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Doebner–Miller synthesis in a two-phase system: practical preparation of quinolines

Masato Matsugi,* Fujio Tabusa and Jun-ichi Minamikawa

Process Research Department, Second Tokushima Factory, Otsuka Pharmaceutical Co., Ltd., 224-18, Ebisuno, Hiraishi, Kawauchi-Cho, Tokushima 771-0182, Japan

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Abstract

Doebner–Miller cyclization was carried out in a two-phase solvent system. The method has shown to be advantageous to the yield and to the ease of the work-up process. © 2000 Elsevier Science Ltd. All rights reserved.

Doebner–Miller synthesis[1] has been frequently used in the preparation of a variety of quinoline derivatives[2] due to its simplicity even though the usual yields are not always high.[3] One of the serious drawbacks of the reaction is the tedious isolation procedure from complex reaction mixtures.[4] It can be seen that the acid-catalysed polymerisation of α,β-unsaturated

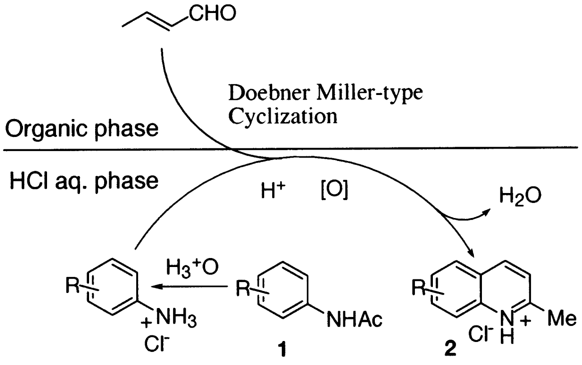

Figure 1.

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* Corresponding author. Present address: Department of Materials Chemistry, Graduate School of Engineering, Osaka University, Suita Osaka 565-0871, Japan. Tel/fax: +81-6-6879-7930; e-mail: matsugi@ap.chem.eng.osaka-u.ac.jp

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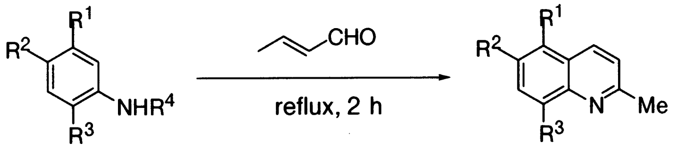
aldehyde lowers the yield and makes the isolation of the target product difficult. We found that the Doebner–Miller reaction in a two-phase solvent system (Fig. 1), which consists of an organic phase and an aqueous acid phase, decreases the polymerisation of the aldehyde. The reaction proceeded smoothly even in the absence of oxidants. The marked improvement is shown in Table 1.

Table 1



1a : R^1 = F, R^2 = F, R^3 = F, R^4 = Ac
b : R^1 = Me, R^2 = H, R^3 = H, R^4 = H
c : R^1 = H, R^2 = OMe, R^3 = H, R^4 = H

2(a-c)

Entry	Substrate	Conditions	Isolated yield of **2** (%)
1	**1a**	EtOH containing conc. H_2SO_4[5]	10[a,b]
2	**1a**	Toluene containing TsOH	3[a,b]
3	**1a**	6 M HCl	47[a,b]
4	**1a**	Heptane/6 M HCl	54[a,b]
5	**1a**	EDC[c]/6 M HCl	60[b,d]
6	**1a**	Xylene/6 M HCl	68[b,d]
7	**1a**	Toluene/6 M HCl	70[d,e]
8	**1a**	Toluene/6 M HCl	80[d,f]
9	**1b**	Toluene/6 M HCl	69[g,h] (62)[i]
10	**1c**	Toluene/6 M HCl	61[g] (45)[i]

[a] The colour of the product was dark brown.
[b] The time taken to add the aldehyde was 30 min.
[c] EDC = 1,2-dichloroethane.
[d] An almost colourless product was obtained.
[e] It was confirmed that a similar result was obtained irrespective of the time taken to add the aldehyde.
[f] Crude yield in 5 kg scale.
[g] The time taken to add the aldehyde was 1 min.
[h] A mixture of regio-isomers; 7-methylquinaldine/5-methylquinaldine = 1.8/1.
[i] Reported yields in a homogenic phase reaction.[2]

The following are the highlights of this method:[†] (1) Relatively high yields are obtained as compared to the single-phase reaction (entry 3 vs 7, entries 9–10). (2) The dropping rate of the aldehyde has no significant influence on the yield. Since the original Doebner–Miller reaction requires strict control over the addition of the aldehyde, this feature is particularly useful for a

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[†] Typical procedure: **1a** (1.12 g, 4.46 mmol) was hydrolysed to the corresponding aniline by heating with 6 M HCl (22.4 ml) at 100°C (bath temp). After the disappearance of **1a** on TLC, toluene (5.8 ml) and then crotonaldehyde (0.74 ml, 8.92 mmol) were added dropwise at 100°C. Stirring was continued for 2 h at 100°C and the mixture was allowed to cool to room temperature. The aqueous layer was separated and neutralized with aqueous NaOH to afford crude **2a** as a crystalline solid. The crude product was purified by silica gel chromatography (hexane/AcOEt, 5/1) to give 802 mg (70.2%) of pure **2a** as colourless crystals with mp 103°C.

large-scale synthesis. (3) Simply neutralising the aqueous phase could isolate almost colourless pure product. All of these advantages (1)–(3) were finally confirmed in a 5 kg-scale production (entry 8). Further examples and applications of the reaction are now under investigation.

References

1. Doebner, O.; Miller, W. *Bericht* **1883**, *16*, 2464–2472.
2. Manske, R. H.; Kulka, M. *Org. React.* **1953**, *7*, 59–98.
3. Ranu, B. C.; Hajra, A.; Jana, U. *Tetrahedron Lett.* **2000**, *41*, 531–533.
4. Leir, C. M. *J. Org. Chem.* **1977**, *42*, 911–913.
5. Ismailova, L. A.; Kudratova, M. K.; Kuchkarov, A. B.; Yasupov, D. *Dokl. Akad. Nauk USSR* **1989**, *2*, 35–36.