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Transition-Metal-Free Indirect Friedländer Synthesis of Quinolines from Alcohols†

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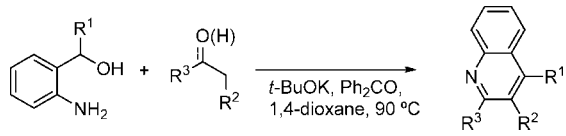

The synthesis of polysubstituted quinolines can be easily and greenly accomplished by the direct reaction between the corresponding 2-aminobenzylic alcohol derivative and either a ketone or alcohol in the presence of a base, without any transition-metal catalyst.

The presence of quinoline scaffolds in the frameworks of various pharmacologically active compounds, as well as in various natural products, has spurred the development of many different methodologies for their synthesis.[1] Among their different applications,[2] functionalized quinolines are widely used as a result of their antimalarial,[3] anti-inflamatory,[4] antiasthmatic,[5] antibacterial,[6] and antihypersensitive activities.[7]

Several different strategies for the preparation of substituted quinolines are known, with the Friedländer annulation being the most simple, straightforward, and widely used approach.[8] Nevertheless, most of the synthetic approaches reported so far suffer from need of high temperatures or harsh reaction conditions, low yields, use of hazardous and often expensive catalysts, and problems associated with the storage of carbonyl reagents. Moreover, the usual solvents employed result in very tedious workup procedures.

Some of the aforementioned drawbacks have been overcome by the use of the so-called indirect Friedländer strategy, which uses different 2-aminobenzylic alcohol derivatives **1** and ketones **2**, and it has been catalyzed by different transition-metal complexes derived from ruthenium,[9] palladium,[10] iridium,[11] rhodium,[12] and copper.[13] Even the ketone could be replaced by the corresponding alcohol.[14] However, this indirect method gave final products contaminated with traces of transition metals, which are not tolerated in some industrial applications.

The Meerwein−Ponndorf−Verley reaction is typically conducted using transition-metal catalysts.[15] However, the reaction can be performed in the absence of any type of catalysts, neither base nor metal complexes, although the reaction must be conducted under very high reaction conditions (temperatures higher than 200 °C).[16] On the other hand, the direct hydrogenation of ketones can be performed in the presence of anionic base catalysts such potassium *tert*-butoxide.[17]

† In memory of Prof. Dr. Albert I. Meyers.

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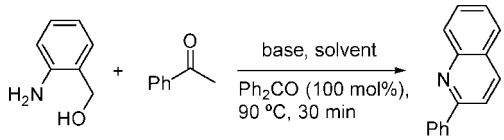
TABLE 1. Screening of the Reaction Conditions

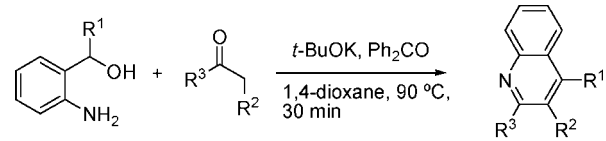


1a **2a** **3a**

entry	base	solvent	yield[a] (%)
1	KOH	1,4-dioxane	75
2	K_2CO_3	1,4-dioxane	0[b]
3	Bu_4NOH	1,4-dioxane	25
4	*t*-BuOK	1,4-dioxane	99
5	*t*-BuONa	1,4-dioxane	97
6	*t*-BuOK[c]	1,4-dioxane	40
7	*t*-BuOK	1,4-dioxane	65[d]
8	*t*-BuOK	THF	97
9	*t*-BuOK	PhMe	95
10	*t*-BuOK	*e*	98

[a] Isolated yields after acid/base extraction, using 1 equiv of compounds **1a**, **2a**, Ph_2CO, and base. [b] 2 h reaction time. [c] Reaction performed using only 10 mol% of base. [d] Reaction performed in absence of benzophenone. [e] Reaction performed under solvent-free conditions.

TABLE 2. Synthesis of Polysubstituted Quinolines



1 **2** **3**

entry	R^1	R^2	R^3	no.	yield[a] (%)
1	H	H	Ph	**3a**	99
2	H	H	4-MeC_6H_4	**3b**	99
3	H	H	pyridin-2-yl	**3c**	95
4	H	H	furan-2-yl	**3d**	96
5	H	H	thiophene-2-yl	**3e**	92
6	H	Me	Ph	**3f**	90
7	H	Et	Ph	**3g**	92
8	H	Me	Et	**3h**	99
9	H		$-(CH_2)_4-$	**3i**	92
10	Ph	H	Ph	**3j**	96
11	Ph	H	$Me(CH_2)_4$	**3k**	95[b]

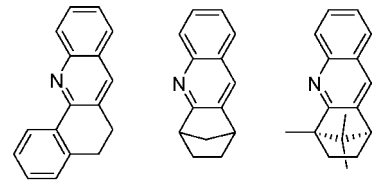
[a] Isolated yields after acid/base extraction, using 1 equiv of compounds **1**, **2**, Ph_2CO, and potassium *tert*-butoxide. [b] Only this isomer could be detected from the crude mixture.

