Tetrahedron Letters 56 (2015) 6758–6761

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Transition-metal-free synthesis of quinolines from 2-nitrobenzyl alcohol in water

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ARTICLE INFO

Article history:
Received 21 September 2015
Revised 14 October 2015
Accepted 18 October 2015
Available online 19 October 2015

Keywords:
Quinolines
2-Nitrobenzyl alcohol
Ketones
Aqueous reaction
Base

ABSTRACT

A method for the synthesis of quinolines from cheap and readily available 2-nitrobenzyl alcohol without a transition-metal catalyst in water has been developed, providing a convenient method for accessing quinolines. The reaction features an intramolecular redox process, which generates the key intermediate leading to product formation.

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Quinoline scaffold exists widely in natural products and drug molecules.[1] Due to its importance, several name reactions, e.g. Skraup,[2] Doebner Miller,[3] Conrad-Limpach,[2] Gould-Jacobs,[4] Knorr[2] and Friedländer synthesis,[5] have been developed to access quinoline compounds.[6] In the Friedländer synthesis, 2-aminobenzaldehyde, which is unstable[7] and is generally formed in-situ by the reduction of 2-nitrobenzaldehyde with stoichiometric Fe/HCl,[8] is used to react with ketones. Recent development of Friedländer synthesis has allowed the use of relatively stable 2-aminobenzyl alcohol as a precursor, which generates 2-aminobenzaldehyde through transition metal or base catalysed hydrogen transfer to ketone substrates.[9] Very recently, Jiang and co-workers reported the use of stable and easily available 2-nitrobenzyl alcohol as a precursor via a Ru catalysed hydrogen transfer strategy to synthesise quinolines at 150 °C.[10] Herein, we disclose our finding that 2-nitrobenzyl alcohol could react with ketones to form quinolines without any transition metal catalysts with water as solvent (Scheme 1).

Our initial idea was to use a metal catalyst and an alcohol as reductant to promote the reaction of 2-nitrobenzyl alcohol with a ketone to form quinolines. The reaction between 2-nitrobenzyl alcohol and propiophenone was chosen as a model, as the yield of the quinoline product from them could be easily monitored by ^{1}H NMR with an internal standard.

Various transition-metal catalysts, including iridicyles developed in our group,[11] was tested for the model substrates with isopropanol as solvent and NaOH as base at 90 °C for 12 h. The quinoline product was indeed observed, albeit with low yield (ca. 5% for all the metal catalysts tested, see Table S1). Surprisingly, running a background reaction revealed that the formation of the quinoline product did not require any transition metal catalysts (Table 1, entry 1). However, the addition of NaOH (1 equiv) is essential for the product formation. As base promoted reduction reactions have been reported,[12] the effect of different bases was then examined (Table 1, entries 1–6). A strong base, *t*-BuOK, improved the yield to 10% (Table 1, entry 5). Various solvents were then screened with *t*-BuOK as base (Table 1, entries 7–12), and the results showed that the desired product was obtained only in alcohols and water, with water giving the highest yield (Table 1, entry 12). By increasing the reaction temperature to 120 °C, the yield could be further improved to 35% in 12 h (Table 1, entry 13). With 2 equiv of *t*-BuOK at 120 °C, the yield of the desired product rose to 49% (Table 1, entry 14). When the amount of propiophenone was decreased to 1 equiv, the reaction also took place, but the yield was lower than that with 2 equiv (Table 1, entry 15). Prolonging the reaction time to 24 h led to full conversion of 2-nitrobenzalcohol, with the quinoline product isolated in 54% yield (Table 1, entry 16). Analysis of the reaction mixture revealed that ca. 37% of 2-aminobenzoic acid was formed. As *t*-BuOK will react with water to form KOH and *t*-BuOH, KOH was tested as a base in water and a similar of 53% was obtained (Table 1, entry 17).

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http://dx.doi.org/10.1016/j.tetlet.2015.10.062
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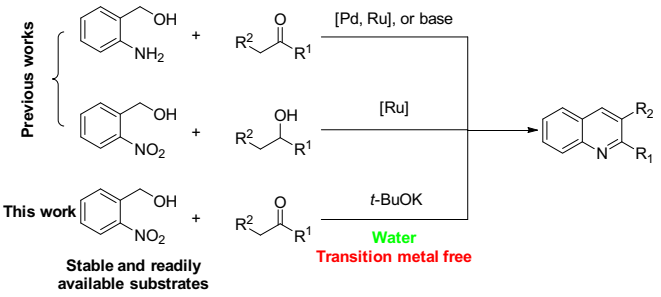
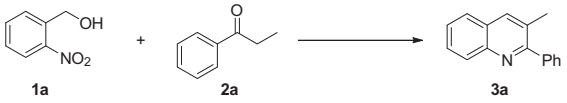


Scheme 1. Synthesis of quinolines via metal-catalysed and metal-free reactions.

