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

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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.

Quinoline scaffold exists widely in natural products and drug molecules. Due to its importance, several name reactions, e.g. Skraup, Doebrner Miller, Conrad-Limpach, Gould-Jacobs, Knorr and Friedländer synthesis, have been developed to access quinoline compounds. In the Friedländer synthesis, 2-aminobenzaldehyde, which is unstable and is generally formed in-situ by the reduction of 2-nitrobenzaldehyde with stoichiometric Fe/HCl, 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. 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. 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 1H NMR with an internal standard.

Various transition-metal catalysts, including iridicyles developed in our group, 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, 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).
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-CF₃ 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. Thus, experiments were carried out to check the possibility

<table>
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<th>Entry</th>
<th>Ketone</th>
<th>Product</th>
<th>Yield (%)</th>
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<td>3a</td>
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</tr>
<tr>
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<td></td>
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<tr>
<td>14</td>
<td></td>
<td>3n</td>
<td>28</td>
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</table>

* a Reaction conditions: 2-nitrobenzyl alcohol (0.5 mmol), ketone (1.0 mmol), t-BuOK (1.0 mmol), H₂O (3 mL), 120 °C, 24 h, under Ar.
  * b Isolated yield.
was reported that nitro groups could be reduced to amino groups with alcohols in the presence of bases.\textsuperscript{12c} 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).\textsuperscript{24,26}()

Acknowledgments

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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.

References and notes


