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Research Article

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[Hydroxy(tosyloxy)iodo]benzene mediated synthesis of 2-(4-methoxy-phenyl) quinoline salicylic acid using Pfitzinger reaction

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ABSTRACT

Procedure for the synthesis of 2-(4-methoxy-phenyl) quinoline salicylic acid has been developed by the α-tosyloxylation of acetophenone with [hydroxy(tosyloxy)iodo]benzene, followed by treatment with KOH and isatin.

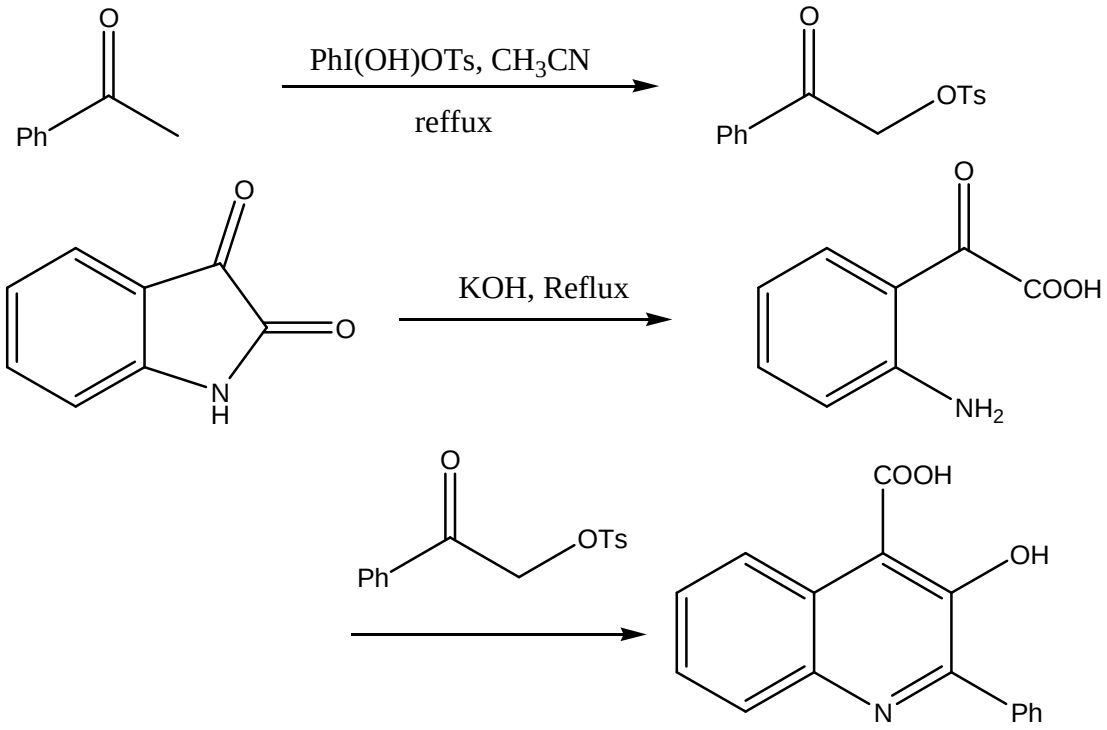
Keywords: Isatin, HTIB, quinoline salicylic acid.

INTRODUCTION

The 2-aryl-quinoline salicylic acid possesses diverse physiological and biological properties as like P-selectin antagonists for the treatment of inflammatory diseases such as rheumatoid arthritis [1-2]. Moreover, 2-aryl-quinoline salicylic acid are the promising lead structures for the novel synthetic drugs, ester derivatives of 2-aryl-quinoline salicylic acid posses antiarthritic [3] and amide derivatives of 2-aryl-quinoline salicylic acid are claimed to be potent, selective, competitive and orally active nonpeptide tachykinin NK(3) receptor antagonists that are useful for the treatment of pulmonary, CNS, and neurodegenerative disorders [4-7]. They are also applicable as pharmacological tools for elucidating the function and pathophysiological role of NK(3) receptors [4,7]. Bromodecarboxylation of quinoline salicylic acids increases the diversity of accessible substituted quinolines [8].

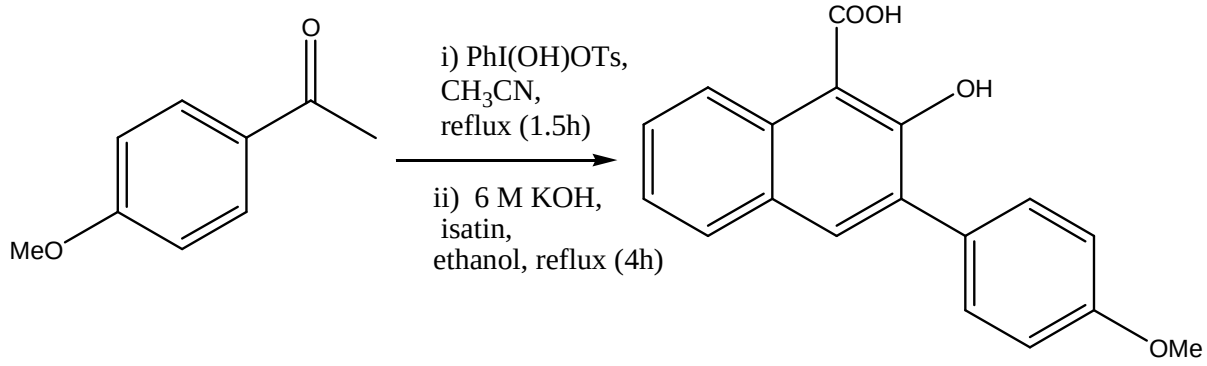
In addition to medicinal significance, quinoline derivatives are important components of optoelectronic materials and are valuable component in preparation of nano and meso structures with enhanced electronic and photonic properties [9-11]. Principally, carboxylic acid part of 2-aryl-quinoline salicylic acid can be used for anchoring over TiO_2 in DSSCs [12] and the hydroxyl group can be used for putting alkyl chain to tune solubility of the material.

