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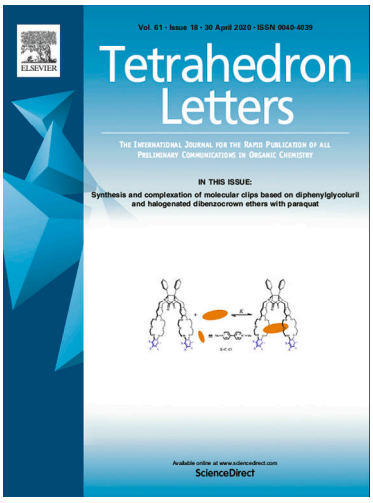

Synthesis of 5-phenoxyisobenzofuran-1(3H)-one as a Key Intermedate of the Drug Roxadustat

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Synthesis of 5-phenoxyisobenzofuran-1(3H)-one as a Key Intermedate of the Drug Roxadustat

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ABSTRACT

In this paper, a novel synthetic route to the key intermediate of the drug Roxadustat, 5-phenoxyisobenzofuran-1(3H)-one, was achieved in two steps in overall 78 % yield by using (3-phenoxyphenyl) methanol as the starting material. The synthetic route has the advantages of fewer steps, good regioselectivity, low catalyst consumption, high yield and lower raw material costs which are beneficial to realize industrial production.

Introduction

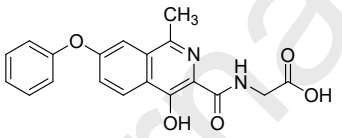

Figure 1. Structure of the Roxadustat.

Roxadustat (Figure 1) is a novel new-generation oral small molecule inhibitor of hypoxia-inducible factor (HIF) prolyl hydroxylases to be effective in the treatment and prevention of chronic kidney disease, ischemia, and hypoxia[1]. On Februry 11, 2020, FibroGen announces U.S. FDA acceptance of new drug application for Roxadustat for the treatment of anemia of chronic kidney disease.To date, a number of synthesis routes for the preparation of this class of compounds have been published[2]. In this work, we disclosed a novel and efficient synthetic route to the key intermediate **1** for the preparation of Roxadustat and potential other derivatives of isoquinoline. The compound **1** is chemically known as 5-phenoxyisobenzofuran-1(3H)-one with a phenoxy substituted benzo five-membered ring lactone structure as follows (Figure 2). So far, there are many reports about the synthesis of similar benzo five-membered ring lactone structures[3].

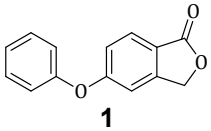

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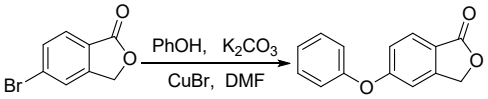
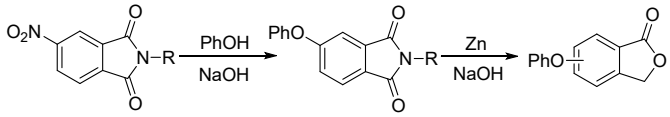
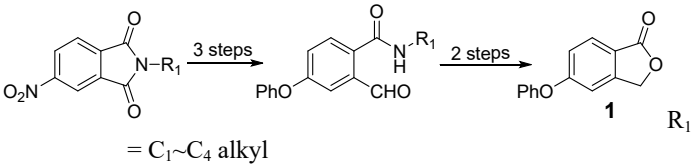
Figure 2. Structure of the 5-phenoxyisobenzofuran-1(3H)-one



Scheme 1. Copper-catalyzed coupling reaction for preparation of compound **1**.



Scheme 2. Preparation of 5 or 6-phenoxyisobenzofuran-1(3H)-one (Wang's work).



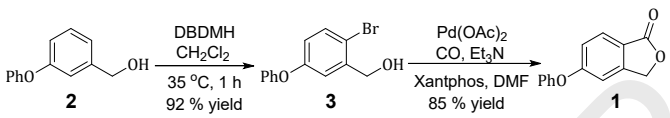
= C_1~C_4 alkyl

Scheme 3. Preparation of 5-phenoxyisobenzofuran-1(3H)-one (Zou's work).

In the past few years, the most common method of preparing compound **1** was utilized the copper-catalyzed coupling reaction of 5-bromophthalide and phenol in the presence of a base (Scheme 1) [4]. However, the synthetic routes

of ene drawbacks, such as long synthetic steps, low yield and environmental problems[5][6]. Moreover, Wang's group has disclosed a new synthetic approach to compound **1**, in which *N*-substituted-4-nitro-phthalimide condensed with sodium phenoxide to afford *N*-substituted-4-phenoxy-phthalimide and then reacted with zinc in the presence of a base to give a mixture of 5- and 6-position phenoxy products (Scheme 2) [6]. Zou's group reported that the target compound **1** was synthesized through the intermediate 2-formyl-*N*-methyl-4-phenoxybenzamide in five steps starting from 4-nitrophthalimide including coupling, hydrolysis, reduction and cyclization reactions (Scheme 3) [7].

