimidazoles 5 and alkyl halide in the presence of a base produced...
benzimidazolones. The Mamedov group synthesized highly functionalized N-pyrylbenzimidazol-2-ones through the rearrangement of substituted quinoxalin-2(1H)-ones. In this regard, it is noteworthy to highlight the efforts by Bolm and co-workers for the development of a mild method to access such heterocycles. Moreover, work on N-arylated and N-alkylated benzimidazol-2-ones is less explored. Here, we have developed a mild method for the decarbonylation of easily accessible quinoxalinediones to form benzimidazol-2-ones using potassium hydroxide (KOH) in dimethyl sulfoxide (DMSO). To the best of our knowledge, this transformation has not been reported in the literature (Scheme 1).

Scheme 1. Selected Routes to Benzimidazol-2-ones and Our Work

As part of one of the ongoing projects in our group, we were interested in the synthesis of tetracyclic N-heterocyclic carbones from the corresponding tetracyclic compound which in turn was readily prepared from quinoxalinedione through prenylation followed by Friedel–Crafts alkylation (Scheme 2). We have attempted hydrolysis of 1,1,10,10-tetramethyl-1,2,3,8,9,10-hexahydropyrazino[1,2,3,4-mn]-11-pyrron-5,6-dione using KOH and DMSO at room temperature to have the corresponding diamine. Fortuitously, a new product was isolated from the reaction, which showed similar proton nuclear magnetic resonance spectrum with ~0.3 ppm difference with respect to starting dicarbonyl compound, but carbon nuclear magnetic resonance (13C NMR) spectrum showed a considerable difference in most of the peaks including the presence of one peak for carbonyl carbon at δ 152.6 ppm (Figure 2). The assigned structure was further supported by high-resolution mass spectrometry analysis (271.1798) which corresponds to a ring-contracted product 10a. The structure of 10a was further confirmed by comparing its spectral data where it was synthesized differently. Having made this interesting observation, compound 11 was chosen for further optimization and subjected to various conditions listed in Table 1. By changing the base, equivalent, and temperature, we were settled with the optimized condition as 10 equiv of KOH in DMSO at room temperature. After optimization, we tested the scope of the method with different substrates and prepared several substituted quinoxalinediones. The results along with the yields of the isolated products are summarized in Table 2. Initially, we have subjected different N-alkylated 6,7-dimethyl 1,4-dihydroquinoxaline-2,3-diones (compounds 13–18) for the decarbonylative ring contraction and found that all of them are well-tolerated and gave good yields. To our surprise, attempts to afford the desired product in the case of N-unsubstituted quinoxaline-2,3-diones (12 and 25) were unsuccessful. This may be due to the fact that secondary amides exist in their tautomeric form, that is, imidic acid, probably which hindered the hydrolysis step. Aromatic ring without any substitution also gave a good yield of products (compounds 19 and 20). Methoxy substitution on the aromatic ring (compounds 21–24) was also tolerated but obtained moderate yield along with the recovery of the starting material. We could not improve the yield by increasing the reaction time to 36 h. Furthermore, to broaden the substrate scope, we have synthesized unsymmetrical N,N-di-substitution on the quinoxaline-2,3-dione core which is part of our antibacterial research interest. All of these compounds with unsymmetrical substitution were subjected to previously optimized condition and resulted in better yields of the desired products (compounds 26–33). Almost in all cases, we have observed the formation ~5–10% of the corresponding diamine (resulting from complete hydrolysis). As a direct application and to demonstrate the usefulness of the method developed, we decided to perform late-stage transformation on hunanamycin A, an antibiotic natural product derived from marine source, which contains a quinoxaline-2,3-dione core. Hunanamycin

![Scheme 1](link)

![Scheme 2](link)

| entry | base | equivalent | temp | yield (%) |
|-------|------|------------|------|-----------|
| 1     | NaOH | 2          | rt   | poor conversion |
| 2     | NaOH | 5          | rt   | 18 |
| 3     | KOH  | 2          | rt   | 22 |
| 4     | KOH  | 5          | rt   | 5 |
| 5     | KOH  | 5          | 60 °C| decomposed |
| 6     | KOH  | 10         | rt   | 64 |
| 7     | KOH  | 10         | rt   | 34 |

*Reaction tried on 50 mg scale in DMSO solvent, stirred for 24 h and isolated yield. Starting material (SM) recovered. Stirred for 12 h. Dimethylformamide (DMF) solvent.

Table 1. Optimization for Decarbonylative Ring Contraction
showed potent antibiotic activity against *Salmonella enterica* which causes food poisoning. Pleasingly, the reaction went smoothly to furnish benzimidazol-2-one 35, a new analogue of hunanamycin A in one step. All of the spectral data are in agreement with the drawn structure (Scheme 3).

The same methodology was applied for the synthesis of fibanserin, also known as “female viagra”, which is the first approved medication for treating HSDD in women and is classified as a multifunctional serotonin agonist antagonist.

Our synthesis of fibanserin commenced with 1-benzyl-1,4-dihydroquinoxaline-2,3-dione 36, which was reacted with known chloride 37 under the basic condition in DMF to give the desired product 38 in good yield. Compound 38 was subjected for the decarbonylative cyclization under the optimized condition to afford the product 39 in 59% yield. Finally, the benzyl group was deprotected using trifluorome-
thanesulfonic acid in toluene under microwave irradiation\(^{8d,18}\) which gave flibanserin in excellent yield (Scheme 4). The final product was isolated as HCl salt, and all of the spectral data are in agreement with the published data.\(^{15c}\)

**Scheme 4. Synthesis of Flibanserin through Ring Contraction**

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**CONCLUSIONS**

We have developed a mild and new protocol for the synthesis of benzimidazol-2-ones from quinoxalinediones through decarboxylation. The present methodology can be an addition to the toolbox to prepare benzimidazolones, and it will be useful in medicinal chemistry, particularly, late-stage functionalization of natural products, drug scaffolds, or an intermediate containing quinoxaline-2,3-diones. As direct application of this method, we have successfully developed a new route for the synthesis of recently approved drug flibanserin and a urea analogue of antibiotic natural product hunanamycin A. Later application demonstrates the utility of the present method in late-stage functionalization.

**ASSOCIATED CONTENT**

\* Supporting Information The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b00819.

Further experimental procedure and NMR spectrum of the products (PDF)

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**NOTES**

The authors declare no competing financial interest.
The synthesis of benzimidazol-2-ones.

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