With all these ideas on mind, we thought that a transition-metal-free Meerwein−Ponndorf−Verley reaction between 2-aminobenzyl alcohols **1** and benzophenone could be coupled to a Friedländer annulation reaction to yield the expected quinoline. To test this hypothesis, we initially performed the reaction of the alcohol **1a**, acetophenone (**2a**, 100 mol%), KOH (100 mol%), and benzophenone (100 mol%) as hydride scavenger in dioxane at 90 °C (Table 1). Surprisingly, all reagents disappeared after 30 min, giving the corresponding quinoline **3a** in a 75% yield after acidic−basic extraction (entry 1). After this initial promising result, we studied the effect of the base. The reaction with a weaker base such as the carbonate did not produce the expected quinoline after 2 h. The use of the more soluble ammonium hydroxide did not give the expected result. However, the use of a stronger base such as *tert*-butoxide, independently of the cation, gave an unbeatable result (compare entries 1−5 in Table 1). The decrease of the amount of base from stoichiometric to only 10 mol % had an impact on the result but shows that it is possible to carried out the reaction under substoichiometric conditions (entry 6). When the reaction was performed in absence of the hydride scavenger a yield higher than 50% was obtained (entry 7). That could be an important outcome to the possible mechanism since, if the hydride scavenger is necessary, the maximum yield would be 50%. The use of other solvents such as THF, toluene, or the absence of solvent did not change the results (compare entries 4 and 8−10 in Table 1), with the small differences being connected to the isolation process.

Once we found the best reaction conditions for the synthesis of quinoline **3a** (Table 1, entry 4), we expanded the protocol to other systems starting from ketones. The reaction with methyl aryl ketones gave the expected compound with excellent yields, even in the cases of using hetereoaryl ketones (see entries 1−5 in Table 2). The use of other aryl ketones with longer chains did not present any problem (compare entries 1, 6, and 7 in Table 2). Moreover, the protocol could be employed also with aliphatic ketones, with similar excellent results (entries 8 and 9 in Table 2).

The same reaction could be also performed using α-phenyl-substituted benzyl alcohol **1b** (R^1 = Ph) as shown in entries 10 and 11 in Table 2. The use of this 2-amino alcohol derivative is important since it has been described that the simple thermal or base-catalyzed Friedländer reaction with the related 2-aminobenzophenone failed to react with simple ketones, which opened the possibility of using acid catalsyts.[18] However, under these new conditions, the reaction gave the expected 4-substituted quinoline with similar results to those obtained for unsubstituted ones. It should be pointed out that the reaction is also regioselective, conducting the process through the methyl position of ketone **2** and not through the methylene one (entry 11).

Other possible challenging substrates are the corresponding bicyclic ketones. Thus, the reaction of different systems such as α-tetralone, 2-norbornanone, and (+)-camphor with the benzyl alcohol **1a** gave the corresponding polycyclic quinolines **3l**−**m** with excellent yields.



3l (99%) **3m** (97%) **3n** (60%)

Finally, it is worth noting that the reaction could be performed using simply the corresponding alcohols as depicted in Scheme 1. The reaction of 2-aminobenzylic alcohol derivative **1** with different alcohols **4**, not only secondary but also primary ones, gave the expected quinoline just by adding a double amount of the base and the hydride scavenger. The results were somewhat lower but still very competitive.

Concerning to the possible mechanism, it seems that the reaction starts with an acid−base reaction between the base and the amino alcohol **1** to give the corresponding alcoxide, which suffers a Meerwein−Ponndorf−Verley process with benzophenone giving the corresponding 2-amino aldehyde or ketone derivative and diphenylmethanol. In fact, when the reaction was performed using the related 2-aminophenyldideuteromethyl alcohol and benzophenone, deuterodiphenylmethenol was de-

