JOC Notes

Skraup−Doebner−Von Miller Quinoline Synthesis Revisited: Reversal of the Regiochemistry for γ-Aryl-β,γ-unsaturated α-Ketoesters

Yan-Chao Wu,[†,‡] Li Liu,[†] Hui-Jing Li,[†,‡] Dong Wang,[†] and Yong-Jun Chen*,[†]

Center for Molecular Science, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, China, and Graduate School of Chinese Academy of Sciences, Beijing 100049, China

yjchen@iccas.ac.cn

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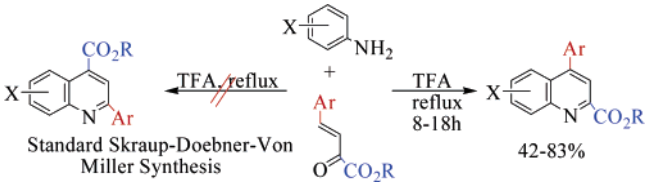
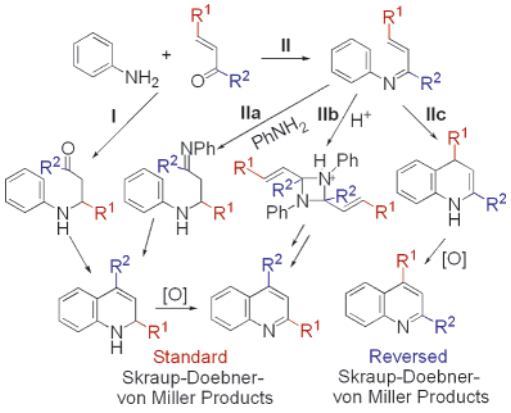


A reversal of the standard regiochemistry of the Skraup−Doebner−Von Miller quinoline synthesis was observed when anilines were condensed with γ-aryl-β,γ-unsaturated α-ketoesters in refluxing TFA. The reaction is proposed to involve 1,2-addition of the anilines to γ-aryl-β,γ-unsaturated α-ketoesters to form Schiff's base adducts, followed by cyclization and oxidation. The products were unambiguously shown to the 2-carboxy-4-arylquinolines by spectroscopy and X-ray crystallographic analysis.

The Skraup−Doebner−Von Miller quinoline synthesis, which generally refers to the reaction of α,β-unsaturated carbonyl compounds with anilines to give quinolines, has been of great value for constructing the quinoline system since its discovery one and a quarter centuries ago.[1] Many protocols for this reaction have been developed because of the importance of quinolines as pharmaceuticals, [2] ligands, and functional materials.[3] It is well documented that the Skraup−Doebner−Von Miller synthesis, which is often carried out using protic acids or Lewis acids, gives predominantly 2-substituted quinolines from the reaction of 3-substituted α,β-unsaturated carbonyl compounds.[1,4] One plausible explanation for this regioselectivity is that the reaction proceeds via 1,4-addition of anilines to α,β-unsaturated carbonyl compounds, followed by dehydrative ring closure and oxidation via route **I** (Scheme 1).[1e−g] In this case, an added oxidant[1a,b] (such as nitrobenzene) or a Schiff's base[1c] aromatizes the 1,2-dihydro intermediate to the final quinoline. Eisch and Dluzniewski studied the mechanism of the Skraup−Doebner−Von Miller quinoline synthesis and proposed that direct Schiff's base formation might be the critical step in the reaction mechanism,[5] as suggested by Skraup himself [6] (route **II** in Scheme 1). Because directly heating the substrates under the conditions of the Skraup−Doebner−Von Miller quinoline synthesis first forms a Schiff's base, the 1,4-addition of aniline to the α,β-unsaturated carbonyl component (route **I**) is probably only a minor pathway.[5] Bischler proposed that the Schiff's bases undergo the 1,4-addition to another molecule of aniline, followed by cyclization and oxidation to 2-substituted quinolines via route **IIa** (Scheme 1).[4] Eisch and Dluzniewski[5] found that heating a Schiff's base under strictly anhydrous conditions in DMSO or acetonitrile led to a putative diazetidinium cation intermediate which then rearranged rapidly to a 2-substituted quinoline (Scheme 1, route **IIb**), a process subsequently supported by labeling studies.[7] In this case, a Schiff's base aromatizes the 1,2-dihydro intermediate to the final quinoline.[7] The lack of formation of 4-substituted quinolines in these reactions [1,4−6]

SCHEME 1



† Center for Molecular Science, Institute of Chemistry, Chinese Academy of Sciences.

