HETEROCYCLES, Vol. 85, No. 6, 2012, pp. 1457 - 1463. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 4th April, 2012, Accepted, 24th April, 2012, Published online, 2nd May, 2012
DOI: 10.3987/COM-12-12479

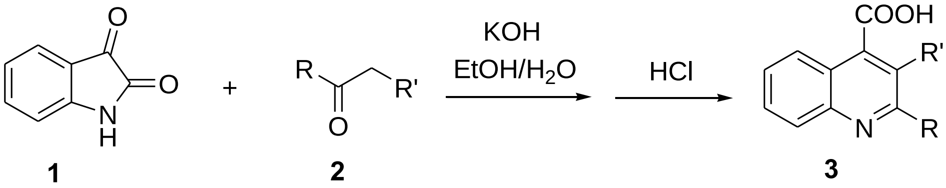
IMPROVED SYNTHESIS OF 1-OXO-1,2,3,4-TETRAHYDROACRIDINE-9-CARBOXYLIC ACIDS FROM ISATINS AND 1,3-CYCLOHEXANEDIONE

Qinghua Lv,[1] Lizhen Fang,[1]* Chenjuan Lu,[1] and Pengfei Wang[1]

[1]College of Pharmacy, Xinxiang Medical University, Henan, 453003, P. R. China
E-mail: 2002flz@163.com

Abstract – An improved protocol for the preparation of 1-oxo-1,2,3,4-tetrahydroacridine-9-carboxylic acid derivatives *via* Pfitzinger condensation under acidic conditions is described, it provides a simple one-pot synthetic method for some useful 1-oxo-1,2,3,4-tetrahydroacridine-9-carboxylic acids which could not be synthesized successfully by Pfitzinger reactions under usual conditions using the corresponding isatins and 1,3-diketones. All the synthesized compounds are characterized by spectral data.

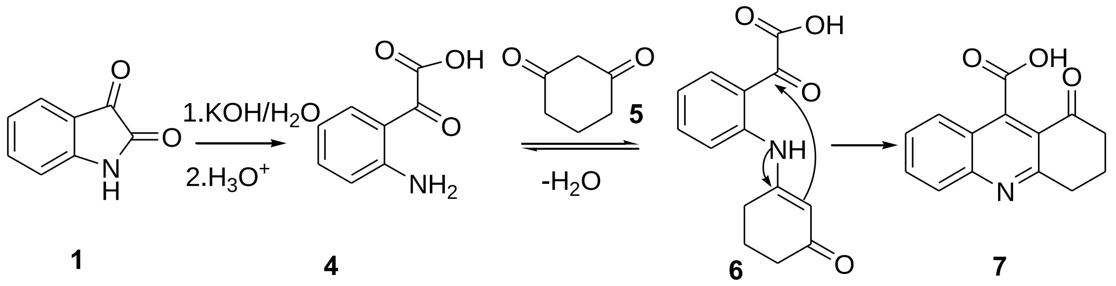
The Pfitzinger reaction[1] of isatins with α-methylene carbonyl compounds is widely used for the synthesis of physiologically active derivatives of substituted quinoline-4-carboxylic acids.[2] This condensation reaction is commonly performed by boiling isatins with ketones (or aldehydes) and KOH in water/ethanol and subsequent adjustment of pH then filtering or extraction and recrystallization to obtain the various quinoline-4-carboxylic acid derivatives (**Scheme 1**).



Scheme 1

However, as some studies[3] showed that it was impossible to obtain the corresponding pure 1-oxo-1,2,3,4-tetrahydroacridine-9-carboxylic acids by the reaction of isatins with some diketones such as 1,3-cyclohexandione in aqueous KOH (the usual conditions for Pfitzinger reaction) because of the large amounts of resin-like reaction byproducts. Though many years ago two similar derivatives were prepared under solvent free condition,[4] the results were not satisfactory for the harsh reaction conditions and modest yields. Moreover, for the preparation of quinolinecarboxylic acids by Pfitzinger reaction using isatin and the cyclic diketones, most of the previous methods are waste of reagents due to the large excess of cyclic ketones added in order to raise the yields of the target productions.[5] Therefore, a simple, convenient and efficient method for preparation of these important heterocyclic compounds is still in demand. Herein, we would like to report the simple one-pot synthesis of 1-oxo-1,2,3,4-tetrahydroacridine-9-carboxylic acid derivatives *via* the Pfitzinger reaction which the condensation is performed under acidic conditions in aqueous media.