To get the multifunctional scaffold 2-aryl-quinoline salicylic acid usually Pfitzinger reaction is employed, where α-acetates are used in Pfitzinger reaction, which are often obtained in two steps from acetophenones. The acetophenones are initially converted to toxic, lachrymatory α-halo acetophenones which are somewhat difficult to prepare and purify then followed by displacement of halo group by acetate, these many steps ultimately results in low overall yields of 2-aryl-quinoline salicylic acid [1-2, 13-14] and the method [15] developed in our laboratory. According to which mixture of acetophenone (1.0 mmol) and Kosser's reagent [hydroxy(tosyloxy)iodo]benzene (HTIB) (1.1 mmol) was refluxed in 5 mL of CH_3CN for 1.5 h with TLC monitoring of the reaction. After the complete consumption of acetophenone and successful formation of α-tosyloxyacetophenone, 5 mL of ethanol is added to the reaction mixture and further without purification this reaction mixture is directly added by syringe in small portions over the course of 1 h to 50-mL two-necked round-bottomed flask fitted with a reflux condenser, in which isatin (1.0 mmol) in 2 mL of 6 M aqueous KOH was heated to 100° C. After the addition had been completed, the reaction mixture was refluxed for an additional 4 h. It was then cooled to room temperature and was diluted with 5 mL of water, treated with charcoal, and filtered, and the clear solution was slightly acidified to pH 6.5 with 1M aqueous HCl. The precipitate was collected by filtration, washed with water, and dried under vacuum. Trituration with boiling 3 mL of ethanol gave a yellow product [15].



Scheme 1

Kosser's reagent is commonly used for inducing α-toxyloxylation of enolisable ketones [16-20]. These α-tosyloxyketones need not be isolated or purified after its formation and which had been used as strategic components for the synthesis of wide range of heterocyclic compounds such as thiazoles, selenazoles, oxazoles, imidazoles, pyrazoles, benzofurans and 3-carbomethoxy-4-arylfuran-2-(-5H)-ones [21-28]. For the synthesis of 2-phenyl-quinoline salicylic acid approach [15] avoids hazardous α-halo acetophenone and reduces number of steps but it was anticipated that this method can be made more simple, rather than adding requisite α–tosyloxyacetophenone to round bottom flask in which isatin was preheated in aqueous KOH to 100 °C, aqueous KOH and isatin was added to round bottom flask in which requisite α–tosyloxyacetophenone was synthesised. This avoids separate preparation of requisite α–tosyloxyacetophenone and hydrolysis of amide linkage in isatin. Therefore, to carry out synthesis of 2-(4-methoxy-phenyl)-quinoline salicylic acid the method [15] was modified. Modified method can possibly be extended in general for the synthesis of variety of 2-aryl-quinoline salicylic acids (Scheme **2**).



Scheme 2

EXPERIMENTAL SECTION

To carry out synthesis of 2-(4-methoxy-phenyl)-quinoline salicylic acid (3), requisite α-tosyloxyacetophenone (1a) was prepared in *situ* by refluxing 4-methoxy acetophenone (1.0 mmol) (scheme 1) with HTIB (1.1 mmol) in 5 mL of acetonitrile for 1.5 h with TLC monitoring of the reaction and then to synthesize the 2-(4-methoxy-phenyl)-quinoline salicylic acid, sequentially 2 mL of 6 M KOH, isatin (1.0 mmol) and 5 mL of ethanol was added directly to in *situ* prepared α-tosyloxyacetophenone. The reaction mixture was refluxed for further 4 h. The reaction mixture was then cooled to room temperature and was diluted with 5 mL of water, treated with charcoal, and filtered, and the clear solution was slightly acidified to pH 6.5 with 1M aqueous HCl. The precipitate was collected by filtration,

washed with water, and dried under vacuum. Trituration with 5 mL of boiling ethanol gave a yellow powder. The reactions involved in the complete synthesis of the 2-(4-methoxy-phenyl)-quinoline salicylic acid along with the reagents used are shown in the Scheme 2.

RESULT AND DISCUSSION

Synthesis of the 2-(4-methoxy-phenyl)-quinoline salicylic acid is carried out and the yield obtained is 70%.

^{1}H NMR (DMSO-*d*6): δ 3.83-3.87 (s, 3H), 6.5-6.58 (s, 1H), 6.94-7.02 (d, 2H), 7.30-7.42 (m, 2H), 7.82-7.86 (d, 1H), 8.18-8.26 (d, 2H), 9.32-9.38 (d, 1H).

MS: (ES+) 296.

CONCLUSION

A procedure for the synthesis of 2-(4-methoxy-phenyl)-quinoline salicylic acid has been developed by the α-tosyloxylation of acetophenone with [hydroxy(tosyloxy)iodo] benzene, followed by treatment with KOH and isatin.

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