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# Heterogeneous Catalytic Solvent-free Synthesis of Quinoline Derivatives via the Friedländer Reaction

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**Abstract** A simple solvent-free heterogeneous catalytic method was developed for the synthesis of substituted quinoline derivatives via the Friedländer cyclization.

**Keywords** Quinolines · Friedländer reaction · Montmorillonite · Green chemistry

## 1 Introduction

It is known that quinoline derivatives are important compounds in the bioorganic and medicinal chemistry. The oldest known quinoline derivative is quinine which, together with its synthetic derivatives, is used as antimalarial agent, and a wide variety of other quinoline derivatives are used e.g. as antiasthmatic, antiinflammatory, antibiotic and tyrosine kinase inhibiting agents [1]. In the synthesis of nicotinic acid derivatives quinolines are also often used as starting material.

There are several methods for the formation of the quinoline ring system such as Skraup [2], Knorr, [3] Conrad-Limpach [4], Döbner-von Miller [5], Combes [6], Friedländer [7] reactions, etc. In the classic Friedländer quinoline synthesis the reactants are an aromatic amine having carbonyl compound in the *ortho* position and another carbonyl compound which contains at least two α-protons. The first step of the reaction is the formation of an enamine, this is followed by an aldol-type cyclization yielding the 2,3-disubstituted quinoline (Fig. 1). The cyclization can be provoked by both acidic and basic catalysts. Originally strong bases were used but in certain cases piperidine is also suitable. The acid catalysts were more extensively investigated. Lewis acids such as $ZnCl_2$, $FeCl_3$, $BiCl_3$, $SnCl_4$ [8] were most frequently used but the method has also been described with phosphoric acid, trifluoroacetic acid, or *p*-toluenesulfonic acid, too [8]. Recent methods were published about the Friedländer reaction in the presence of elemental iodine [9], in microwave oven [8], or in ionic liquids [10].

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## 2 Experimental

The commercial starting materials were purchased from Merck-Hungary Ltd. except E4a, which was the product of Erdőkémia-ker Ltd., Hungary and K10, which was the product of Fluka AG.

Pretreatment of the catalyst: before the experiments the sample was powdered and heated at 120 °C for 2 h.

Béchamp reduction: to a mixture of 40 g iron powder, 120 mL water and 1.5 mL conc. HCl 0.1 mol **1a** or **1b** was added portion by portion at 95 °C under vigorous stirring. Then the solid was filtered off, the filtrate was extracted with 3× 10 mL methyl *tert*-butyl ether, the organic phase was dried over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. Yield: 70% and 92% for **1a** and **1b**, respectively.

Cyclization: 5 mmol of **1**, 15 mmol of **2**, 0.5 g catalyst were heated under stirring in the solvent, at the temperature and for the reaction time indicated in Tables 1–3. Then the catalyst was filtered off (in the solvent-free experiments the cooled reaction mixture was before diluted with acetone), the filtrate was evaporated, the residue characterized by $^1$H-NMR spectroscopy.

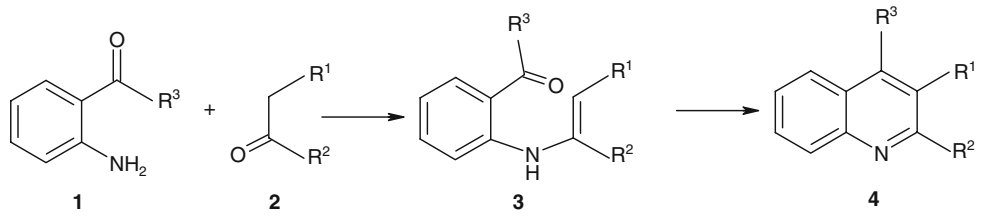



**Fig. 1**

Representative physical and spectroscopic data of the products:

4-Methyl–2-phenyl-quinoline, **4f**

$^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 2.7 (s, 3H, $CH_3$); 7.4–7.6 (m, 3H, Ar); 7.6–7.8 (m, 2H, Ar); 7.9–8.0 (m, 2H,CH); 8.1–8.3 (m, 3H, Ar).

