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Research Article

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A Facile β-Cyclodextrin-Catalyzed synthesis of substituted benzofuran from salicyaldehyde and alpha tosyl ketone

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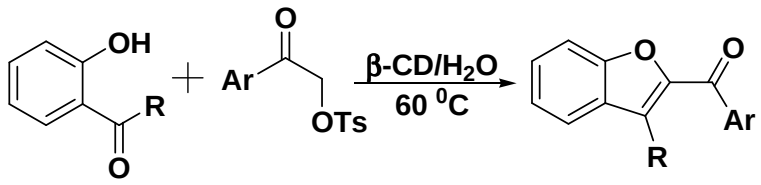
ABSTRACT

A simple and highly efficient protocol for the synthesis of substituted benzofuran from various salicylaldehydewith α- tosyl ketones under catalyst β-Cyclodextrin in water is reported. This protocol gives wide range of substituted benzofuranwith high yields.



Scheme-1

Keywords: β-Cyclodextrin, benzofuran, α-tosylate, salicyaldehyde, cyclization.

INTRODUCTION

Benzofuranones have attracted considerable attention with regard to their pharmaceutical activity and the various approaches directed towards their synthesis [1].The simple benzofuran derivatives like 2-nitrobenzofuran[2], 2-acetyl benzofurans are well known as bio-dynamic agents possessing various pharmacological properties[i.e].spasmolytic activity on the intestine of the guinea pig[3] and dilatory effects on the heart of the rabbit[4]. Most of the benzofuran compounds frequently occur in natural products and are good chelating agents. The compound amiodarone hydrochloride used as an idealantiarrhythmic drug[5] contains a 2, 3-substituted benzofuran moiety. The Schiffs bases exhibit a broad spectrum of pharmacological and biological properties[6]such as analgesic, anticancerous, anti-inflammatory etc. that may be due to the azomethine linkage. The Schiffs bases bearing methoxy groups have pronouncedantimicrobial activities[7]. The Schiffs bases derived from sulfa drugs and salicylaldehydes act as good chelating, bactericidal and fungicidal agents.

Benzofurans, often found in naturally occurring or synthetic compounds, are attractive to chemists for their various biological activities. For example, 5-benzofuranol has potent anti-allergic and anti-inflammatory activities; [8]Machicendiol, a benzofuran isolated from the extracts of Machilusglaucescens, a folk medicine, has been used in the treatment of asthma, rheumatism, and ulcers;[9] 2,5-disubstituted benzofurans are active in enhancing insulin sensitivity,[10]benzofuran-fused benzocarbazoles have potential antitumor and antibiotic activities;[11]ailanthoidol, a 2-arylbenzofuran natural product isolated froma Chinese herbal plant, and synthesized by Chern possesses various biological activities;[12] and so on. [13] The strategies for the construction of benzofurans are various, such as coupling

of conjugated dienynes with Fisher carbene complexes, [14] anion-accelerated palladium-mediated intramolecular cyclization,[15] utilizing of o-ydroxyphenyl ketones or o-(1-hydroxy-2,2-dimethylpropyl)phenol with 1-benzotriazol-1-ylalkyl chloride in two or three steps to synthesize 2,3-disubstituted benzofurans,[16]palladium-catalyzed intramolecular coupling of aryl halideswith phenols, [17]condensation of o-hydroxyacetophenone derivatives with phenacyl bromides under PTC (phase transfer catalysis) conditions in a two phase system, using aqueous K_2CO_3 (20%) as a base[18]and cyclocondensation of α-halo-ketones with o-hydroxybenzophenone and salicylaldehyde[19]have been reported. However, those methods still have some disadvantages including tedious reaction conditions,low yield, and commercially unavailable key intermediates.Therefore to develop a simple and straightforward method is requisite.

Herein, we report new applications of β-cyclodextrinfor the one-pot synthesis of substituted benzofuran. The direct one-pot synthesis of substituted benzofuranfrom salicylaldehydewith α- tosylketoneswas achieved under neutral conditions using β-cyclodextrin and water.

EXPERIMENTAL SECTION

Synthesis (benzofuran-2-yl)(phenyl)methanone:
The reaction was carried out as follows: β-CD (1 mmol)was dissolved in water (15 ml) by warming up to 60^0Cuntil a clear solution was formed and then the sylicylaldehyde(1 mmol) dissolved in acetone (1 ml) was added slowlywith stirring. After 15 min at this temperature α-tosylate (1mmol) were added and the mixturestirred at that temperature until the reaction was complete(Table 1). The organic material was extracted with ethylacetate and dried the resulting product, as though seen as singlecompound by TLC, was further purified by passing overa column of silica gel. The β-CD was recovered by filtrationand reused.

