Limitations of the 'Two-Phase' Doebner–Miller Reaction for the Synthesis of Quinolines

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Abstract: The Doebner–Miller synthesis of quinolines under modified biphasic conditions was investigated. Crotonaldehyde, reacted readily with aniline to produce 2-methylquinoline. However, cinnamaldehyde and other γ -substituted α,β -unsaturated aldehydes yielded complex mixtures with substituted anilines to provide only trace quantities of quinolines. The Doebner–Miller reaction under these conditions is only suitable for sterically accessible α,β -unsaturated aldehydes.

Key words: α,β -unsaturated aldehyde, aniline, quinoline, Doebner–Miller reaction, heterocycle

Quinoline rings feature in a variety of naturally occurring and medicinally active compounds,^{1,2} including metabolites derived from various flora and fauna.³ These compounds exhibit a broad range of antimicrobial,⁴ antitubercular,⁵ antimalarial,^{1,6} antiallergic,⁷ and antiasthmatic activity.⁷

The Doebner–Miller reaction between aromatic amines and α,β -unsaturated carbonyl compounds is regarded as a relatively general method for synthesizing quinolines from readily available starting materials (Scheme 1).⁸ The mechanism is complex⁹ and dependent on reagents and reaction conditions, but generally appears to proceed via an initial conjugate attack by the aniline on the Michael acceptor when catalyzed by Brønsted acids under aqueous conditions. Synthetic⁸ and mechanistic¹⁰ studies of the Doebner–Miller reaction and the related Skraup reaction have been reviewed elsewhere.^{8–10}

Scheme 1 Doebner–Miller reaction of aniline and crotonaldehyde (THAB = tetrahexylammonium bromide)

In recent years modification of the Doebner–Miller reaction conditions have included the use of two-phase systems with toluene,¹¹ other strong acids, such as

trifluoroacetic acid,⁸ and phase-transfer catalysts.¹² Although low yields are sometimes obtained, the easy formation of quinolines from inexpensive starting materials makes this reaction a potentially attractive route. The advantage of the two-phase solvent system is that it decreases polymerization of the aldehyde and makes products easier to isolate.¹¹ This is particularly true if the acid is a polyoxometallate¹² and the reaction is performed with microwave irradiation. However, the latter conditions are still not suitable for highly polymerizable substrates like acrolein and propenals and it is necessary to immobilize the aldehyde on silica. In a quest to develop more general, user-friendly conditions we have examined the two-phase Doebner–Miller reaction with aqueous acid and a range of aldehydes and anilines. This study revealed the narrow range of substrates suitable for this methodology.

The reaction between aniline and cinnamaldehyde (**2**) under modified Doebner–Miller conditions (toluene, 10 M HCl, THAB, 80–90 °C, 2 h) did not yield 2-phenylquinoline (**10**) (Figures 1 and 2).¹³ The electron-rich 4-methoxyaniline provided some of quinoline **11** but in low conversion (1.6%). The more electrophilic crotonaldehyde did react with aniline in a moderate yield (40%) (Table 1, entry 1) and surprisingly, in a reduced yield with 4-methoxyaniline using this aldehyde (entry 2).

The effect of substitution at the γ -position was explored, with 4-methylpent-2-enal (**3**), cyclohex-1-ene-1-carbaldehyde (**4**), and 2-myrtanal (**5**) under the general conditions (Figure 1). These substrates gave complex mixtures with no identifiable products present; quinolines **12**,¹⁴ **13**, and **14** were not isolated (Figure 2). These results are consistent with other examples reported in the literature, where only unsubstituted α,β -unsaturated aldehydes, such as **8** and **9**, gave quinolines with aniline^{22,15} or substituted anilines^{23,16} under similar conditions.

We attempted to obtain aldehyde **19** (Scheme 2), where a benzyloxy group would be introduced at the 8-position of the quinoline product. Hydrolysis of 1,1,3,3-tetraethoxypropane (**17**) followed by treatment with sodium hydroxide gave the sodium salt **18**. In an NMR-scale experiment, an equivalent each of **18** and benzyl bromide were shaken and left to react in DMSO-*d*₆. After 24 hours, conversion of **18** into aldehyde **19** was complete, as determined by ¹H NMR spectroscopic analysis. Attempts to carry out this on a preparative scale of > 1 gram were unsuccessful.