**Table 1** Reaction of 2-amino-benzaldehyde **1a** with different ketones[a]

| Entry | $R^1$ | $R^2$ | Catalyst | Solvent | Reaction temperature (°C) | Reaction time (h) | Product (yield)[b] |
|---|---|---|---|---|---|---|---|
| 1 | $CH_3CO$ | $CH_3$ | HT | Ethanol | 80 | 10 | **3a** (45) |
| 2 | H | $C_6H_5$ | HT | Ethanol | 80 | 10 | **3b** (37) |
| 3 | $COOC_2H_5$ | $CH_3$ | HT | Ethanol | 80 | 6 | **3′c** (42) |
| 4 | H | $C_6H_5$ | E4a | Ethanol | 80 | 8 | **3b** (56) |
| 5 | H | $CH_3$ | E4a | Acetone, | 60 | 10 | **4d** (5)+ |
| | | | | then xylene | 140 | 10 | **3d** (53) |
| 6 | H | $CH_3$ | K10 | Acetone, | 60 | 10 | **4d** (23)+ |
| | | | | then xylene | 140 | 10 | **3d** (42) |

[a] **1a** and **2** in 1:3 molar ratio, 1 g catalyst/5 mmol amine

[b] Determined by $^1$H-NMR

**Table 2** Reaction of 2-amino-acetophenone **1b** with different ketones[a]

| Entry | $R^1$ | $R^2$ | Catalyst | Solvent | Reaction temperature (°C) | Reaction time (h) | Product (yield)[a] |
|---|---|---|---|---|---|---|---|
| 1 | H | $CH_3$ | E4a | Acetone, | 60 | 10 | **4e** (14)+ |
| | | | | then neat | 160 | 10 | **3e** (76) |
| 2 | H | $C_6H_5$ | K10 | Xylene | 140 | 10 | **4f** (60)+ |
| | | | | | | | **3f** (35) |
| 3 | H | $C_6H_5$ | K10 | Neat | 160 | 10 | **4f** (79)+ |
| | | | | | | | **3f** (15) |

[a] **1b** and **2** in 1:3 molar ratio, 1 g catalyst/5 mmol amine

[b] Determined by $^1$H-NMR

**Table 3** Reaction of 2-amino-acetophenone **1b** with different ketones in the presence of K10[a]

| Entry | $R^1$ | $R^2$ | $R^3$ | Reaction time (h) | Product (yield)[b] |
|---|---|---|---|---|---|
| 1 | H | $C_6H_5$ | $CH_3$ | 15 | **4f** (83) |
| 2 | H | 4-$CH_3$–$C_6H_4$ | $CH_3$ | 16 | **4g** (97) |
| 3 | Me | $C_6H_5$ | $CH_3$ | 16 | **4h** (96) |
| 4 | H | 4-$NO_2$–$C_6H_4$ | $CH_3$ | 16 | **4i** (98) |
| 5 | Me | 4-$CH_3$–$C_6H_4$ | $CH_3$ | 16 | **4j** (91) |
| 6 | 3,4-$(CH_3O)_2$–$C_6H_3$ | $CH_3$ | $CH_3$ | 16 | **4k** (95) |

[a] **1b** and **2** in 1:3 molar ratio, 1 g catalyst/5 mmol amine, no solvent, 160 °C

[b] Determined by $^1$H-NMR

4-Methyl-2-(4′-methyl-phenyl)-quinoline, **4g**

$^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 2.4 (s, 3H, $CH_3$); 2.7 (s, 3H, $CH_3$); 7.3 (d, 2H, Ar); 7.5 (t, 1H, Ar); 7.6–7.7 (m, 2H, Ar); 7.9 (d, 1H, Ar); 8.0 (d, 2H, Ar); 8.1 (d, 1H, Ar).

3,4-Dimethyl–2-phenyl-quinoline, **4h**

$^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 2.3 (s, 3H, $CH_3$); 2.6 (s, 3H, $CH_3$); 7.3–7.6 (m, 6H, Ar); 7.6–7.7 (t, 1H, Ar); 8.0 (d,1H, Ar); 8.1 (d, 1H, Ar).

4-Methyl-2-(4′-nitro-phenyl)-quinoline, **4i**

$^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 2.8 (s, 3H, $CH_3$); 7.6 (t, 1H, Ar); 7.7–7.8 (m, 2H, Ar); 8.0 (d, 1H, Ar); 8.2 (d, 1H, Ar); 8.3–8.4 (m, 4H, Ar).

3,4-Dimethyl-2-(4′-methyl-phenyl)-quinoline, **4j**

$^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 2.4 (s, 3H, $CH_3$); 2.5 (s, 3H, $CH_3$); 2.6 (s, 3H, $CH_3$); 7.3 (d, 2H, Ar); 7.5 (t, 1H, Ar); 7.6–7.7 (m, 2H, Ar); 7.9 (d, 1H, Ar); 8.0 (d, 2H, Ar); 8.1 (d, 1H, Ar).

3,4-Dimethyl-2-(3′,4′-dimethoxyphenyl)-quinoline, **4k**

$^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 2.4 (s, 3H, $CH_3$); 2.5 (s, 3H, $CH_3$); 3.88 (s, 3H, $OCH_3$); 3.96 (s, 3H, $OCH_3$); 6.99 (d, 2H, Ar); 7.53 (t, 1H, Ar); 7.6–7.7 (m, 2H, Ar); 8.0 (d, 1H, Ar); 8.1 (d, 1H, Ar).