Although the yield of the quinoline product was not high, the by-product could be easily separated from the desired product via simple extraction. Therefore we thought it was worth examining the substrate scope of this protocol. The results are shown in Table 2. The steric and electronic nature of substituents on the aromatic ring of aryl ketones affects the activity of the reaction. Aryl ketones with electron withdrawing *para*-substituents generally showed higher activities than ones with electron donating groups (Table 2, entries 2–9). Thus, over 60% of isolated yields were obtained for 4-Br and 4-CF_3 substituted substrates (Table 2, entries 8, 9). Substituents at *meta*-position to the carbonyl group on the aromatic ring decrease the activity of the reaction (Table 2, entries 10, 11) and only a trace amount of product was formed with *ortho*-substituted substrates. Sulfur containing substrates were tolerated (Table 2, entries 5 and 12). These might be difficult for transition metal catalysed reactions as the sulfur atom might poison the metal catalysts. The protocol is also viable for the sterically bulky 2-naphthyl acetophenone, albeit with low yield (Table 2, entry 13). However, the protocol is not applicable to aliphatic ketones, as only trace yield was obtained. Aromatic ketones other than methyl ketones also reacted, but with lower yield than the corresponding methyl ketones, probably due to their increased steric hindrance (Table 2, entries 1, 14). The practical usefulness of this method is demonstrated by a gram scale reaction of 2-nitrobenzyl alcohol with 4-bromoacetophenone (Scheme 2).

The mechanism of the reaction was next studied. It was reported that *t*-BuOK could react with organic molecules to generate radicals.[13] Thus, experiments were carried out to check the possibility

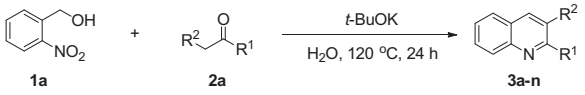
Table 1
Screening of reaction conditions[a]

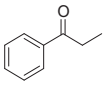
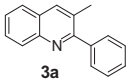
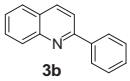
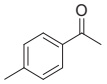
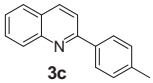
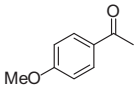
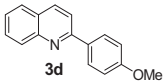
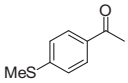
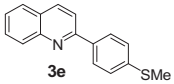
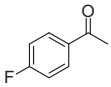
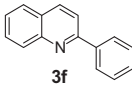
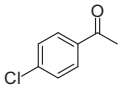
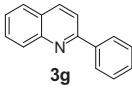
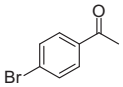
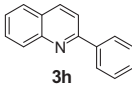
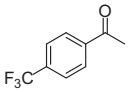
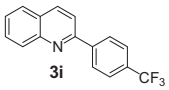
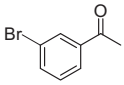
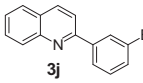
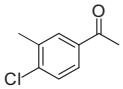
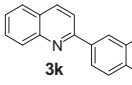
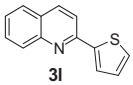
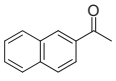
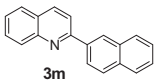
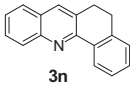


Entry	Base	Solvent	*T* (°C)	Yield (%)[b]
1	NaOH	Isopropanol	90	5
2	CH_3COONa	Isopropanol	90	0
3	K_2CO_3	Isopropanol	90	0
4	$N(Et)_3$	Isopropanol	90	0
5	***t*-BuOK**	**Isopropanol**	**90**	**10**
6	DBU	Isopropanol	90	0
7	*t*-BuOK	EtOH	90	15
8	*t*-BuOK	Pentanol	90	7
9	*t*-BuOK	1,4-dioxane	90	0
10	*t*-BuOK	DMF	90	0
11	*t*-BuOK	DMSO	90	0
12	***t*-BuOK**	**H_2O**	**90**	**22**
13	*t*-BuOK	H_2O	120	35
14[c]	*t*-BuOK	H_2O	120	49
15[d]	*t*-BuOK	H_2O	120	13
16[e]	***t*-BuOK**	**H_2O**	**120**	**54**
17	KOH	H_2O	120	53

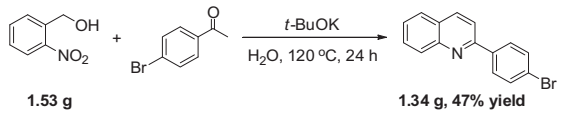
[a] Reaction condition: 2-nitrobenzyl alcohol (0.5 mmol), **2a** (1.0 mmol), base (0.5 mmol), solvent (3 mL), 90 °C, 12 h, under Ar.
[b] The yields were determined by ^1H NMR with 1,3,5-trimethoxylbenzene as internal standard.
[c] Reaction performed using 2 equiv of *t*-BuOK.
[d] The reaction was performed with the addition of 5 mol % of the phase transfer catalyst tetrabutylammonium chloride.
[e] The reaction time was 24 h.