Many efforts have been made to synthesize the target compound **1** as a key intermediate for preparation derivatives of isoquinoline, however, each of the above routes for preparation compound **1** suffers from the lengthy synthetic route, poor regioselectivity or complexity processes etc[4][6][7]. Therefore, a desired process is still a formidable challenge, which has merits of fewer steps, good regioselectivity, lower catalyst consumption, high yield, low raw material costs and easy scaling up. Herein, we report a simple, efficient and economic process for the synthesis of 5-phenoxyisobenzofuran-1(3H)-one using only two steps (Scheme 4). This process is achieved by regioselective bromination with DBDMH in excellent yield and palladium-catalyzed CO inserting reactions in good yield. We also have patent protection for this synthesis route [8]. The synthesis was accomplished in two steps in overall 78 % yield.



Scheme 4. Synthesis of the 5-phenoxyisobenzofuran-1 (3H)-one (**1**)

Results and discussion

The starting material, (3-phenoxyphenyl)methanol (**2**) was obtained from commercial supplier as an intermediate for the synthesis of pyrethroid-type insecticide[9]. In the first step, the compound **2** was treated with 0.5 equiv. 1, 3-dibromo-5, 5-dimethylimidazolidine-2, 4-dione (DBDMH) in dichloromethane (DCM) at 35 ° C for 1 h to afford the bromide **3** in 92 % yield. Due to the larger 4-and 6-position steric hindrance, the bromination mainly occurs at the 2-position. If the brominating reagent is more active or less sterically hindered, it will cause the 4- or 6-position brominated products (Figure 3). We compared the bromination effect between NBS and DBDMH in terms of yield, purity and impurities, *etc.* in accordance with the relevant bromination literature[10], and the results demonstrated that the bromination using NBS achieved bromide **3** in a purity of 85 %, and the 2, 4-dibrominated impurity is up to 10 %, by contrast, the bromination using DBDMH afforded bromide **3** in a purity of 93 % and dibrominated impurity less than 3 %.

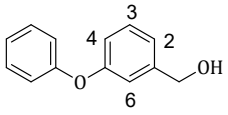


Figure 3. The position of bromination

In the second step, the target compound **1** was obtained by palladium-catalyzed carbonylation reaction. In an initial study, a mixture of the bromide **3**, 1.0 mol % $Pd(OAc)_2$, 1.2 mol % Xantphos ((9, 9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenyl-phosphine)) and 1.4 equiv triethylamine in toluene was heated at 120 ° C with stirring in an autoclave under carbon monoxide (8-10 atm) for 10 h to afford the compound **1** in 88 % yield. superior to others in 86 % and 88 % yields, respectively. Due to much better solubility of DMF than toluene, DMF was finally selected as reaction solvent. Considering the cost of palladium acetate, the loading of catalyst was screened. To our delight, the reaction proceeded well with 0.5 mol % $Pd(OAc)_2$ in 85 % yield. When the loading of catalyst was further reduced, the yield would be significantly reduced. Encouraged by this result, we further tested the ligands such as DPPF (1, 1'-bis(diphenypho-sphino)ferrocene), DPPB (1, 4-Bis (diphenylphosphino) butane), Xantphos and the results showed that Xantphos is the best choice.

Conclusion

In summary, we have developed a novel and efficient synthetic route for desired compound **1** with fewer steps, good regioselectivity, lower catalyst loading, high yield, lower raw material cost and easy scaling up. The bromination of (3-phenoxyphenyl) methanol (**2**) with DBDMH exhibited excellent regioselectivity and (2-bromo-5-phenoxyphenyl)methanol (**3**) was obtained in 92% yield. Subsequently, the desired compound, 5-phenoxyisobenzofuran-1 (3H)-one (**1**) was effectively synthesized *via* the palladium-catalyzed CO inserting reaction in two steps and overall 78 % yield.

Acknowledgments

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Dear Editor John Wood:

Thank you very much for giving us an opportunity to revise our manuscript. We appreciate editor and reviewers very much for your positive and constructive comments on our manuscript entitled **“Synthesis of 5-**

Intermedate of the Drug Roxadustat". (Manuscript ID: TETL-D-20-00547). The manuscript is an original work for only academic research (not for commercial aim) and has not been published or submitted elsewhere. All above-mentioned authors have agreed to the final version of the manuscript and do not have any possible conflicts of interest.

I am looking forward to hearing from you soon about the outcome. If you have any queries, please don't hesitate to contact me.

Thanks for your time and consideration.
Best wishes.

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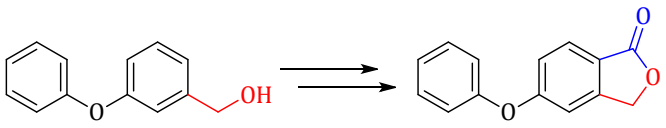
Graphical Abstract



(3-phenoxyphenyl)methanol 5-pphenoxyisobenzofuran-1(3H)-one

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[b] Jiangsu Hengpei Pharmaceutical Technology Co., Ltd, Suzhou 215123, P. R. of China

- A route to synthesize the intermediate of the drug Roxadustat was achieved
- The synthesis was accomplished in two steps in overall 78 % yield
- The main advantages of synthesis include fewer steps and good regioselectivity
- Lower raw material costs are beneficial to realize industrial production

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