11-Methyl-cyclohepta[*b*]quinoline, 5

M.p.: 93 °C, $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 1.69–1.9 (m, 6 H, $CH_2$); 2.63 (s, 3H, $CH_3$); 3.0 (d, 2H, $CH_2$); 3.2 (d, 2H, $CH_2$); 7.48 (m, 1H, Ar); 7.59 (m, 1H, Ar); 7.97 (m, 2H, Ar).

## 3 Results and Discussion

During our work concerning the elaboration of the synthesis of different heterocycles in the presence of different mineral-based heterogeneous catalysts we described the synthesis of oxazoline [11] and imidazoline [12] derivatives, benzoxazoles [12], benzimidazoles [13], benzodiazepines [14], isoxazoles [15], isochromans [16], as well as tetrahydro- [17] and dihydroisoquinolines [18] in the Pictet-Spengler and the Bischler-Napieralsky reactions, respectively.

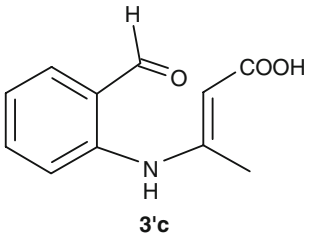
In continuation of this research work we examined the possible synthetic ways to obtain differently substituted quinoline derivatives. Recently we have published the synthesis of 2,4-disubstituted 1,2-dihydroquinolines in the modified Döbner-von Miller reaction [19].In this paper we present our results obtained during the examination of the Friedländer synthesis.

The main problem of the synthesis is the access to the starting materials. The simplest amine, *o*-amino-benzaldehyde **1a** reacts quickly in a self-condensation reaction yielding polymers. Thus, it cannot be stored for a longtime even at low temperature either. The commercially available products contain a considerable amount of polymer contaminant. Therefore we prepared the amine freshly from 2-nitro-benzaldehyde using the classical Béchamp reduction and obtained it with good yield (70%) and good purity. The other starting amine, 2-amino-acetophenone **1b** was obtained in the same way from 2-nitro-acetophenone in 92% yield.

Based on our former results we expected a one-step reaction without the isolation of any intermediate. First the reaction of the aldehyde **1a** with different ketones was tested in the presence of different acidic and basic catalysts (Fig. 2, Table 1). To suppress the polymerization of the aldehyde, 3 moles of ketones were added. In the reaction of **1a** and acetylacetone or acetophenone in the presence of the basic Mg:Al 3:1 hydrotalcite (HT) in ethanol at 60 °C for 4 h no cyclization was observed, only the intermediate enamines **3** were obtained (Table 1, entries 1 and 2).

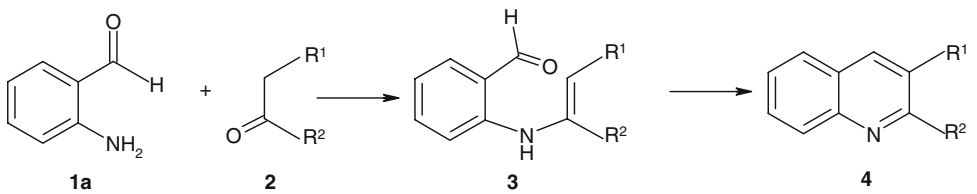
In the reaction of **1a** and ethyl acetoacetate in the presence of HT parallel with the formation of the enamine the complete hydrolysis of the ester function occurred yielding the enamine-acid **3′c** (Table 1, entry 3, Fig. 3).

As the basic HT showed no chance to obtain the desired heterocycles, we continued to work with acidic catalysts. The moderately acidic small pore-size zeolite Ersorb-4a




