Optimization of Ullman reaction conditions for the synthesis of pirfenidone.

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Abstract

Pirfenidone, the only drug approved by FDA to treat idiopathic pulmonary fibrosis, was synthesized in quite good yield and purity by an optimization of Ulman reaction.

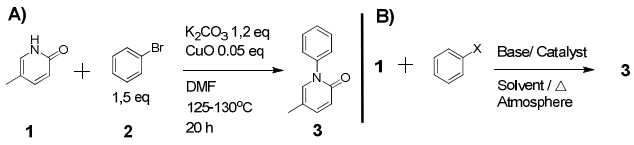
Introduction

Pirfenidone is an anti-fibrotic drug, with anti-inflammatory and anti-oxidant properties. It was recently approved by FDA, under the trade name Esbriet, for the treatment of idiopathic pulmonary fibrosis (IPF), being the single orally administrated drug for the treatment of this disease. Despite its unique therapeutic relevance, there are relatively few methods published about the synthesis of pirfenidone. All of them are based in the Ullman reaction, which uses copper as catalyst and different halogenoarenes, and can be considered an attractive strategy since the low cost of the catalyst. The reaction between boronic acids (as aryl donors) and cupper acetate as catalyst was employed in the synthesis of pirfenidone in very low yield (12%).[1] A remarkable improvement was achieved by Crifar and co-workers which synthetized pirfenidone in 98% yield, using trivalent organobismuthanes.[2] However, the disadvantages of this method includes: a) the demand for previous preparation and purification of arylbismuthanes and b) the impossibility to scale up, in order to prepare multi-gram of pirfenidone. Recently, Eadara and colleagues published an attractive and inexpensive synthesis of pirfenidone and related compounds with a yield of 70%.[3] The conditions of this reaction include the use of CuO as catalyst, bromobenzene as aryl donor, K_2CO_3 as base and ambient air.

In the present study, we describe the attempt to develop an optimize and reproducible methodology based on Ullman reaction in order to prepare pirfenidone.

Results and Discussion

Starting with reaction conditions described by Eadara and co-workers[3] we were not able to obtain pirfenidone. Therefore, several modifications were proposed (Scheme 1). Initially we changed the base to K_3PO_4 without good results, showing that the strength of the base hasn't impact in the course of this reaction. Another aspect to consider in the Ullman reaction is the copper source, so we performed the reaction directly with CuI, however pirfenidone wasn't obtained. Similarly, when DMF was replaced with dioxane the *N*-arylation did not happen, even adding *N,N'*-dimethylethylenediamine, as a 1,2 diamine ligand.[4] On the other hand, when the aryl halide was replaced by iodobenzene, the pirfenidone was obtained, but with poor yield (10%). This result confirmed the observed reactivity of the haloarenes in the aromatic nucleophilic substitutions through Ullman reaction, where the order is I>Br.[5] Similar results were obtained when the reaction was performed using CuO as catalyst. Otherwise, it is known that Cu is able to form many complexes with molecular oxygen, broadening the variability of complexes in solution and in consequence, the yield of the reaction. With this idea in mind, we carried out the reaction in anhydrous DMF under an inert atmosphere, using iodobenzene or bromobenzene. Interestingly, pirfenidone was obtained in good yield (60%) just with I-Ph, with possibility to scale up. These results indicate that anhydrous solvent, inert atmosphere and iodobenzene, like aryl donor, are required to attain the target drug in good yields.



Scheme 1: A) Eadara and co-workers methodology to obtain pirfenidone (3); B) Studied Ullman reaction conditions

Conclusions

We report an optimized method for the preparation of pirfenidone in quite good yield and purity.

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