Interested in synthetic methodology of organic compounds and their bioactivities,[6] we explored the Pfitzinger reaction using isatin **1** and 1,3-cyclohexandione **5** under the usual condition for synthesis of 1-oxo-1,2,3,4-tetrahydroacridine-9-carboxylic acid **7**, and obtained little of target material but a large amount of resin-like reaction byproduct. The reasons why such type of compounds could not be synthesized by this system were discussed in the related literatures.[3] Thinking of the condensation reaction may proceed under the acidic conditions too, we decided to modify the usual procedures to avoid the decomposition of 1,3-cyclohexandione **5** and some other analogous cyclic diketone substrates with the formation of resinous by-product under basic conditions. In our improved procedure, we hydrolyzed isatin **1** in aqueous potassium hydroxide and subsequently adjusted pH with caution to give the keto-acid **4** (**Scheme 2**), then added the 1,3-cyclohexandione **5** into the flask to react immediately without any separation. Fortunately, the consequent condensation reaction went soomthly and the desired white 1-oxo-1,2,3,4-tetrahydroacridine-9-carboxylic acid **7** formed and precipitated from water soon. Unlike the usual Pfitzinger reaction, not the keto-acid salt but the intermediate keto-acid **4** was obtained to for condensation reaction with the 1,3-diketone **5** under the acid condition to give **6** in our improved protocol. The alteration may seem to trivial but it provided the different and more stable reactants and conditions for condensation, and was indeed the key to prepare the 1-oxo-1,2,3,4-tetrahydroacridine-9-carboxylic acid **7** successfully. The mechanism of this condensation may by way of enamine **6** as the proposed mechanism in the Friedlander synthesis,[7] as shown in **Scheme 2**.



Scheme 2

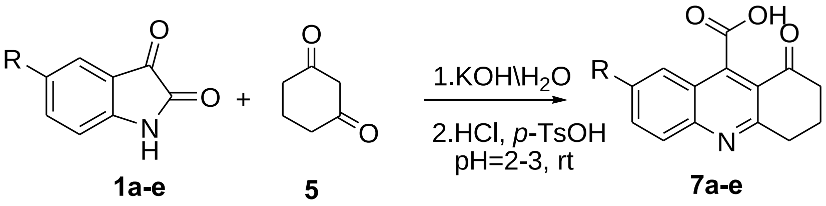
Optimization studies were then carried out for this typical procedure and resulted in an improvement of the isolated yield of 1-oxo-1,2,3,4-tetrahydroacridine-9-carboxylic acid **7** to 87% by using 2.0 equivalent 1,3-cyclohexandione and *p*-TsOH·H_2O as the catalyst at room temperature (**Table 1**, entry 11). It was of no significant effect by further increasing the amount of 1,3-cyclohexandione **5** on the product yield (**Table 1**, entry 9). It should be noted that the formation of the intermediate keto-acid **4** was essential for this method by addition of hydrochloric acid and the target product formed in best yield when the pH always kept at 2-3 with hydrochloric acid till the product **7** precipitated from water completely. At higher pH(≥5) the product **7** formed in low yield less than 10% and could not precipitate from water (**Table 1**, entries 1, 2, 3). At lower pH (≤2) the yield of **7** was modest in 2% (**Table 1**, entry 7) and most of the remained reactant was determined to be the isatin which converted from the keto-acid **4** by excessive acidification. The Brønsted acid such as *p*-TsOH·H_2O showed to be helpful for the reaction and obviously shorten the reaction time (**Table 1**, entries 10 and 11), and we deduced it may benefit the condensation reaction of the keto-acid with the diketone by accelerating the generation of enamine intermediate **6**, and it was very commonly used as the catalyst in such type of condensations.[8] Other catalysts used in the same protocol and the detailed mechanism will be investigated in the future.

Table 1. The reaction conditions and yields for the synthesis of **7** with different pH values

Entry	pH	Catalyst	Ratio (1,3-diketone **5**: isatin **1**)	Time (h)	Isolated Yield(%)
1	≥7	no	1.0	24	3-5
2	6-7	no	1.0	24	7-9
3	5-6	no	1.0	24	10
4	4-5	no	1.0	24	25
5	3-4	no	1.0	18	44
6	2-3	no	1.0	18	55
7	1-2	no	1.0	14	2
8	2-3	no	2.0	14	84
9	2-3	no	4.0	10	82
10	2-3	p-TsOH	1.0	6	60
11	2-3	p-TsOH	2.0	5	87

The generality of this procedure was also explored (**Table 2**). The same protocol used to prepare **7** could also be applied to other similar 1-oxo-1,2,3,4-tetrahydroacridine-9-carboxylic acid systems from the corresponding alkyl or halogen-substituted acid salts and 1,3-cyclohexandione. The highest yield was achieved with 5-methylindoline-2,3-dione (**Table 2**, entry 1), and the lowest, with 5-bromoindoline-2,3-dione (**Table 2**, entry 4). Although the yields were not very high, the corresponding tetrahydroacridine-9-carboxylic acid can be conveniently prepared by this method with isatins except the 5-nitro isatin. It is noted that 5-nitro isatin acid is not soluble and precipitated soon from water, the subsequent reaction can not follow up.

