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Graphical Abstract

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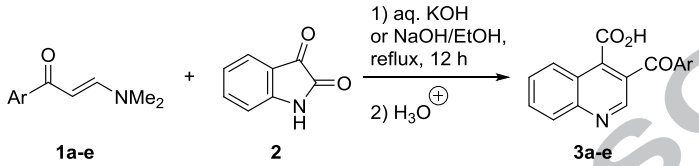

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A simple one-pot synthesis of quinoline-4-carboxylic acids by the Pfitzinger reaction of isatin with enaminones in water

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ABSTRACT

A simple one-pot method for synthesizing quinoline-4-carboxylic acids (**3**) by the reaction of enaminones (**1**) and isatin (**2**) using the Pfitzinger reaction conditions is described. Additionally, a plausible mechanism for this transformation is presented.

Introduction

The quinoline ring system has attracted considerable interest due to its important applications in various fields. Substituted quinolones have industrial applications that include their use as corrosion inhibitors,[1] precursors of oil-soluble food colorants and as chemosensors in luminescence chemistry.[2] Quinolines also have diverse biological and pharmacological activities such as, antibacterial,[3] antitumor,[4] antileishmanial,[5] antifungal,[6] and antiamoebic[7] and chloroquinolines are widely used for the treatment of malaria.[8] Furthermore, quinoline-4-carboxamides have been used as a pharmacophoric model with selective affinity towards non-peptide human neurokinin-3 (hNK-3) receptors which are implicated in a wide range of pathophysiological conditions such as inflammatory and immunoregulatory processes, skin disorders and various CNS disorders.[9] Recently, quinoline-4-carboxylic acid derivatives have also shown caspase-3 enzymes inhibition[10] which belongs to a family of cysteine-dependent aspartate-directed proteases enzymes that play important roles in apoptotic cell death.[11]

The most common method for the synthesis of quinoline-4-carboxylic acids is the Pfitzinger reaction which involve the reaction of isatin or its derivatives with α-methylene ketones in the presence of potassium hydroxide to yield quinolone-4-carboxylic acids.[12,13] However, when utilizing simple 1,3-dicarbonyls, the corresponding quinoline-4-carboxylic acids were obtained in low yield due to the formation of large amounts of undesired by-products.[14] Furthermore, the desired quinolone-4-carboxylic acids have been obtained *via* a two-step protocol from the *in situ* formation of the isatinate, as the basic hydrolysis ~~product o~~f isatin, followed by the addition of a 1,3-diketone in acidic medium.[15] To overcome these limitations, herein, we report a one-step synthesis of these compounds by a simple one-pot reaction of isatin and enaminones in the presence of aqueous KOH or NaOH.

Results and Discussion

Isatins can react with α-methylene ketones or 1,3-dicarbonyl compounds in different ways depending on the catalysts and solvents used in the reaction. Generally, two main protocols have been reported in the literature for this reaction. Firstly, an aldol-type reaction gives 3-hydroxyindole adducts as the main products from the reaction of isatins with α-methylene ketones or 1,3-dicarbonyls when moderate to weak bases (DABCO, TEA, DBU, proline, piperidine, imidazole, or DMAP) were used in organic solvents.[16] Secondly, the Pfitzinger-type reaction gives the quionoline-4-carboxylic acid derivatives when the reaction takes place in strong base (KOH) followed by acidification with HCl.[12,13] As previously reported, the latter protocol has limitations when simple 1,3-dicarbonyls were reacted with isatins under Pfitzinger conditions. Therefore, to overcome these limitations and as a continuation of our interest in the chemistry of enaminones and their utility as synthons for the synthesis of biologically active and industrially important compounds,[17] herein, we report the utility of enaminone building blocks for the synthesis of quinoline-4-carboxylic acids.

The reactivity and regioselectivity of enaminones can be attributed to their ability to function both as nucleophiles or electrophiles depending on the reaction conditions.[18] Thus, we expected that enaminones (**1**) could act as a suitable substitute for 1,3-dicarbonyls in the Pfitzinger reaction. Therefore, isatin (**2**)

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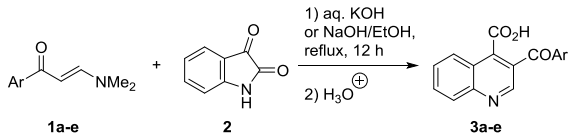
was heated at reflux with enaminones (**1a-e**) in the presence of an aqueous solution of KOH or NaOH, followed by subsequent acidification with dilute hydrochloric acid to give the quinoline-4-carboxylic acids (**3a-e**) in good to excellent yields (75-90% Table 1).

Table 1 Synthesis of quinoline-4-carboxylic acids **(3a-e)**



Entry	Substrate	Ar	Product [a]	Yield[b] % (m.p. °C)[c]
1	**1a**	Ph	**3a**	90 (220)[d]
2	**1b**	4-MeC_6H_4	**3b**	75 (222)
3	**1c**	4-MeOC_6H_4	**3c**	86 (204)
4	**1d**	4-BrC_6H_4	**3d**	90 (253)
5	**1e**	4-ClC_6H_4	**3e**	80 (243)

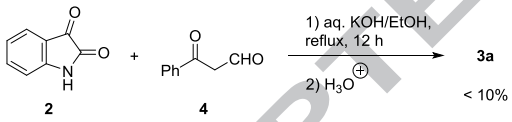
[a] All new compounds gave elemental analysis for C, H, N, within 0.2% of the calculated value and the structures were confirmed by IR, MS, and ^{1}HNMR, ^{13}CNMR spectroscopy .