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Table 1 Quinoline Derivatives **1**, **20–23** Produced Using Crotonaldehyde via Scheme 1

Entry	Aniline	Aldehyde	Conditions	Quinoline	Isolated yield (%)
1			10 M HCl, toluene, THAB, ^a 80–90 °C, 90 min		40
2			10 M HCl, toluene, THAB, ^a 80–90 °C, 90 min		8 ^b
3			10 M HCl, toluene, THAB, ^a 80–90 °C, 90 min		7 ^b
4			10 M HCl, toluene, THAB, ^a 80–90 °C, 90 min		23
5			10 M HCl, toluene, THAB, ^a 80–90 °C, 90 min		16
6			10 M HCl, toluene, THAB, ^a 80–90 °C, 90 min		57 ^c
7			10 M HCl, toluene, THAB, ^a 80–90 °C, 90 min		— ^d

^a THAB = tetrahexylammonium bromide.^b Yield after purification by chromatography.^c From ref. 13.^d Complex mixture. **Figure 1**

Instead, reaction of aniline with either 2-nitrocinnamaldehyde (**6**) or 2-methoxycinnamaldehyde (**7**) under the general conditions gave traces of 2-(2-nitrophenyl)quinoline (**15**) and a complex mixture not containing quinoline **16**, respectively.

The effect of substitution on the aromatic ring of aniline was examined (Table 1). Anilines with electron-donating

Figure 2

(4-MeO, 2-Me), electron-withdrawing (4-NO₂, 2-CO₂H, or 4-CO₂H), or halogen (4-Br) groups were reacted with crotonaldehyde under the general conditions (entries 2–7). One literature example¹³ (entry 6) is included in Table 1 for comparison. All anilines gave the corresponding substituted quinolines **20–24** in low to moderate yields; compound **25** was not obtained. The purification method provided variations in yield. Therefore, no corre-

Scheme 2 Formation of aldehyde 19

lation between the potential influence of electron-donating or electron-withdrawing groups on the aniline and the isolated yield of the quinoline product was apparent.

In the crude ¹H NMR spectra and in the workups of reactions involving crotonaldehyde significant amounts of polymeric material were observed, and this both lowered product yields and hampered isolation. While some quinoline products could be readily purified by recrystallization (22 and 23), others required multiple chromatography (20 and 21) resulting in some decomposition and low yields.

Steric bulk at the γ-position of the α,β-unsaturated aldehyde prevented the formation of quinolines in the Doebner–Miller reaction. More than one mechanism for the Doebner–Miller reaction has been proposed. Formation of products from a sterically accessible crotonaldehyde lend support to a mechanism invoking conjugate addition of the aniline on the α,β-unsaturated aldehyde Michael acceptor.

In conclusion, the two-phase Doebner–Miller reaction catalyzed with aqueous hydrochloric acid is limited to sterically accessible aldehydes, such as crotonaldehyde. Other sterically hindered aldehyde examples studied resulted in predominant polymerization under these conditions.

All chemicals were commercially available and used without further purification. Substituted aldehyde and aniline derivatives were purchased from Sigma-Aldrich and used as received. The ¹H and ¹³C NMR spectra were obtained using a 300 MHz (Varian Gemini 300) or a 400 MHz (Varian Unity 400) spectrometer in CDCl₃. ¹H and ¹³C NMR are referenced to solvent, i.e. CDCl₃ (δ = 7.24 and δ = 77.0, respectively). Mass spectra were recorded on a Fisons VG-Platform II spectrometer, using electrospray as the ionization technique with HCO₂H–MeCN (4:6). Mass Lynx Version I (IBM) software was used to acquire and process the data. HRMS (ESI) were recorded on a Bruker Daltonix 4.7T FT ion cyclotron resonance mass spectrometer (FTICR MS) fitted with an Apollo ESI source in positive ion or negative ion as stated. All MS samples were prepared as solns in MeOH or MeCN. FTIR spectra were recorded in the range 4000–400 cm^{−1} on a Perkin-Elmer FTIR 1725X spectrophotometer; spectra were recorded using a KBr disc. Analytical TLC was carried out on Merck precoated aluminum TLC plates coated with silica gel 60 F254 (0.2 mm).

