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I_2-catalyzed one-pot synthesis of benzofuro/thieno[2,3-*b*]pyrrole motifs

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ABSTRACT

A novel I_2-catalyzed one-pot multicomponent protocol for the synthesis of a variety of elusive furo[2,3-*b*]pyrrole and thieno[2,3-*b*]pyrrole libraries has been established. To date, cyclization among alkanone, hydrazine and 2-bromobenzofuran or 2-bromobenzo[*b*]thiophene has not been explored in one-pot. Thus, the proposed single step protocol provides a versatile alternative to existing routes for accessing useful furo[2,3-*b*]pyrrole and thieno[2,3-*b*]pyrrole libraries.

1. Introduction

Pyrrole cores are prevalent foundational building blocks in many biologically active molecules, natural products and drugs. They exhibit interesting biological profiles such as antitumour,[1] antibacterial,[2] muscle relaxant, tranquilizers,[3] antifungal,[4] anti-inflammatory,[5] antimicrobial,[6] analgesic,[7] chemotherapeutic,[8] anti-glaucoma,[9] neurodegenerative and psychiatric disorder[10] drugs. Pyrrole scaffolds like Tensidol A and Tensidol B showed miconazole activity as well as antimicrobial activity.[4a] Lysine (K)-specific demethylase 1A (KDM1A) is an anticancer drug (Fig. 1).[4b] A family of pyrrole exists as a key structural motif in the construction of hallucinogen and serotonin agonists.[5] It should be noted that pyrrole ring systems have been attracted researchers to design light emitting diodes and transistors.[11] Considering these impressive biological and chemophysical properties of pyrrole derivatives and their significant role in organic synthesis, the development of versatile, convenient, and efficient methods for the synthesis of these core moieties has been attracted considerable attention from both the academic and industrial communities. The classical routes to pyrrole-fused heterocyclic system proceeded from the (i) reaction of *O*-phenyl-conjugated oxime ether with an alkyl radical,[12] (ii) Baldwin's cyclization of 3-substituted pyrrolidine-diones,[13] (iii) thermolysis of the methyl 2-azido-3-(3-furyl)propenoate,[14] (iv) reaction between 1,2-diaza-1,3-butadienes and diethyl or dimethyl acetylsuccinate,[15] (v) Gewald reaction of 1,3-dicarbonyl compound, alkyl or aryl isothiocyanates *via* ketene N,S-acetal intermediate, followed by a Dieckmann type cyclization,[16] (vi) reductive cyclization of 3-(2-nitrophenyl)thiophenes *via* nitrene intermediates,[17] (vii) radical or palladium catalyzed cyclization of 3-(2-bromoindol-3-yl)acrylonitriles.[18] Despite these advances, to the best of our knowledge, the utilization of three-component domino reaction strategy for the construction of furo[2,3-*b*]pyrroles and thieno[2,3-*b*]pyrroles has not yet been documented. Thus, it is highly desirable to develop an easy and efficient protocol to construct these novel structural units in one-pot, especially with the readily available starting materials.

Usually iodine catalyzed reactions are preferred over metal catalyzed reactions due to low cost, being environmentally benign, operational simplicity and to avoid the need of removal of metal impurities. Several research groups have been used iodine as a catalyst in various organic transformations such as the Lieben iodoform reaction, iodolactonization reactions, dehydration of diacetone alcohol, Michael reactions,[19] oxidative cyclization of acylhydrazones,[20] and for the synthesis of imino-1,2,4-

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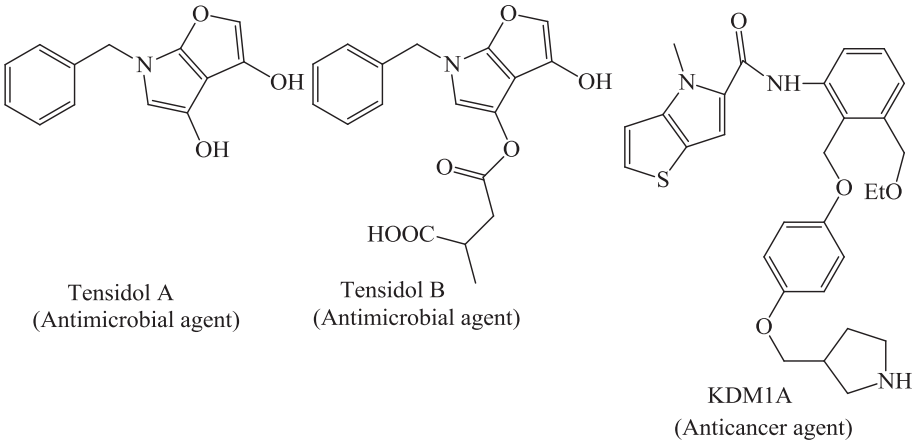

Fig. 1. Examples of some pyrrole based pharmacologically active molecules.

thiadiazoles.[21] Very recently, our team also reported several organic reactions using molecular iodine.[22]

As part of an ongoing development of efficient protocols for the preparation of significant heterocycles[23] and in a continuation of our work on multicomponent reactions,[24] herein, we report a single, unique method for the preparation of both furo[2,3-*b*]pyrroles and thieno[2,3-*b*]pyrroles using a single step, one-pot protocol. The yields are higher than the previous multistep protocols,[25] making this method advantageous for the synthesis of these fused heterocyclic motifs.