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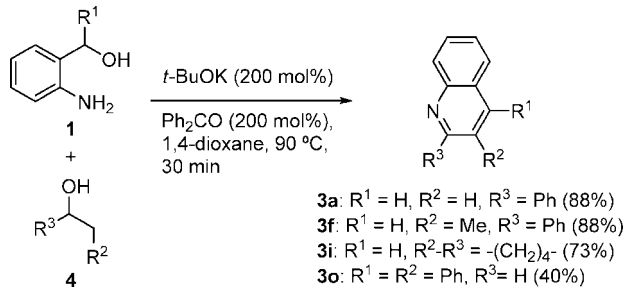
SCHEME 1. Synthesis of Quinolines Using Only Equimolecular Amounts of Alcohols



tected by ^{13}C NMR and EI-MS (three-peak multiplet at 75.5 ppm with $J_{D-C} = 22.0$ MHz and $m/z = 185$, respectively), with a yield near to 95%. It should be pointed out that the direct treatment of benzylic alcohol with potassium *tert*-butoxide under similar reaction conditions did not give any appreciable amount of benzaldehyde.[19] The process finishes with the proper Friedländer annulation.

In conclusion, we have shown that this new protocol could successfully substitute any other method for the synthesis of polysubstituted quinolines using the either classical or indirect Friedländer approach. The method is simple, environmentally benign, does not use transition metals, does not need difficult to handle and store carbonyl compounds (as the amino component), and has a very broad reagent scope, which makes it very interesting for industrial purposes.

Experimental Section

General Procedure for the Prepartion of Quinolines from 2-Aminobenzilic Alcohol Derivatives and Ketones. To a solution of the corresponding 2-aminobenzyl alcohol derivative **1** (2 mmol) in 1,4-dioxane (6 mL) were added the corresponding ketone **2** (2 mmol), benzophenone (0.36 g, 2 mmol), and potassium *tert*-butoxide (0.24 g, 2 mmol) under an argon atmosphere. The resulting mixture was heated at 90 °C with stirring for 30 min. Then,the reaction was filtered through Celite and cooled to room temperature. The resulting solution was added to a saturated solution of NH_4Cl (10 mL) and extracted with acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to give a residue, which was purified either by column chromatography on silica gel using suitable mixtures of hexane/ethyl acetate or by solving the residue in ethyl acetate (10 mL) and extracting with HCl (2 M, 3 × 10 mL) for quinolines **3a**,**b**,**f**,**g**,**j**,**l**,**n**; the resulting aqueous solution was subsequently basified with a solution of NaOH (3 M) until pH 13 to obtain a suspension that was finally extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to afford the pure quinoline **3**. Yields are included in Tables 1, 2, and in the text. Physical and spectroscopic data as well as the literature reference for the representative compound **3a** follow:

2-Phenylquinoline (3a)[9c]**:** mp 80−82 °C; $R_f = 0.61$ (hexane/EtOAc 4:1); IR (KBr) ν 3053, 1601, 1546 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.50 (m, 4H), 7.60−7.80 (m, 3H), 8.00−8.20 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.8, 126.1, 127.0, 127.3, 127.4, 128.7, 129.15, 129.5, 129.55, 136.6, 139.45, 148.1, 157.1; EI-MS m/z 206 ($M^+ + 1$, 15), 205 (M^+, 100), 204 (95), 203 (12), 102 (15).

General Procedure for the Preparation of Quinolines from 2-Aminobenzilic Alcohol Derivatives and Alcohols. The procedure was as above but the corresponding alcohol **4** (2 mmol), benzophenone (0.73 g, 4 mmol), and potassium *tert*-butoxide (0.48 g, 4 mmol) were added. The purification was performed by acid/base extraction as above for compounds **3a**,**f**,**o** and by column chromatography for compound **3i**. Yields are included in Scheme 1. Physical and spectroscopic data as well as the literature reference for representative compound **3o** follow:

3,4-Diphenylquinoline (3o)[20]**:** $R_f = 0.45$ (hexane/EtOAc 4:1); IR (KBr) ν 3063, 1560,1501 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15−7.25 (m, 7H), 7.30−7.35 (m, 3H), 7.45−7.50 (m, 1H), 7.70−7.75 (m, 2H), 8.19 (d, $J = 8.2$ Hz, 1H), 9.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.5, 126.8, 127.0, 127.2, 127.7, 128.0, 128.1, 129.0, 129.4, 130.1, 130.5, 133.1, 136.2, 138.1, 145.4, 147.5, 151.7; EI-MS m/z 282 ($M^+ + 1$, 21), 281 (M^+, 100), 280 (63), 278 (12), 266 (11), 252 (17), 139 (11).

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Supporting Information Available: Characterization and copies of ^1H and ^{13}C spectra of all compounds **3a**−**o**, as well as preparation procedures for compound **1b** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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