Table 2. Preparation of quinolines with isatin and various ketones[a]



Entry	**1**	**7** (Yield/ %)[b]
1	**1a** (R=Me)	**7a** (63)
2	**1b** (R=F)	**7b** (51)
3	**1c** (R=Cl)	**7c** (40)
4	**1d** (R=Br)	**7d** (36)
5	**1e** (R=NO_2)	/

Note: [a] Reaction conditions as exemplified in the typical experimental procedure; [b] Isolated yields.

In conclusion, we have demonstrated that a straightforward and highly cost-effective synthesis of biologically active tetrahydroacridine-9-carboxylic acid can be achieved by *p*-TsOH-catalyzed Pfitzinger reaction in water. 1-oxo-1,2,3,4-tetrahydroacridine-9-carboxylic acid **7**, **7a-d** were synthesized for the first time by this improved protocol. The current method presents a very appealing synthetic process for tetrahydroacridine-9-carboxylic acids because of the following advantages: (1) use of water as environmentally benign reaction media, (2) use of very cheap and readily available materials, (3) short reaction time and easy work-up procedure.

EXPERIMENTAL

The melting points were measured on WRS-1B digital melting points apparatus and are uncorrected. The progress of the reaction was monitored by TLC. ^{1}H NMR spectra were determined on a Brucker AVANCE 400 NMR spectrometer at 400 MHz in DMSO-d_6 using TMS as internal standard. Elemental analysis were estimated on an Elementar Vario EL-III element analyzer.

General procedure for the synthesis of 1-oxo-1,2,3,4-tetrahydroacridine-9-carboxylic acids: The mixture of isatin (147 mg, 1 mmol) and potassium hydroxide (250 mg) in water (5 mL) was stirred at room temperature for 5-30 min (**Table 1**). Then the mixture was acidified with concentrated hydrochloric acid to pH 2-3 and added 1,3-cyclohexandione(224 mg, 2 mmol), *p*-TsOH·H_2O (17 mg, 0.1 mmol). The resulting mixture was stirred and the precipitate appeared. The reaction progress was monitored by TLC (silica gel; $CHCl_3$/MeOH, 19:3, v/v). After the starting material had vanished, the precipitate was filtered out, washed with water, and recrystalized to afford the pure product 1-oxo-1,2,3,4-tetrahydroacridine-9-carboxylic acid (**7**, 210 mg, 87%).

1-Oxo-1,2,3,4-tetrahydroacridine-9-carboxylic acid (**7**): A white powder; mp 279-280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.11–2.24 (m, 2H), 2.79 (t, J = 6.4 Hz, 2H), 3.21–3.29 (t, J = 6.2 Hz, 2H), 7.70 (dd, J = 7.4, 7.2 Hz, 1H), 7.84 (d, J = 7.2 Hz, 1H), 7.92 (dd, J = 7.7, 7.4 Hz, 1H), 8.05 (d, J = 7.7 Hz, 1H), 13.98 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.9, 33.1, 38.6, 120.4, 122.2, 126.2, 127.7, 128.6, 132.7, 142.3, 148.6, 162.3, 168.5, 196.8. Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81; O, 19.90. Found: C, 69.69; H, 4.62; N, 5.81; O, 19.88.

7-Methyl-1-oxo-1,2,3,4-tetrahydroacridine-9-carboxylic acid (7a, Table 2) A pale yellow powder; mp 293-294 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.11 – 2.22 (m, 2H), 2.52 (s, 3H), 2.76 (t, J = 6.0 Hz, 2H), 3.24 (t, J = 6.0 Hz, 2H), 7.57 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 13.79 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.0, 21.2, 33.0, 38.7, 120.3, 122.2, 124.6, 128.4, 134.9, 137.3, 141.6, 147.4, 161.4, 168.6, 196.9. Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49; O, 18.80. Found: C, 70.57; H, 5.15; N, 5.50; O, 18.79.

7-Fluoro-1-oxo-1,2,3,4-tetrahydroacridine-9-carboxylic acid (7b, Table 2) A pale yellow powder; mp 286-287 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.12 – 2.22 (m, 2H), 2.80 (t, J = 6.0 Hz, 2H), 3.26 (t, J = 5.6Hz, 2H), 7.46 (ddd, J = 8.0, 7.9, 2.0Hz, 1H), 7.87 (dd, J = 8.0, 2.0 Hz, 1H), 8.13 (dd, J = 7.9, 4.9Hz, 1H), 13.98 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.8, 32.9, 38.6, 109.2 (d, J = 23 Hz), 121.0, 122.8 (d, J = 26 Hz), 123.1 (d, J = 8 Hz), 131.7 (d, J = 9 Hz), 141.8 (d, J = 6 Hz), 145.9, 158.8 (d, J = 246 Hz), 161.9, 168.2, 196.8. Anal. Calcd for $C_{14}H_{10}FNO_3$: C, 64.86; H, 3.89; F, 7.33; N, 5.40; O, 18.52. Found: C, 64.82; H, 3.89; F, 7.36; N, 5.39; O, 18.54.

