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Expedient synthesis of pyrrolo[1,2-*a*]quinoxalines through one-pot three-component reactions of *o*-phenylenediamines, 2-alkoxy-2,3-dihydrofurans and ketones

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ABSTRACT

Pyrrolo[1,2-*a*]quinoxalines were synthesized through a three-component reaction of 2-alkoxy-2,3-dihydrofuran, *o*-phenylenediamine and ketone. This reaction was performed in nitromethane by using boron trifluoride etherate as catalyst. Mechanism of this reaction involves the following two steps: (i) a condensation reaction of the dihydrofuran with *o*-phenylenediamine, which produced a *N*-(2-aminophenyl)pyrrole derivative that can act as a 1,5-bisnucleophile, and (ii) an intramolecular Mannich-type reaction of the bisnucleophile and ketone to produce the pyrrolo[1,2-*a*]quinoxaline derivative.

1. Introduction

Pyrrolo[1,2-*a*]quinoxalines scaffold and their analogues are very important heterocycles.[1] Many of these tricyclic compounds exhibit broad pharmacological profiles. Until now, these heterocycles have been reported to be able to act as 5-HT_3 receptor agonists,[2,3] anti-HIV agents,[4] anticancer agents,[5,6] PARP-1 inhibitors,[7] antimalarial agents,[8] and antiulcer agents.[9] Some of these compounds also have displayed unique fluorescence properties, which enabled uses for amyloid fibril detection.[10] Therefore, the development of novel and highly efficient methods to construct these fused angular heterocyclic architectures is highly desirable for drug discovery.

For this reason, the synthesis of pyrrolo[1,2-*a*]quinoxalines has gained much attention.[11] A survey of the literature revealed that it can be assembled by various methods, such as 1,3-dipolar cycloaddition of quinoxalinium *N*-ylide to alkene,[12] copper-catalyzed annulation of 2-formylazoles with 2-haloanilines,[13] $Ir(acac)_3$-catalyzed annulation of 2-methyl-3-phenylquinoxaline with glycerol,[14] and thermal cycloisomerization of 2-propargylquinoxaline.[15] However, the most commonly used strategy for the synthesis of pyrrolo[1,2-*a*]quinoxalines was established on the basis of cyclization reaction of a functionalized *N*-phenyl pyrroles, which generally have a nitro,[16] amino,[17] halogeno[18] or isocyano group[19] at the 2-position of their phenyl group. By the same token, the C2-functionalized *N*-phenyl pyrroles can also be used as substrates. For example, 1-(*N*-arylpyrrol-2-yl)ethanone *O*-acetyl oximes have recently been used in the synthesis of pyrrolo[1,2-*a*]quinoxaline derivatives through N–O bond cleavage and intramolecular directed C–H arylation reactions with the aid of $Fe(acac)_3$ catalyst.[20] However, the applications of these approaches have been limited by the lack of suitable substrates for diverse synthesis because the phenyl group or the pyrrole ring must be decorated with a functional group prior to the reaction. Some pyrrolo[1,2-*a*]quinoxaline derivatives have also been synthesized through one-pot multi-component reactions (MCRs) by using easily available chemicals as substrates.[21] These approaches also have some advantages, such as mild conditions and good yield of the reaction products. However, the product diversity of the MCRs has been very limited until now.

We have recently been attracted by the unique reactivities of aldo-X bifunctional building blocks, which are important synthons for the synthesis of heterocycles.[22] Particularly, we envisaged that a class of easily accessible masked aldo-X bifunctional building blocks, 2-alkoxy-2,3-dihydrofurans,[23] may be able to react with *o*-phenylenediamine to construct a NH_2-containing 1,5-bisnucleophile. This reaction, if proceeded, coupling together with Mannich-type reaction of a ketone or aldehyde,[24] may trigger a three-component reaction of *o*-phenylenediamine, 2-alkoxy-2,3-

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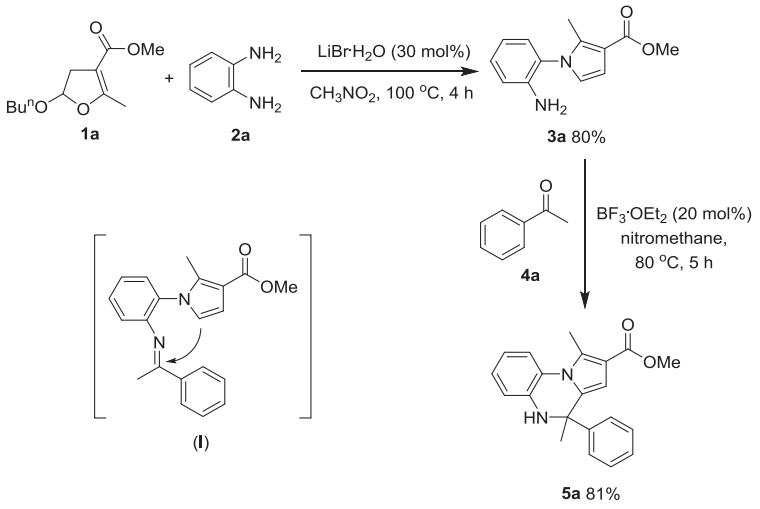
dihydrofuran and a ketone or aldehyde, with which a new type of pyrrolo[1,2-*a*]quinoxaline derivative could be synthesized. Out of this consideration, we started a program to explore the possibility of establishing a new way to synthesize pyrrolo[1,2-*a*]quinoxalines through a one-pot three-component reaction of easily available chemicals. And now, we will report in this paper the successful outcome of this endeavor.

