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ORIGINAL PAPER

# A simple one-pot synthesis of quinoline-4-carboxylic acid derivatives by Pfitzinger reaction of isatin with ketones in water

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**Abstract** An improved Pfitzinger condensation reaction performed under acidic conditions is established. It provides a simple and efficient synthetic method for some useful quinoline-4-carboxylic acid derivatives using isatins and ketones that cannot be obtained easily under ordinary conditions. The generality of this methodology and the catalysts used for this protocol are explored in this paper. Structures of all the synthesized compounds are characterized by spectral data.

**Keywords** Pfitzinger reaction · Isatin · Ketone · Quinoline-4-carboxylic acid · Quinoline

## Introduction

The Pfitzinger reaction of isatins with α-methylidene carbonyl compounds is used widely for the synthesis of physiologically active derivatives of substituted quinoline-4-carboxylic acids [1–6]. This condensation reaction is commonly performed under basic conditions, and subsequently acidified to obtain the various quinoline-4-carboxylic acid derivatives after filtering or extraction and recrystallization (Scheme 1).

However, for some simple diketones such as 1,3-cyclohexandione, some studies found it impossible to obtain the corresponding pure quinolinecarboxylic acids in aqueous KOH/ethanol (the usual conditions for Pfitzinger reaction) due to large amounts of resin-like reaction by-products [7]. To overcome the limitation, we explored the Pfitzinger reaction and established an improved protocol during our investigation of synthetic methodologies [8, 9]. Herein, we report a simple one-pot synthesis of quinoline-4-carboxylic acid derivatives by an improved Pfitzinger reaction of isatins with various ketones and catalysts in aqueous medium.

## Results and discussion

We explored the Pfitzinger reaction of isatin (**1**) with 1,3-cyclohexandione (**5**) and KOH in water/ethanol according to the literature [7]. As a result, we obtained little 1,2,3,4-tetrahydro-1-oxoacridine-9-carboxylic acid (**7**) but a large amount of a resin-like reaction by-product. The reasons why this type of compound could not be synthesized using this system were discussed briefly in previous studies [10, 11]. It might be due to the decomposition of diketones with formation of resinous by-products under the usual reaction conditions. In seeking an alternative route to these systems, we first hydrolyzed isatin (**1**) in aqueous potassium hydroxide and subsequently adjusted the pH with caution to give the keto-acid **4**, then added 1,3-cyclohexandione (**5**) to the flask to react immediately without any separation (Scheme 2). Fortunately, the desired white 1,2,3,4-tetrahydro-1-oxoacridine-9-carboxylic acid was formed, and precipitated rapidly from water. Unlike the usual conditions, in our improved protocol under acidic conditions, not the keto-acid salt but the keto-acid **4** was obtained in the condensation reaction with 1,3-diketone **5** to give **7**.

Optimization of this method resulted in an improvement of the isolated yield of **7** to 87 % by using 2.0 equiv. of

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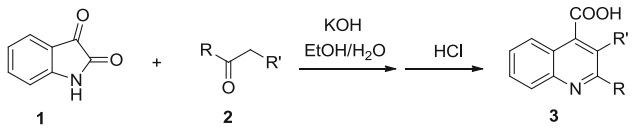
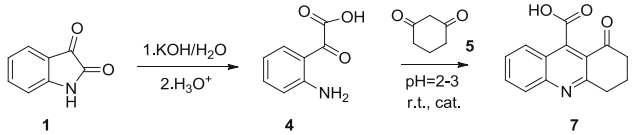



**Scheme 1**




**Scheme 2**

1, 3-cyclohexandione at room temperature and keeping the pH at 2–3 with hydrochloric acid until product **7** precipitated from water completely. To achieve convincing results, we repeated the experiments on the scale from 150 mg to 1.5 g with isatin and obtained the target production successfully in similar yields.

The effect of a Brønsted acid such as *p*-TsOH·$H_2O$ on the yield of product **7** was examined. This catalyst proved helpful for the reaction and obviously shortened the reaction time. Other Lewis acid catalysts used in the same protocol were also investigated as shown in Table 1.

Both *p*-TsOH·$H_2O$ and the Lewis acids showed an excellent catalytic effect in our protocol. Among them, copper sulfate appeared to be the best (Table 1, entry 4). We deduced that these catalysts might benefit the condensation reactions of keto-acids with ketones [12]. The detailed mechanisms of the Pfitzinger reaction are still not completely understood to date: two different reaction paths involving Schiff base formation and Claisen condensation, respectively, have been postulated [2]. In terms of our experimental results, we lean towards the Claisen condensation path as shown in Scheme 3 because the intermediate from Claisen condensation was obtained when we investigated the generality of this procedure.