7-Chloro-1-oxo-1,2,3,4-tetrahydroacridine-9-carboxylic acid (7c, Table 2) A yellow powder; mp 286-287 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.11-2.20 (m, 2H), 2.80 (t, J = 6.0 Hz, 2H), 3.26 (t, J =5.6 Hz, 2H), 7.76 (s, 1H), 7.95 (d, J = 8.8 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 14.06(s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.7, 33.0, 38.5, 121.1, 123.0, 124.4, 130.8, 131.9, 133.0, 141.6, 147.0, 163.0, 168.0, 196.6. Anal. Calcd for $C_{14}H_{10}ClNO_3$: C, 60.99; H, 3.66; Cl, 12.86; N, 5.08; O, 17.41. Found: C, 60.96; H, 3.68; Cl, 12.85; N, 5.13; O, 17.40.

7-Bromo-1-oxo-1,2,3,4-tetrahydroacridine-9-carboxylic acid (7d, Table 2) A white powder; mp 287-288 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.13 – 2.23 (m, 2H), 2.81 (t, J = 6.0 Hz, 2H), 3.26 (t, J = 6.0 Hz, 2H), 7.91 (s, 1H), 8.00 (d, J = 8.8 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 14.06 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.7, 33.0, 38.5, 120.5, 121.1, 123.5, 127.6, 130.9, 135.6, 141.2, 147.2, 163.1, 168.0, 196.6. Anal. Calcd for $C_{14}H_{10}BrNO_3$: C, 52.52; H, 3.15; Br, 24.96; N, 4.38; O, 14.99. Found: C, 52.52; H, 3.17; Br, 24.95; N, 4.39; O, 14.97.

ACKNOWLEDGEMENTS

This project was supported by the National Natural Science Foundation of China (81172952), the Natural Science Program of the Education Department of Henan Province (2010B32007) and the fund of key disciplines in Xinxiang Medical University (ZD200969).

REFERENCES (AND NOTES)

1. W. Pfitzinger, *J. Prakt. Chem.*, 1886, **33**, 100; M. G. A. Shvekhgeimer, *Chem. Heterocycl. Compd.*, 2004, **40**, 257.
2. G. Eastland, J. Prous, and J. Castacer, *Drugs Future*, 1988, **13**, 13; L. Dejmek, *Drugs Future*, 1990, **15**, 126; G. A. M Giardina, L. F. Raveglia, M. Grugni, H. M. Sarau, C. Farina, A. D. Medhurst, D. Graziani, D. B. Schmidt, R. Rigolio, M. Luttmann, S. Cavagnera, J. J. Foley, V. Vecchietti, and D. W. P. Hay, *J. Med. Chem.*, 1999, **42**, 1053; L. W. Deady, J. Desneves, A. J. Kaye, G. J. Finlay, B. C. Baguley, and W. A. Denny, *Bioorg. Med. Chem.*, 2000, **8**, 977.
3. A. V. Ivachtchenko, V. V. Kobak, A. P. Il'yin, A. S. Trifilenkov, and A. A. Busel, *J. Comb. Chem.*, 2003, **5**, 645.
4. G. Stefanović, M. Pavičić-Woss, L. Lorenc, and M. L. Mihailović, *Tetrahedron*, 1959, **6**, 97.
5. M. T. Shipchandler and P. G. Mattingly, *Heterocycles*, 1990, **31**, 555; E. S. H. E. Ashry, E. S. Ramadan, H. A. Hamid, and M. Hagar, *Synth. Commun.*, 2005, **35**, 2243.

6. L. Z. Fang and J. K. Liu, *Heterocycles*, 2009, **78**, 2107; L. Z. Fang, J. M. Shen, Q. H. Lv, and F. L. Yan, *Asian. J. Chem.*, 2010, **23**, 3425.
7. C. C. Cheng and S. J. Yan, in ‘*Organic Reactions*’, Vol. 28, ed. by W. G. Dauben *et al*., John Wiley & Sons, Inc., 1982, pp. 39–41.
8. S. Paul, M. Gupta, R. Guptaa, and A Loupy, *Tetrahedron Lett.*, 2001, **42**, 3827; X. M. Han, H. Q. Ma, and Y. L. Wang, *ARKIVOC*, 2007, **13**, 150.