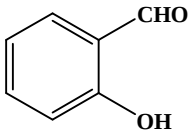
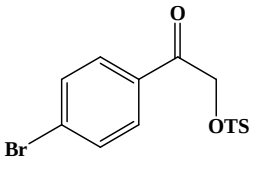
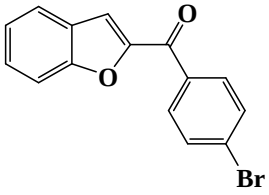
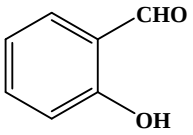
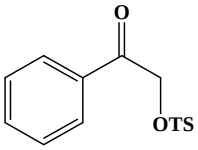
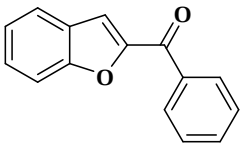
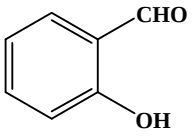
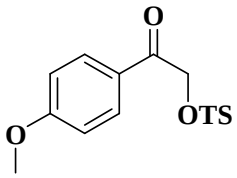
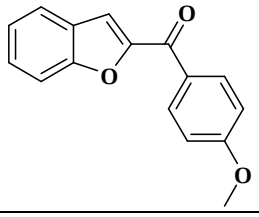
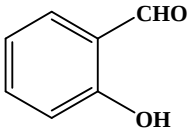
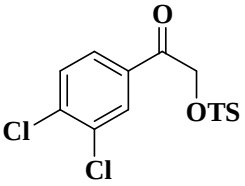
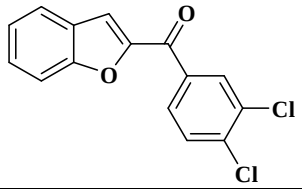
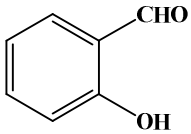
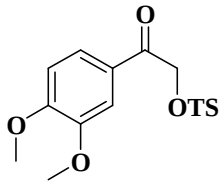
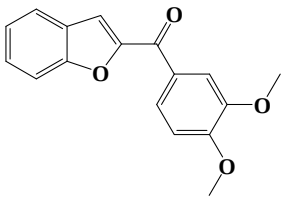
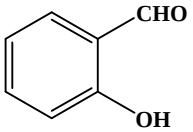
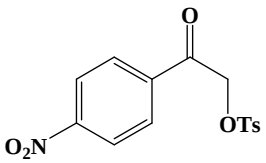
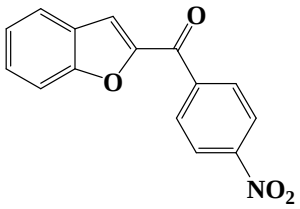
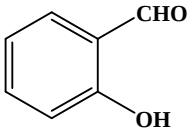
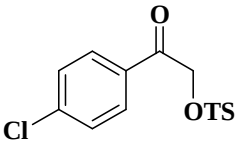
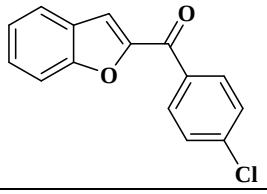
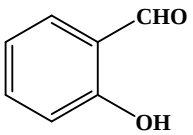
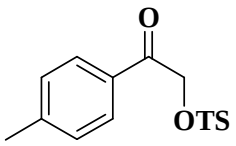
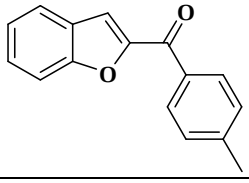
RESULTS AND DISCUSSION

However, some of these methods suffer from one or more of the following drawbacks such as strong acidic conditions, long reaction times, low yields of the products, tedious work-up; need to use excess amounts of reagent and the use of toxic reagents, catalysts and solvents. Therefore, there is a strong demand for a highly efficient and environmentally benign method for the synthesis of these heterocycles. In recent years, studies of low-waste routes and reusable reaction media for enhanced selectivity and energy minimization have occupied the interests of synthetic organic chemists.

β-cyclodextrinmediated cyclisation of sylicylaldehyde and 1-(4-chlorophenyl)-2-tosylethanoneto (benzofuran-2-yl)(4-chlorophenyl)methanonewas investigated. In a typical experimentβ-CD (1 mmol)was dissolved in water (15 ml) by warming up to 60^0Cuntil a clear solution was formed and then the sylicylaldehyde(1 mmol) dissolved in acetone (1 ml) was added slowlywith stirring. After 15 min at this temperature 1-(4-chlorophenyl)-2-tosylethanone (1mmol) were added and the mixturestirred for 3 hr. at 60^0C.The organic material was extracted with ethylacetate and dried. The resulting product was further purified by passing overa column of silica gel.The reaction proceeds for the formation of cyclisation in satisfactory yield.

Next, we examined the scope of the reaction of sylicylaldehydewith a variety of α-tosylate. As shown in Table-1, it was observed that a series of α-tosylatesbearing either electron-donating or electron-withdrawing groups on aromatic ring were investigated. The α-tosylates with strongly electron-withdrawing groups on aromatic ring such as 1-(4-nitrophenyl)-2-tosylethanone gave the product of with good yield in a long reaction time.

Table-1:- Synthesis of substituted benzofurans from salicylaldehydeand α- tosyl ketones

Sr no	Reactant	Tosylate	Product	Yield %	Time (h)
1				84	2
2				86	2
3				80	2.5
4				81	3
5				79	3
6				87	3.5
7				84	3
8				80	2.5

CONCLUSION

In conclusion, we have presented for the first time a simplemethodology for the cyclisation of a variety of α-tosylates and sylicylaldehyde using β-CD in water. Itis an economical and user-friendly protocol.

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