**3'c**

**Fig. 3**




**1a** **2** **3** **4**

**Fig. 2**

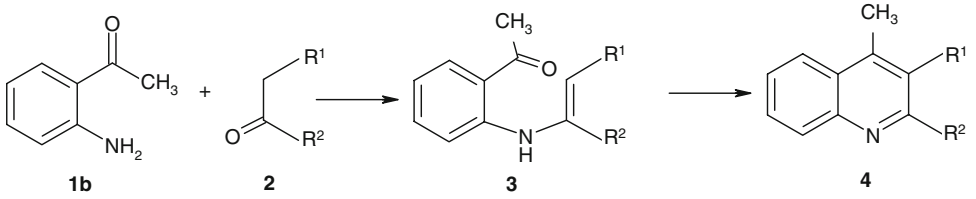



**Fig. 4**

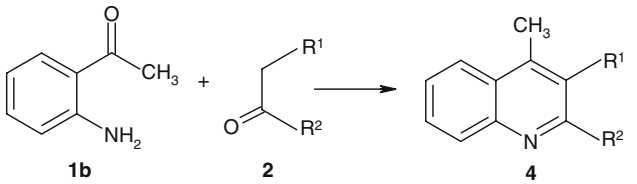



**Fig. 5**

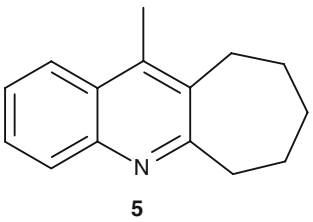



**Fig. 6**

(E4a) [19] in ethanol at 80 °C proved to be inefficient for the cyclization of **1a** and acetophenone. We tried acetone as substrate and solvent as well, in these experiments after the formation of the enamine, acetone was exchanged to xylene and the reaction was continued at 140 °C. Using E4a as catalyst an appreciable amount of the desired quinoline **4d** was observed (Table 1, entry 5). Replacing the catalyst to the known heterogeneous acid catalyst K10 montmorillonite, the yield of the desired quinoline increased to 23% (entry 6).

Whatever the reaction conditions were, large amount of polymer was obtained in these experiments. The polymerization of 2-amino-acetophenone **1b** is less dominant, thus we continued the work with this ketone (Fig. 4). When **1b** was reacted with acetone in the presence of E4a, first in acetone, then in xylene, the desired **4e** was formed in low yield (Table 2, entry 1). Acetophenone as ketone component gave better results either in xylene or without solvent (Table 2, entries 2 and 3).

Based on these results, we have reacted **1b** with different ketones without solvent, at 160 °C, in the presence of K10. The appropriate quinoline derivatives were obtained in good yield (Fig. 5, Table 3). No significant substituent effect was observed. The required amount of catalyst was 0.5 g for 5 mmol amine. None of the cases were enamine observed, but a small amount of polymer arising from **1b** was always detected on TLC. This polymer formation can explain that the conversion was not quantitative.

Under the same reaction conditions cycloheptanone gave the tricyclic 11-methyl-cyclohepta[*b*]quinoline 5 (Fig. 6) quantitatively.

This way a new, simple preparation of 2,3-substituted quinolines was developed via the simple Friedländer reaction. The method is simple and environmentally friendly.

## References


1. (a) Larsen RD, Corley EG, King AO, Carrol JD, Davis P, Verhoeven TR, Reider PJ, Labelle M, Gauthier JY, Xiang YB, Zamboni R (1996) J Org Chem 61:3398; (b) Chen YL, Fang KC, Sheu JY, Hsu SL, Tzeng CC (2001) J Med Chem 44:2374; (c) Roma G, Braccio MD, Grossi G, Chia M (2000) Eur J Med Chem 35:1021; (d) Doube D, Bloun M, Brideau C, Chan C, Desmarais S, Eithier D, Falgueyeret JP, Friesen RW, Girad M, Girad M, Guay J, Tagari P, Yong RN (1998) Bioorg Med Chem Lett 8:1255; Maguire MP, Sheets KR, Mcvety K, Spada AP, Zilberstein A (1994) J Med Chem 37:2129
2. Skraup ZH (1880) Chem Ber 13:2086
3. (a) Knorr L (1886) Annalen 236:69; (b) Hauser CR, Reynolds GA (1948) J Am Chem Soc 70:2402
4. Conrad M, Limpach L (1887) Chem Ber 20:944
5. Döbner O, Miller Wv (1883) Chem Ber 16:246
6. Combes A (1888) Bull Soc Chim 49:89
7. Friedländer P (1882) Chem Ber 15:2572
8. Jia C-S, Zhang Z, Tu S-J, Wang G-W (2006) Org Biomol Chem 4:104
9. Wu J, Xia H-G, Gao K (2006) Org Biomol Chem 4:126
10. Karthikeyan G, Perumal PT (2004) J Heterocyclic Chem 41:1039
11. Cwik A, Hell Z, Hegedüs A, Finta Z, Horváth Z (2002) Tetrahedron Lett 43:3985
12. Hegedüs A, Vígh I, Hell Z (2004) Heteroatom Chem 15:428
13. Hegedüs A, Hell Z, Potor A (2006) Synth Commun 36:3625
14. Hegedüs A, Hell Z, Potor A (2005) Catal Lett 105:229
15. Cwik A, Hell Z, Fuchs A, Halmai D (2005) Tetrahedron Lett 46:6563
16. Hegedüs A, Hell Z (2006) Org Biomol Chem 4:1220
17. Hegedüs A, Hell Z (2004) Tetrahedron Lett 45:8553
18. Hegedüs A, Hell Z, Potor A (2006) Catal Commun 7:1022
19. Hegedüs A, Hell Z, Vargadi T, Potor A, Gresits I (2007) Catal Lett 117:99