‡ Graduate School of Chinese Academy of Sciences.

(1) (a) Skraup, Z. H. *Ber. Dtsch. Chem. Ges.* **1880**, *13*, 2086. (b) Doebner, O.; von Miller, W. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 2812. (c) Mills, W. H.; Harris, J. E. G.; Lambourne, H. *J. Chem. Soc.* **1921**, *119*, 1294. (d) Manske, R. H. F.; Kulka, M. *Organic Reactions;* Adams, R., Ed.; John Why & Sons: New York; 1953, Vol. 7, p 59. (e) Weissberger, A.; Taylor, E. C. In *The Chemistry of Heterocyclic Compounds- Quinolines;* Gurnos, J., Ed.; Stonebridge Press: Bristol, 1977; p 93. (f) Matsugi, M.; Tabusa, F.; Minamikawa, J. *Tetrahedron Lett.* **2000**, *41*, 8523. (g) Ranu, B. C.; Hajra, A.; Dey, S. S.; Jana, U. *Tetrahedron* **2003**, 59, 813. (h) Strell, M.; Kopp, E. *Chem. Ber.* **1958**, *91*, 2854. (i) Martin, von, P.; Winkler, T. *Helv. Chim. Acta* **1994**, *77*, 100. (j) For the latest leading reference on the mechanism of Skraup−Doebner−Von Miller quinoline synthesis, see: Denmark, S. E.; Venkatraman, S. *J. Org. Chem.* **2006**, *71*, 1668.

(2) (a) Robert, A.; Dechy-Cabaret, O.; Cazelles, J.; Meunier, B. *Acc. Chem. Res.* **2002**, *35*, 167. (b) Siim, B. G.; Atwell, G. J.; Anderson, R. F.; Wardman, P.; Pullen, S. M.; Wilson, W. R.; Denny, W. A. *J. Med. Chem.* **1997**, *40*, 1381. (c) Sadana, A. K.; Mirza, Y.; Aneja, K. P.; Prakash, O. *Eur. J. Med. Chem.* **2003**, *38*, 533. (d) Oliva, A.; Meepagala, K. M.; Wedge, D. E.; Harries, D.; Hale, A. L.; Aliotta, G.; Duke, S. O. *J. Agric. Food Chem.* **2003**, *51*, 890. (e) Chen, J. J.; Drach, J. C.; Townsend, L. B. *J. Org. Chem.* **2003**, *68*, 4170.

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(4) Bischler, A. *Ber. Dtsch. Chem.* Ges. **1892**, *25*, 2864.

(5) Eisch, J. J.; Dluzniewski, T. *J. Org. Chem.* **1989**, *54*, 1269.

(6) Skraup, Z. H. *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 897.

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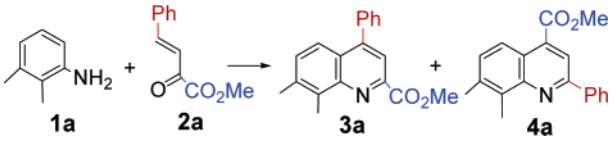
TABLE 1. Selected Results of Reaction Conditions[a]



entry	reaction conditions	yields (%)[b] 3a	4a
1	10 mol % of $Hf(OTf)_4$, CH_2Cl_2, rt, 48 h	18	44
2	HCl (37%, H_2O), rt, 24 h	<2	<2
3	hydrogen chloride, $-CH_2Cl_2$, rt, 24 h	<2	<2
4	hydrogen chloride, $-CH_2Cl_2$, reflux, 24 h	<2	<2
5	hydrogen chloride, −PhMe, reflux, 24 h	<2	<2
6	1 equiv of H_2SO_4, CH_2Cl_2, reflux, 24 h	<2	<2
7	1 equiv of TFA, CH_2Cl_2, reflux, 24 h	18	46
8	1 equiv of TFA, PhMe, reflux, 24 h	29	33
9	TFA, reflux, 12 h	61	<2
10[c]	**TFA, reflux, 12 h**	**80**	**<2**
11[c]	HCO_2H, reflux, 12 h	76	<2
12[c]	AcOH, reflux, 12 h	<2	<2

[a] **1a** (0.2 mmol) and **2a** (0.2 mmol) in the solvents indicated (2 mL). [b] Isolated yields based on **1a**. [c] **1a** (0.2 mmol) and **2a** (0.4 mmol) were used.