Potassium 3-Oxoprop-1-en-1-olate (18)

1,1,3,3-Tetraethoxypropane (17, 5 g, 22.69 mmol), 1 M HCl (5 mL), and H₂O (5 mL) were stirred vigorously at r.t. for 75 min. The resulting homogenous soln was cooled to 0 °C and adjusted to pH 10 with 5 M KOH. Acetone (80 mL) was added slowly to the soln until crystals separated. The precipitate was filtered, washed with acetone, and dried at r.t. The salt was dissolved in boiling MeOH, treated with charcoal, and filtered. Solvent was removed in vacuo to give an orange gum; yield: 1.94 g (78%).

¹H NMR (400 MHz, CD₃OD): δ = 5.23 (t, *J* = 10, 7.2 Hz, 1 H), 8.61 (d, *J* = 7.2 Hz, 2 H).

MS (ESI): *m/z* (%) = 110.50 (100) [*M* + 1].

3-(Benzyloxy)propenal (19)

Potassium 3-oxoprop-1-en-1-olate (18, 0.5 g, 7.04 mmol), BnBr (0.82 mL, 6.68 mmol), and anhyd DMSO (10 mL) were stirred and the mixture was heated to 40 °C for 48 h under an atmosphere of N₂. The mixture was quenched with H₂O (50 mL) and extracted with Et₂O (4 × 40 mL). The combined organic layers were washed with brine (40 mL), dried (anhyd MgSO₄), and concentrated in vacuo to give an orange oil; yield: 736 mg (49%).

as a complex mixture.

¹H NMR Spectroscopic Study of 3-(Benzyloxy)propenal (19)

Potassium 3-oxoprop-1-en-1-olate (50 mg, 0.704 mmol) and BnBr (83.6 μL, 0.704 mmol) were dissolved in DMSO-*d*₆ (1 mL) in a 5-mm NMR tube the reaction was mixed and left for 24 h. A ¹H NMR spectrum was obtained.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 5.080 (s, 1 H, H1'), 5.633 (dd, *J* = 8.4, 4, 8.4 Hz, 1 H, H2'), 7.2–7.5 (m, 5 H, H3', H7'), 7.932 (d, *J* = 12.4 Hz, 1 H, H3'), 9.340 [d, *J* = 8 Hz, 1 H, C(O)H].

MS (ESI): *m/z* (%) = 163.87 (10) [*M* + 1].

Quinolines 1, 10, 11, 15, 20–23; General Procedure

A soln of toluene (10 mL), substituted aniline, THAB (5%), and concd HCl (10 M, 40 mL) was heated to 80–90 °C. α,β-Unsaturated aldehyde was added slowly and the mixture stirred for 1.5 h. After cooling to r.t., the mixture was neutralized with 2 M NaOH, and the resulting mixture was extracted with CHCl₃. The organic layer was washed with brine and dried (anhyd MgSO₄), and the solvent was removed in vacuo to afford the crude product. The crude product was either recrystallized (EtOAc–hexane) (22) or purified by column chromatography (silica gel, hexane–EtOAc, 5:1) (1, 10, 11, 15, 20, 21, and 23), and in some cases recrystallized (EtOAc) again (22).

2-Methylquinoline (1)

Following the general procedure using aniline (0.98 mL, 10.74 mmol) and crotonaldehyde (1.78 mL, 21.48 mmol), with purification by chromatography gave a yellow oil; yield: 600 mg (40%).

The ¹H NMR spectrum was consistent with previously reported data.^{12, 13}

2-Phenylquinoline (10)

Following the general procedure using aniline (0.49 mL, 5.36 mmol) and cinnamaldehyde (1.35 mL, 10.73 mmol), with purification by chromatography and recrystallization gave an orange solid; yield: 2 mg (<1%); mp 77–80 °C (Lit.²⁰ 67–69 °C).