[b] Yield of the crude product.

[c] All products were crystallized from ethanol no further purification was required.

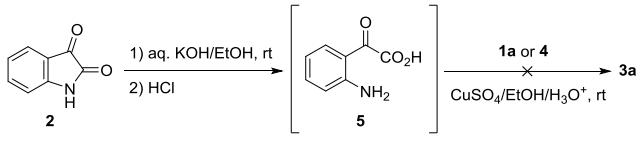
[d] Decomposes >220 °C.[20]

In order to evaluate this synthetic approach, the corresponding 1,3-dicarbonyl (**4**) was prepared[20] and reacted with isatin under the same reaction conditions. As expected the quinoline-4-carboxylic acid (**3a**) was obtained in very poor yield (<10% Scheme 1).



Scheme 1. Reaction of isatin (**2**) with 1,3-dicarbonyl (**4**)

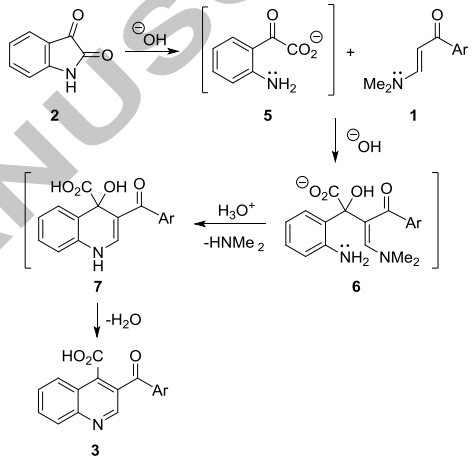
Furthermore, the recently reported two-step synthetic route[15] involving preparation of isatinate (**5**), as a basic hydrolysis product of isatin followed by acidification with dilute HCl, then addition of 1,3-dicarbonyl (**4**) or enaminone (**1a**) with $CuSO_4$•$5H_2O$ as a Lewis acid was examined (Scheme 2). The desired quinoline-4- carboxylic acid (**3a**) was not detected using either the 1,3-dicarbonyl (**4**) or enaminone (**1a**) after a period of 10 hours (TLC).



Scheme 2. Two-step, one pot reaction of isatin (**2**) with enaminone (**1a**) and 1,3-dicarbonyl (**4**) under acidic conditions

The chemical structures of quinoline-4-carboxylic acids (**3a-e**) were determined by spectroscopy (^{1}HNMR, ^{13}CNMR, MS, and IR). Thus, the ^{1}HNMR spectra of compounds **3a-e** revealed a singlet in the range of 8.42-8.50 ppm which was attributed to the C-2 proton in the quinoline ring. A broad singlet for the more deshielded proton at ~14.0 ppm which was assigned to the carboxylic acid group was also observed. The ^{13}CNMR spectra revealed three down-field carbons in the ranges of 167.4-167.6 ppm, and 154.5-160.9 ppm and at 148 ppm which were assigned to the carbonyl carbons of the carboxylic acid and ketone groups and the C-2 position of the quinoline ring respectively. Furthermore, mass spectra of the quinoline 4-carboxylic acids (**3a-e**) revealed a characteristic fragment at *m/z* = 204 accounting for loss of the aryl side chain at position three of the quinoline ring.[21]

There are surprisingly few details reported for the mechanism of the Pfitzinger reaction. Primarily, two types of reactions are involved: Claisen condensation of the ketone group of isatinic acid with the active methylene of the 1,3-dicarbonyl and Schiff base formation between the amine group of isatinic acid and the ketone carbonyl .[13] In the present study a plausible mechanism was suggested as depicted in Scheme 3.



Scheme 3 Proposed mechanism for the formation of quinoline-4-carboxylic acids (**3a-e**)

Thus, the reaction starts with hydrolysis of the five-membered ring of isatin to give isatinate (**5**). Then, aldol-type nucleophilic addition of the electron rich enaminone carbon (C-2) to the ketone carbon of the isatinate (**5**) gives adduct **6**. Under acidic conditions, this intermediate undergoes cyclization *via* dimethylamine elimination to give intermediate **7** which further rearranges and aromatized by dehydration to give the final quinoline-4-carboxylic acids (**3a-e**).

In conclusion, we report a new method for the synthesis of quinoline-4-carboxylic acids using enaminones as a substitute for 1,3-dicarbonyl compounds in the Pfitzinger reaction. The high yield coupled with the purity of the products makes this method favorable over the previously reported methods for the synthesis of such ring systems.

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Supplementary data
Supplementary data (^{1}HNMR, ^{13}CNMR, IR, and MS spectra) and experimental information associated with this article can be found in the online version at

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