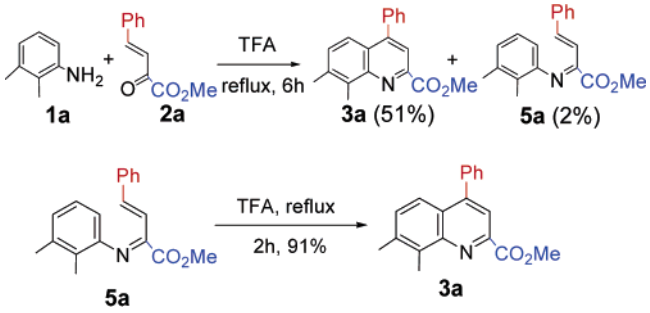
suggested that the direct cyclization of Schiff's bases to 4-substituted 1,4-dihydroquinolines (Scheme 1, route **IIc**) might be a less-favored pathway.

In the present study, we wished to obtain 2-carboxy-4-substituted quinolines by increasing the intramolecular cyclization reactivity of Schiff's base intermediates via route **IIc** (Scheme 1), thereby causing a reverse of the regiochemistry of the standard Skraup−Doebner−Von Miller quinoline process. We envisioned that introducing an electron-withdrawing group on the α,β-unsaturated carbonyl component might increase the electrophilic reactivity of the Schiff's base C═C double bond and facilitate subsequent cyclization.[8] Accordingly, (3*E*)-2-oxo-4-phenylbut-3-enoate methyl ester (**2a**) was chosen to react with 2,3-dimethylaniline (**1a**) under various reaction conditions. Several representative results are summarized in Table 1. It was found that the 2-phenyl-4-carboxy quinoline **4a** was produced in 44% yield when a solution of **1a** (0.2 mmol), **2a** (0.2 mmol), and $Hf(OTf)_4$ (10 mol %) in 2 mL of dichloromethane was stirred at room temperature for 48 h. Surprisingly, a small amount of 2-carboxy-4-phenylquinoline **3a** (18%) was also isolated (entry 1). Hydrochloric acid (entry 2), hydrogen chloride (entries 3−5), and sulfuric acid (entry 6), often effective for the Skraup−Doebner−Von Miller quinoline synthesis, were ineffective for this reaction. It was noted that TFA/solvent systems were effective for the formation of **3a** and **4a** in different ratios (entries 7 and 8). Dramatically, the formation of **4a** was inhibited and the yield of **3a** increased to 61% when TFA alone was used (entry 9) and to 80% when the molar ratio of **2a** to **1a** increased from 1:1 to 2:1 (entry 10, isolated yields were based on **1a**). Formic acid was also an effective solvent for this reaction (entry 11) and might be useful for a large-scale process. However, TFA was chosen in our investigations because it led to the best overall isolated yield (entries 7−10). The structures of **3a** and **4a** were determined from their spectra and by single-crystal X-ray analysis. To the best of our knowledge, this is the first example of regiochemical reversal for the standard Skraup−Doebner−Von Miller quinoline synthesis.

A series of substituted anilines **1a**−**m** and γ-aryl-β,γ-unsaturated α-ketoesters **2a**−**g** were examined to better understand the reaction mechanism as well as to examine the scope and limitation of the method. Listed in Table 2 (entries 1−19) are representative results. Either anilines or γ-aryl-β,γ-unsaturated α-ketoesters bearing strong electron-withdrawing groups such as nitro resulted in decreased yields (entries 5, 12, and 17). There were decreases in yields with 2-substituted anilines in comparison to 4-substituted analogues (entries 13−18), indicating the steric effects are greater than the electronic effects. When 4-aminophenol (**1m**) was used, 6-hydroxy quinoline **3s** was obtained in 79% yield (entry 19), demonstrating excellent chemoselectivity. Although this approach was ineffective for the simple α,β-unsaturated aldehyde and ketone (entry 20), the use of γ-aryl-β,γ-unsaturated α-ketoesters appears to be a general and direct route to quinoline derivatives that might not be easily accessible otherwise. As in the case of **3a** and **4a**, the structures of **3o** and **3s** were assigned from spectral and single-crystal data.