**Table 1** Reaction time and yields for synthesis of **7** with different catalysts

| Entry | Catalyst | Time/min | Yield/% |
|---|---|---|---|
| 1 | None | 90 | 74 |
| 2 | *p*-TsOH | 54 | 87 |
| 3 | CAN | 52 | 83 |
| 4 | $CuSO_4·5H_2O$ | 22 | 87 |
| 5 | $ZnCl_2$ | 26 | 82 |
| 6 | $FeCl_3$ | 37 | 81 |
| 7 | $MnSO_4·H_2O$ | 55 | 78 |
| 8 | $AlCl_3$ | 35 | 82 |
| 9 | $CeCl_2·7H_2O$ | 30 | 77 |

The generality of this procedure was also explored as shown in Table 2. The same protocol used to prepare 1,2,3,4-tetrahydro-1-oxoacridine-9-carboxylic acid from 1,3-cyclohexandione could be applied to other similar quinoline-4-carboxylic acid systems. The highest yield of 95 % was achieved with pentane-2,4-dione (Table 2, entry b), and the lowest (12 %) with methyl ethyl ketone (Table 2, entry c). The experimental results indicated that the improved protocol was more suited to simple 1,3-diketones, *β*-keto esters and some cyclic ketones than to alkyl ketones. In addition, for 5,5-dimethylcyclohexane-1,3-dione, the main product was the condensation intermediate 3-hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl) indolin-2-one, which could be further converted into 1,2,3,4-tetrahydro-3,3-dimethyl-1-oxo-9-acridinecarboxylic acid by heating (Table 2, entry f) [16]. For 1,3-indanedione, the final product was 2,2′-(2-oxoindoline-3,3-diyl)bis(1*H*-indene-1,3(2*H*)-dione) (Table 2, entry g).

In conclusion, we have demonstrated a straightforward and highly cost-effective synthetic method for some useful quinoline-4-carboxylic acid derivatives using simple ketones and isatins, which cannot be obtained easily under the ordinary conditions. The current method is a meaningful supplement to classic Pfitzinger reactions.

## Experimental

Melting points were measured on a WRS-1B digital melting point apparatus. The progress of the reaction was monitored by TLC. Infrared spectra were recorded from KBr pellets on an FT/IR-430 spectrophotometer. $^1$H NMR spectra were determined on a Bruker AVANCE 400 NMR spectrometer at 400 MHz in DMSO-$d_6$ using TMS as internal standard. Elemental analysis was estimated on an Elementar Vario EL-III element analyzer. Mass spectra were determined using a MSD VL ESI1 spectrometer.

### *General procedure for the synthesis of quinolinecarboxylic acids*

A mixture of 147 mg isatin (**1**, 1 mmol) and 250 mg potassium hydroxide in 5 $cm^3$ water was stirred at room temperature for 15–30 min (Table 1). The mixture was then acidified to pH 2–3 with 0.38 $cm^3$ concentrated hydrochloric acid, and 224 mg 1,3-cyclohexandione (**5**, 2 mmol) and 25 mg $CuSO_4·5H_2O$ (0.1 mmol) were added. The resulting mixture was stirred and a precipitate appeared. The reaction progress was monitored by TLC ($R_f = 0.35$; $CHCl_3$/MeOH 19:3). After the starting material had vanished, the precipitate was filtered, washed with water, and recrystallized to afford the pure product 1,2,3,4-tetrahydro-1-oxoacridine-9-carboxylic acid (**7**, 210 mg,

**Scheme 3**

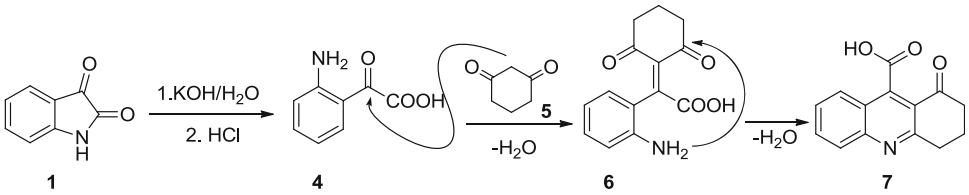
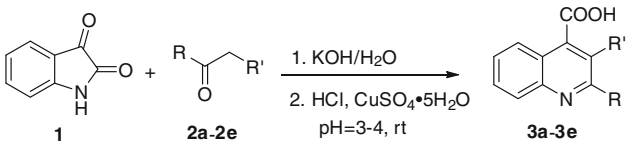
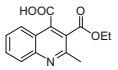
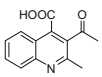
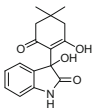
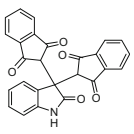