2. Results and discussion

The reaction of 2-bromobenzofuran (**1a**), butan-2-one (**2a**), and hydrazine (**3**) in THF under reflux condition was selected as the model reaction to establish the best reaction conditions. The reaction did not proceed without any catalyst. In the presence of, to our delight, tetrabutylammonium iodide (TBAI) and potassium iodide (KI) yielded 22% and 26% of the desired compound (**4a**) respectively. However, other catalysts like cerium ammonium nitrate (CAN), Co_3O_4, $BiCl_3$, and $ZrCl_3$ found to be ineffective and give an unsatisfactory result under the same reaction conditions. It was found that iodine showed catalytic efficiency better than others and produced the best result of the expected 2,3-dimethyl-1*H*-benzofuro[2,3-*b*]pyrrole (**4a**) in near quantitative yield (69%).

Next, we screened the reaction conditions with a range of solvents, forward yield improvement, and the results are summarized in Table 1. Among all, ethanol revealed to be a significantly better choice and proceeded more rapidly to afford the desired product in quantitative yield. Having established the suitable catalyst and solvent for the synthesis of benzofuro[2,3-*b*]pyrrole, we then focused on the amount of iodine. Increasing the loading of iodine resulted in the desired product **4a** in high yields, and the use of 10 mol% of catalyst delivered the best result (Table 1, entry 16). With further increase of iodine loading into 20 mol%, the yield of **4a** was not augmented. The reaction temperature played a significant role in this process. Thus, improvement of product yield was observed in ethanol at reflux.

Then taking the molar ratio at 1:1:1.1 of 1a/2a/3, catalyzed by 10 mol% iodine in ethanol at reflux temperature for 2 h. The desired product **4a** could be obtained in 81% yield.

The scope and limitations of this three component reaction under the optimized reaction conditions were studied using a variety of alkanones and 2-bromobenzofurans with hydrazine as summarized in Table 2. First the influence of substituents in alkanone was investigated. As expected, all the alkanones gave the corresponding benzofuro[2,3-*b*]pyrroles in excellent yields. Cycloalkanones (**4h, 4i** & **4k**) provided the corresponding benzofuro[2,3-*b*]pyrrole in excellent yield compared to those acyclic ketones. It should be noted that heterocyclic ketones as well as *N*-substituted heterocyclic ketone were well tolerated under this reaction conditions, and the desired benzofuro[2,3-*b*]pyrrole motifs were obtained in excellent yields (**4i**–**4k**).

Under this optimized conditions, the scope of 2-bromobenzofuran was also explored. 2-Bromobenzofuran having electron withdrawing group underwent this cyclization smoothly to afford the cyclized product (**4l**–**4o**) in good yields. In addition, the feasibility of this protocol was also extended by utilizing 2-bromobenzo[*b*]thiophene (**1c**), giving the target compounds (**4p**–**4t**) in good yields.

In the light of above experimental observations and literature reports,[25] a mechanistic rationalisation is depicted in Scheme 1. The first step involves the nucleophilic attack of hydrazine on activated 2-bromobenzofuran to give an intermediate. The intermediate formed undergo condensation reaction with activated carbonyl compound to form the corresponding hydrazones. This is followed by the [3,3] sigmatropic rearrangement to afford enehydrazine intermediate, which forms a cyclic aminoacetal (or aminal). Elimination of NH_3 gives the desired benzofuro[2,3-*b*]pyrrole product. The presence of iodine is likely to enhance the rate and yield of this one-pot synthesis.

3. Conclusion

In summary, we have developed a facile and an efficient multicomponent tandem cyclization reaction for the direct synthesis of benzofuro[2,3-*b*]pyrrole and thieno[2,3-*b*]pyrrole motifs *via* a Fischer-type cyclization. This cyclization has not been explored in one-pot. The present single step protocol provides a versatile alternative to existing multistep routes for accessing useful furo[2,3-*b*]pyrrole and thieno[2,3-*b*]pyrrole libraries.

4. Experimental

4.1. General information

Unless otherwise noted, purchased chemicals were utilized without further purification. Melting points were obtained on an electric melting point apparatus and values are uncorrected. TLC was performed using commercially available 100–400 mesh silica