To better understand the regiochemical reversal in this quinoline synthetic method, we thought it was important to confirm that Schiff's base **5** was indeed involved as an intermediate. For this purpose, we screened various reaction conditions to obtain **5** by increasing the concentration of reactants and shortening the reaction time at different temperatures. In one case, for example, a mixture of 2,3-dimethylaniline (**1a**, 10 mmol) and (3*E*)-2-oxo-4-phenylbut-3-enoate methyl ester (**2a**, 20 mmol) in 10 mL of TFA was stirred at reflux for 6 h to give Schiff's base **5a** (2%) and 2-carboxy-4-arylquinoline **3a** (51%, Scheme 2). It is worth mentioning that the intermediate

SCHEME 2



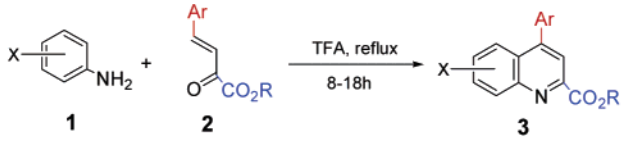
corresponding to aza-Michael addition as sometimes proposed was not detectable. Schiff's base **5a** was isolated and structurally characterized and was converted to the corresponding quinoline **3a** by cyclization and oxidation (air was tentatively proposed to partly be the oxidant) in refluxing TFA for 2 h (Scheme 2).

Although a more detailed mechanistic investigation is in progress, these preliminary results suggest that the reaction might involve 1,2-addition of anilines **1** to γ-aryl-β,γ-unsaturated α-ketoesters **2** in TFA to form the intermediate **5**, followed by direct intramolecular cyclization and oxidation to give 2-carboxy-4-arylquinoline products **3** (Scheme 3).

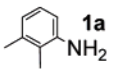
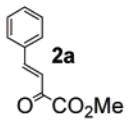
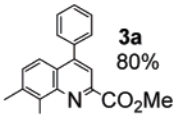
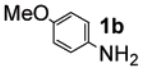
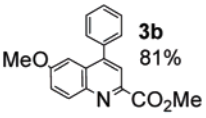
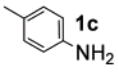
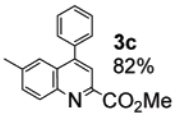
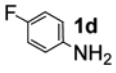
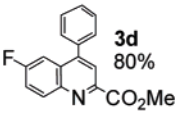
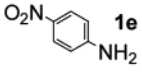
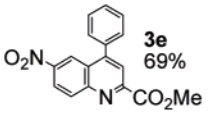
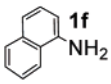
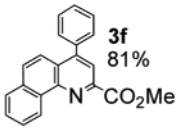
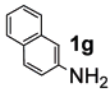
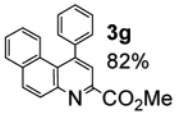
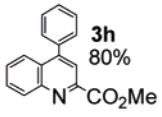
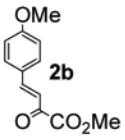
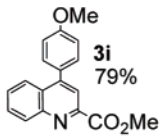
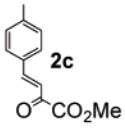
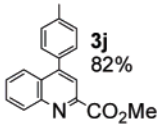
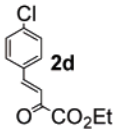
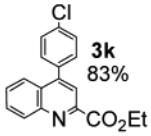
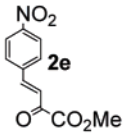
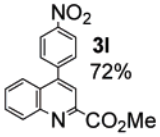
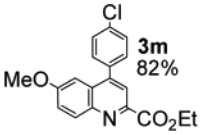
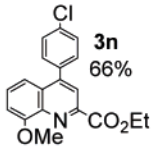
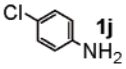
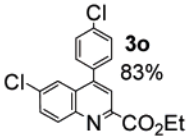
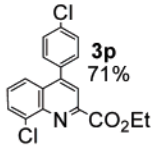
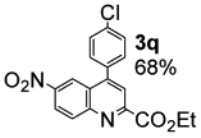
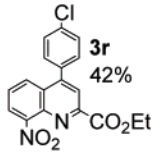
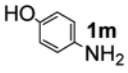
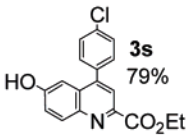
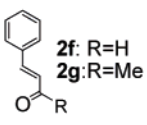
In contrast to the Schiff's bases obtained from γ-aryl-β,γ-unsaturated α-ketoesters in Table 2, Schiff's base **5t**, prepared according to the reported procedure,[5] could not be converted to 1,4-dihydroquinoline **6t** or the corresponding oxidized product **3t** in TFA (Scheme 4), confirming the findings of Eisch and

(7) McKillop, A. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Tarrytown, 1996; Vol 5, p 219.
(8) Linderman, R. J.; Kirollos, K. S. *Tetrahedron Lett.* **1990**, *31*, 2689.