**Table 2** Preparation of quinolines with isatin and various ketones




| Entry | Ketones **2** | Products **3** | Isolated yield/% |
|---|---|---|---|
| a |  |  | 55[a] |
| b |  |  | 95 |
| c |  |  | 12[b] |
| d |  |  | 42 |
| e |  |  | 40 |
| f |  |  | 74[b] |
| g |  |  | 78[b] |

Reaction conditions as exemplified in the typical experimental procedure

[a] The reaction was carried out in EtOH-$H_2O$

[b] The products were characterized by comparison of their spectral and physical data with those of authentic samples in the literature [13–15]

87 %). A scaled-up experiment was performed by the same procedure with 1.47 g isatin (10 mmol) and the yield of **7** was 2.05 g (85 %). Other compounds were all prepared on a scale of 10 mmol isatin and 2.0 equivalents of the corresponding ketones.

*1,2,3,4-Tetrahydro-1-oxoacridine-9-carboxylic acid* (**7**, $C_{14}H_{11}NO_3$)

White powder; $R_f = 0.35$ ($CHCl_3$/MeOH 19:3); m.p.: 279–280 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 13.98$ (s, 1H), 8.05 (d, 1H), 7.92 (t, $J = 7.7$ Hz, 1H), 7.84 (d, 1H), 7.70 (t, $J = 7.2$ Hz, 1H), 3.29-3.21 (m, 3H), 2.79 (t, $J = 6.4$ Hz, 2H), 2.24-2.11 (m, 2H) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 196.8$ (C), 168.5 (C), 162.3 (C), 148.6 (C), 142.3 (C), 132.7 (CH), 128.6 (CH), 127.7 (CH), 126.2 (CH), 122.2(C), 120.4 (CH), 38.6 ($CH_2$), 33.1 ($CH_2$), 20.9 ($CH_2$) ppm.

*3-(Ethoxycarbonyl)-2-methylquinoline-4-carboxylic acid* (**3a**, $C_{14}H_{13}NO_4$)

White powder; $R_f = 0.39$ ($CHCl_3$/MeOH 19:3); m.p.: 187–188 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 14.32$ (s, 1H), 8.05 (m, $J = 8.5$ Hz, 2H), 7.88 (t, $J = 7.5$ Hz, 1H), 7.70 (t, 1H), 4.36 (q, $J = 7.1$ Hz, 2H), 2.74 (s, 3H), 1.33 (t, $J = 7.1$ Hz, 3H) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 167.8$ (C), 167.1 (C), 155.9 (C), 148.1 (C), 140.6 (C), 132.2 (CH), 129.4 (C), 128.4 (CH), 126.2 (CH), 124.0 (CH), 121.7 (C), 62.5 ($OCH_2$), 24.5 ($CH_3$), 14.2 ($CH_3$) ppm.

*3-Acetyl-2-methylquinoline-4-carboxylic acid* (**3b**, $C_{13}H_{11}NO_3$)

White powder; $R_f = 0.75$ ($CHCl_3$/MeOH 10:1); m.p.: 188–189 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta = 8.68$ (d, 1H), 8.22-8.09 (m, 2H), 7.93-7.85 (m, 1H), 7.78 (t, $J = 7.6$ Hz, 1H), 2.82 (s, 3H), 1.92 (s, 3H) ppm; $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 208.7$ (C), 167.2 (C), 154.1 (C), 148.2 (C), 142.8 (C), 130.8 (CH), 128.8 (CH), 128.6 (C), 122.9 (C), 120.9 (CH), 106.7 (CH), 24.6 ($CH_3$), 21.7 ($CH_3$) ppm.

*1, 2, 3, 4-tetrahydroacridine-9-carboxylic acid* (**3d**)

White powder; $R_f = 0.36$ ($CHCl_3$/MeOH 19:3); m.p.: 284–285 °C (Reference [17] 285–286 °C).

*2, 3-dihydro-1H-cyclopenta[b]quinoline-9-carboxylic acid* (**3e**)

Pale yellow powder; $R_f = 0.34$ ($CHCl_3$/MeOH 19:3); m.p.: 304–305 °C (Reference [18] >300 °C).

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