Table 2
Synthesis of quinolines in water[a]

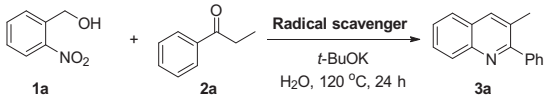


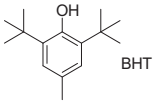
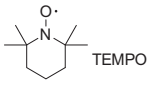
Entry	Ketone	Product	Yield (%)[b]
1		 **3a**	54
2		 **3b**	60
3		 **3c**	34
4		 **3d**	46
5		 **3e**	24
6		 **3f**	56
7		 **3g**	59
8		 **3h**	67
9		 **3i**	69
10		 **3j**	51
11		 **3k**	17
12		 **3l**	65
13		 **3m**	30
14		 **3n**	28

[a] Reaction conditions: 2-nitrobenzyl alcohol (0.5 mmol), ketone (1.0 mmol), *t*-BuOK (1.0 mmol), H_2O (3 mL), 120 °C, 24 h, under Ar.
[b] Isolated yield.

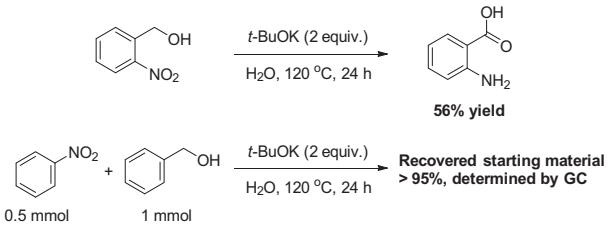


Scheme 2. Gram scale preparation of quinoline.



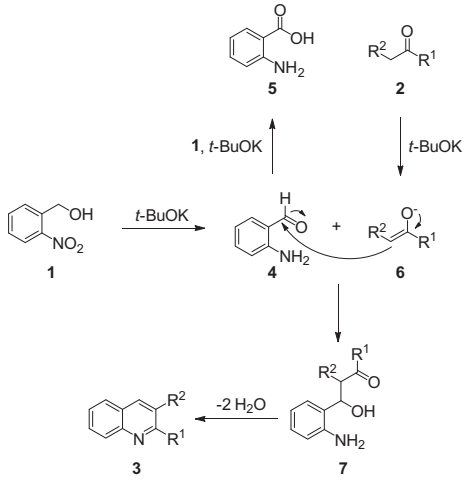
Radical scavengers	Yield (%)
	31
	39

Scheme 3. The effect of radical scavengers. Reaction conditions: 2-nitrobenzyl alcohol (0.5 mmol), radical scavenger (0.5 mmol), **2a** (1.0 mmol), *t*-BuOK (1.0 mmol), H_2O (3 mL), 120 °C, 24 h, under Ar.



Scheme 4. Intramolecular versus intermolecular hydrogen transfer.

of a radical pathway for the reaction. The addition of radical scavengers, such as TEMPO and BHT, did not inhibit the model reaction (Scheme 3), which suggests that the reaction may not proceed via radical intermediates. The drop of yields might stem from the disturbance of the physical mixture of substrates by the additional reagents, as these compounds all have small solubility in water. It



Scheme 5. Proposed reaction mechanism.

was reported that nitro groups could be reduced to amino groups with alcohols in the presence of bases.[12e] Thus, we carried out an experiment in the absence of ketone substrate under standard conditions to see if the key intermediate 2-aminobenzaldehyde could be isolated. 2-Nitrobenzalcohol was converted to 2-aminobenzoic acid instead of 2-aminobenzaldehyde in 56% yield with 2 equiv of *t*-BuOK in water at 120 °C for 24 h under Ar atmosphere (Scheme 4). The formation of 2-aminobenzoic acid might result from the Cannizzaro reaction of 2-aminobenzaldehyde intermediate, which may be formed by intramolecular hydrogen transfer mediated by the base (Scheme 5, from **1** to **5**). Subjecting **5** to the standard conditions, no reaction took place, indicating **5** is not an intermediate for quinoline formation but rather a by-product. Interestingly, little intermolecular reaction took place between nitrobenzene and benzyl alcohol under standard conditions for 24 h (Scheme 4), indicating that the reduction process is initiated by an intramolecular hydrogen transfer process. In the presence of a ketone substrate, the 2-aminobenzaldehyde intermediate will undergo an aldol reaction with the ketone substrate under basic conditions followed by cyclisation to form the quinoline product (Scheme 5).[9d,9k,9m,14]

In conclusion, a transition-metal-free protocol for the synthesis of quinolines starting from cheap and stable 2-nitrobenzyl alcohol with water as solvent has been developed. The reaction is initiated by an intramolecular hydrogen transfer process promoted by a base. This protocol provides a simple approach for the preparation of synthetically important quinolines.

Acknowledgments

We are grateful for the financial support of the National Natural Science Foundation of China (21473109), the Program for Changjiang Scholars and Innovative Research Team in University (IRT_14R33), the 111 project (B14041), Shaanxi Provincial Natural Science Foundation (2014JQ2048), the Fundamental Research Funds for the Central Universities (GK261001316, GK261001329, GK261001095), the Program for Key Science and Technology Innovative Team of Shaanxi Province (2012KCT-21 and 2013KCT-17), and the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.062.

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