TABLE 2. Syntheses of 2-Carboxy-4-arylquinolines[a]

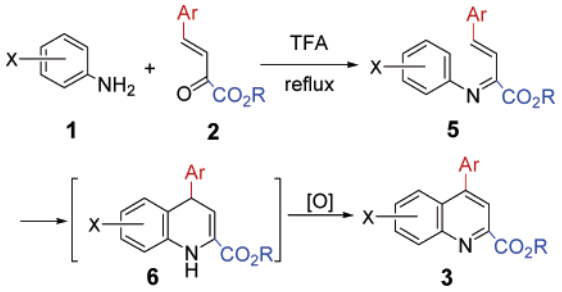


1 2 3

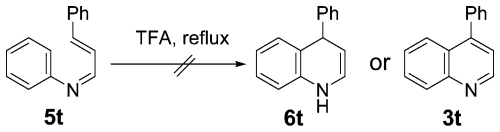
Entry	1	2	Time (h)	Yield[b]
1			12	 **3a** 80%
2		**2a**	8	 **3b** 81%
3		**2a**	12	 **3c** 82%
4		**2a**	12	 **3d** 80%
5		**2a**	18	 **3e** 69%
6		**2a**	12	 **3f** 81%
7		**2a**	12	 **3g** 82%
8		**2a**	12	 **3h** 80%
9	**1h**		8	 **3i** 79%
10	**1h**		12	 **3j** 82%
11	**1h**	 **2d**	12	 **3k** 83%
12	**1h**	 **2e**	18	 **3l** 72%
13	**1b**	**2d**	8	 **3m** 82%
14	 **1i**	**2d**	8	 **3n** 66%
15	 **1j**	**2d**	12	 **3o** 83%
16	 **1k**	**2d**	12	 **3p** 71%
17	**1e**	**2d**	18	 **3q** 68%
18	 **1l**	**2d**	18	 **3r** 42%
19	 **1m**	**2d**	12	 **3s** 79%
20	**1h**	 **2f**: R=H **2g**:R=Me	18	--

[a] **1** (0.2 mmol) and **2** (0.4 mmol) in TFA (2 mL). [b] Isolated yields based on **1**.

SCHEME 3



SCHEME 4



Dluzniewski in DMSO or acetonitrile.[5] It appears that when γ-aryl-β,γ-unsaturated esters **2** are used, as opposed to α,β-unsaturated ketones or aldehydes, the greater electron-withdrawing character of the ester groups in refluxing TFA facilitates electrophilic ring closure, and the following oxidation leads to regiochemical reversal in comparison with the standard Skraup–Doebner–Von Miller quinoline protocol. Further mechanistic investigations as well as applications of this method are in progress in our laboratory.

Experimental Section

General Procedure to Synthesize 2-Carboxy-4-arylquinolines. A mixture of an aniline **1** (0.2 mmol) and an γ-aryl-β,γ-unsaturated α-ketoester **2** (0.4 mmol) in 2 mL of TFA was stirred at reflux for 8−18 h, after which TFA was distilled out for reuse. The residue was redissolved in 20 mL of CH_2Cl_2, and the solution was washed with 5 mL of saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The products **3** were isolated by flash chromatography on silica gel (200−300 mesh) with an ethyl acetate−petroleum ether mixture (1:5, v/v).

Ethyl 6-Chloro-4-(4-chlorophenyl)quinoline-2-carboxylate (3o): 83.0% yield; white solid; mp = 220−221 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 9.0 Hz, 1H), 8.12 (s, 1H), 7.87 (d, J = 2.3 Hz, 1H), 7.73 (dd, J = 9.0, 2.3 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 4.58 (q, J = 7.1 Hz, 2H), 1.50 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 148.0, 147.7, 146.5, 135.4, 135.2, 135.1, 132.8, 131.2, 130.8, 129.2, 128.2, 124.2, 122.0, 62.5, 14.4; FTIR (KBr) 3031, 2985, 1716, 1597, 1485, 1450, 1377, 1273, 1253, 1141, 1087, 1020, 847, 829, 789 cm^{-1}. Anal. calcd for $C_{18}H_{13}Cl_2NO_2$: C, 62.45; H, 3.78; N, 4.05. Found: C, 62.18; H, 3.89; N, 3.93.

Acknowledgment. We thank the National Natural Science Foundation of China (No. 20232010, 20332030) and the Chinese Academy of Sciences for financial support. We appreciate the suggestions and corrections from the reviewers.

Supporting Information Available: Experimental procedures; spectral data for γ-aryl-β,γ-unsaturated α-ketoesters (**2**), quinolines (**3** and **4**), and Schiff's bases **5**; copies of ^{1}H NMR and ^{13}C NMR; and X-ray crystallographic data of **3a**, **3o**, **3s**, and **4a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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