The ¹H NMR spectrum was consistent with previously reported data.^{19, 20}

6-Methoxy-2-phenylquinoline (11)

Following the general procedure using 4-methoxyaniline (0.5 g, 4.06 mmol) and cinnamaldehyde (1.03 mL, 8.119 mmol), with purification by chromatography and recrystallization gave an orange solid; yield: 8 mg (<1%); mp 125–126 °C (Lit.²⁰ 129–130 °C).

The ^1H NMR spectrum was consistent with previously reported data.^{20,21}

2-(2-Nitrophenyl)quinoline (15)

Following the general procedure using aniline (0.98 mL, 10.74 mmol) and *trans*-2-nitrocinnamaldehyde (3.80 g, 21.47 mmol) gave a brown solid; yield: 3 mg (<1%); mp 116–117 °C (Lit.²⁰ 118–119 °C).

^1H NMR (400 MHz, CDCl_3): δ = 7.53 (d, J = 8.4 Hz, 1 H, H3), 7.55–7.61 (m, 2 H, H6, H5'), 7.70–7.76 (m, 3 H, H7, H4', H6'), 7.86 (d, J = 6.8 Hz, 1 H, H8), 7.98 (d, J = 9.2 Hz, 1 H, H3'), 8.09 (d, J = 9.6 Hz, 1 H, H5), 8.23 (d, J = 8.4 Hz, 1 H, H4).

^{13}C NMR (125 MHz, CDCl_3): δ = 120.5, 124.5, 127.0, 127.2, 127.5, 129.3, 129.7, 130.0, 131.6, 132.6, 135.9, 136.8, 147.9, 155.6.

MS (ESI) m/z (%) = 205.68 (100); 250.73 (30) [M + 1].

HRMS: m/z [M + H]⁺ calcd for $\text{C}_{15}\text{H}_{11}\text{N}_2\text{O}_2$: 251.0815; found: 251.0823.

6-Methoxy-2-methylquinoline (20)

Following the general procedure using 4-methoxyaniline (0.94 mL, 8.12 mmol) and crotonaldehyde (1.35 mL, 16.24 mmol) gave a brown solid; yield: 106 mg (8%); mp 60–62 °C (Lit.²² 67–68 °C).

The ^1H NMR spectrum was consistent with previously reported data.^{23–24}

2,8-Dimethylquinoline (21)

Following the general procedure using 2-methylaniline (0.49 mL, 4.66 mmol) and crotonaldehyde (0.77 mL, 9.33 mmol) gave a yellow oil; yield: 54 mg (7%).

The ^1H NMR spectrum was consistent with previously reported data.²⁵

2-Methyl-6-nitroquinoline (22)

Following the general procedure using 4-nitroaniline (0.5 g, 3.62 mmol) and crotonaldehyde (0.60 mL, 7.24 mmol) gave dark-green crystals; yield: 154 mg (23%); mp 162–164 °C (Lit.²⁵ 165 °C).

The ^1H NMR spectrum was consistent with previously reported data.²⁶

6-Bromo-2-methylquinoline (23)

Following the general procedure using 4-bromoaniline (0.5 g, 2.91 mmol) and crotonaldehyde (0.48 mL, 5.81 mmol) gave red-brown crystals; yield: 48 mg (8%); mp 97–99 °C (Lit.²⁷ 95–96 °C).

IR (KBr): 3048, 1488, 646 cm^{-1}

^1H NMR (400 MHz, CDCl_3): δ = 2.752 (s, 3 H, CH_3), 7.319 (d, J = 8.4 Hz, 1 H, H3), 7.754 (d, J = 2.0, 2.0 Hz, 1 H, H4), 7.917 (br s, w ~7.0 Hz, 1 H, H5), 7.942 (d, J = 2.2 Hz, 1 H, H7), 7.981 (d, J = 8.9 Hz, 1 H, H8)

^{13}C NMR (100 MHz, CDCl_3): δ = 25.2, 119.4, 122.8, 127.5, 129.4, 130.2, 132.8, 135.2, 146.2, 159.4.

MS (ESI) m/z (%) = 223.73 (100) [M + H]⁺.

HRMS: m/z [M + H]⁺ calcd for $\text{C}_{10}\text{H}_9\text{BrN}$: 221.9912; found: 221.9902.

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