2-Alkoxy-2,3-dihydrofurans were synthesized according to our previous method.[23] Initially, to testify the feasibility of synthesizing a NH_2-containing 1,5-bisnucleophile from the dihydrofuran, a mixture of 2-butoxy-2,3-dihydrofuran **1a** and *o*-phenylenediamine **2a** was heated in nitromethane in the presence of $LiBr\cdot H_2O$ at 100 °C. After 4 h, a *N*-substituted pyrrole derivative **3a** was obtained in 80% yield (Scheme 1). Interestingly, treatment of **3a** under acidic conditions in the presence of acetophenone **4a** provided a 4,5-dihydropyrrolo[1,2-*a*]quinoxaline derivative **5a** in 81% yield. This reaction should proceed through the formation of a Mannich-type intermediate (**I**), which underwent a Pictet–Spengler type reaction (intramolecular attack of the C2 position of the pyrrole ring to the imine carbon) to form **5a**. This result implies that it is indeed possible to construct a bisnucleophile from **1a** and **2a**, which is able to act as a building block for the synthesis of pyrrolo [1,2-*a*]quinoxaline derivative.

Increase of the catalyst amount was indeed able to improve the reaction yield. And the maximum yield reached 77% when 50 mol % of $BF_3\cdot OEt_2$ was loaded (entries 7 and 8). However, further increase of the $BF_3\cdot OEt_2$ amount was detrimental for the reaction as it resulted in a significant yield drop (entry 9). Under strong acidic conditions, the labile component, dihydrofuran **1a**, tended to form a furan derivative by eliminating a molecule of butanol.[25] Therefore, over-loading of $BF_3\cdot OEt_2$ should be avoided in order to get a good yield. Effect of solvent was then investigated. Toluene and ethanol were found to be inappropriate for this reaction (entries 10 and 11). Tetrahydrofuran (THF) was also found to be improper for this reaction (entry 12). When dimethyl formamide (DMF) was used, the yield of **5a** reached only 20% under the identical conditions (entry 13). Acetonitrile was proved to be suitable for this reaction, but the yield obtained was inferior as compared with that of nitromethane (entry 14). When DCE was used, the yield of **5a** reached only 38% under the identical conditions (entry 15). Further investigation revealed that the reaction was also affected by temperature and reaction time, and the optimal conditions were finally confirmed to be nitromethane solvent, 50 mol % of $BF_3\cdot OEt_2$, 80 °C and 5 h (entries 16 and 17). Under these conditions, the reaction can be scaled up uneventfully to 10 mmol scale with a uniform result (entry 18).



Scheme 1. Synthesis of **3a** and **5a** from **1a**, **2a** and **4a**.

To simplify the procedure of the synthesis of 4,5-dihydropyrrolo [1,2-*a*]quinoxaline with this method, a three-component reaction of **1a**, **2a** and acetophenone **4a** was then investigated, and the results are listed in Table 1. We expect that **4a** can react with the generated **3a** to form **5a** (Mannich-type reaction) without isolating the reaction intermediate. The three-component reaction was initially performed in nitromethane by using PTSA as catalyst. Although **3a** could be clearly observed, no desired product **5a** was formed after 5 h of reaction at 80 °C (entry 1). A commonly used Lewis acid, $FeCl_3$, was then used instead of PTSA, but no significant change could be observed (entry 2). Surprisingly, the expected product **5a** was obtained in 35% yield when $Sc(OTf)_3$ was employed (entry 3). $BF_3\cdot OEt_2$ also displayed the similar performance for catalyzing this model reaction (entry 4). Another two weak Lewis acids, $LiBr\cdot H_2O$ and $SnCl_2\cdot 2H_2O$, could not catalyze the formation of **5a** at all (entries 5 and 6). Considering the fact that $Sc(OTf)_3$ was rather expensive, we then selected $BF_3\cdot OEt_2$ as a catalyst to investigate the effect of the catalyst amount on the reaction yield.

The reaction mechanism of the three-component reaction is shown in Fig. 1. In the beginning of the reaction, **1a** was activated by BF_3 catalyst. Thus, **1a** was converted to an oxonium intermediate (**II**). It was quickly trapped by **2a**, and the formed intermediate (**III**) eliminated one molecule of butanol to form (**IV**). Then, an intramolecular attack of the enamine NH group to β-position of the enol form of 1,3-dicarbonyl fragment leads to the formation of **3a**. Finally, **5a** was generated through the formation of an intermediate (**I**). Based on this mechanism, the key role of nitromethane solvent in this reaction may be related to its unique ability for the stabilization of carbon cation (or oxonium).[26]

The substrate scope of the model reaction was then investigated, and the results are shown in Table 2. First, various ketones were subjected to reactions with **1a** and **2a**. Acetophenones with both electron-donating and electron-withdrawing groups participated in the condensation reaction smoothly, providing the desired products in yields ranging from 28% to 87% (**5b** to **5l**). 2-Acetylfluorene and 2-acetonaphthone also worked well, and the