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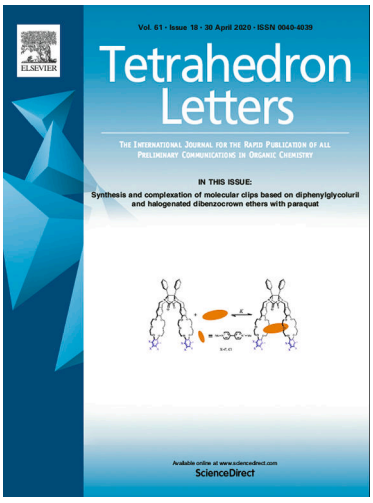

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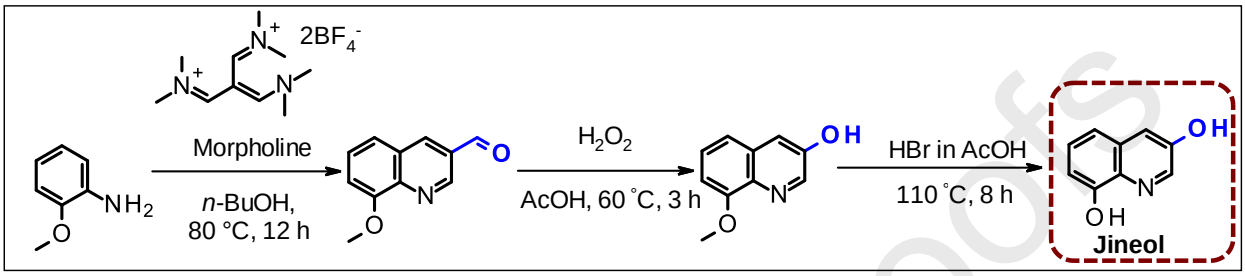

Convenient Synthesis of 3-Hydroxyquinolines via Dakin Oxidation: A Short Synthesis of Jineol

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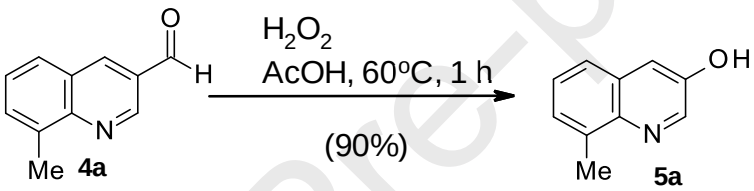
Abstract: A convenient synthesis of 3-hydroxyquinolines has been described via unprecedented Dakin oxidation of quinoline-3-carboxaldehydes. Subsequently, application of the methodology to a high yielding synthesis of quinoline alkaloid Jineol (**1**) is reported.

Keywords: Quinoline, Quinoline-3-carboxaldehyde, 3-Hydroxyquinoline, Dakin Oxidation, Jineol, Total synthesis

The quinoline core is a very common structural motif in both natural products and synthetic organic molecules of biological interest.[1] 3-Hydroxyquinolines and their derivatives possesses various pharmacological activities and also widely occur naturally.[2] Jineol (**1)** is one of such naturally occurring 3-hydroxyquinoline first isolated from the centipede *Scolopendra subspinipes* in 1996 and reports to have antioxidant properties and shows cytotoxic activity *in vitro* against the growth of various human tumor cell lines.[3] Therefore, novel and innovative synthetic methodologies for such 3-hydroxyquinolines are highly desirable. Most commonly employed procedures for the synthesis of 3-hydroxyquinolines involve multi step synthesis starting from suitably substituted aniline or indole via isatin.[4] Direct transformation of 3-functionalized quinolines such as 3-amino quinolines, 3-haloquinolines or quinoline-3-boronic acids to the corresponding 3-hydroxyquinolines are also reported.[5] All of these methodologies either requires expensive metal catalysts or multistep synthesis of starting materials. Herein, we report a simple and efficient methodology for the synthesis of 3-hydroxyquinolines from quinoline-3-carboxaldehydes; which could be easily accessed in single step from aniline by the reaction of vinamidinium salt.[6] We have also shown that the methodology is applicable for the shortest total synthesis of quinoline alkaloid Jineol (**1)**.

There are ample numbers of reports available for direct conversion of substituted benzaldehyde to the corresponding phenol via Dakin oxidation. In general, Dakin oxidation is limited to use for the oxidation of *o*- or *p*-hydroxylated benzaldehydes by alkaline H_2O_2.[7] In some cases H_2O_2 mediated acid catalysed conversion of suitably substituted benzaldehyde to the phenol are also reported.[8] Hydrogen peroxide mediated Dakin oxidation of 4-hydroxy quinoline-3-carboxaldehydes and *m*-CPBA mediated Dakin oxidation of 4-amino quinoline-3-carboxaldehyde have also been reported however, no substrates scope were explored.[9] To the best of our knowledge there is no report for Dakin oxidation of quinoline-3-carboxaldehydes containing no hydroxy or amine substitution. Therefore, we decided to investigate further to develop an efficient and general methodology for the direct oxidation of quinoline-3-carboxaldehydes to 3-hydroxyquinolines.



Scheme 1. Dakin oxidation of 8-methylquinoline-3-carboxaldehyde (**4a**)

We commenced the optimization work with 8-methylquinoline-3-carboxaldehyde (**4a**) and treated with different oxidizing agents under different conditions (such as *m*-CPBA, H_2O_2, *t*-BuOOH, urea hydrogen peroxide etc.) both in acidic and alkaline conditions in different solvents.[10] In most of the cases instead of desired hydroxy quinoline **5a**, acid of **4a** was obtained as major by-product. However, treatment of **4a** with H_2O_2 (3.0 equiv.) in acetic acid at 60 °C afforded the best result and 8-methylquinoline-3-ol (**5a**) was obtained as the major product with an isolated yield of 90% (Scheme1).[11] It seems peracetic acid, which is generated in-situ from acetic acid and hydrogen peroxide play the key role for the desired oxidation. This was confirmed by doing the reaction with peracetic acid (3.0 equiv.) in acetonitrile under same reaction condition, which afforded comparable result as H_2O_2/AcOH condition (for details see supporting information).[10]

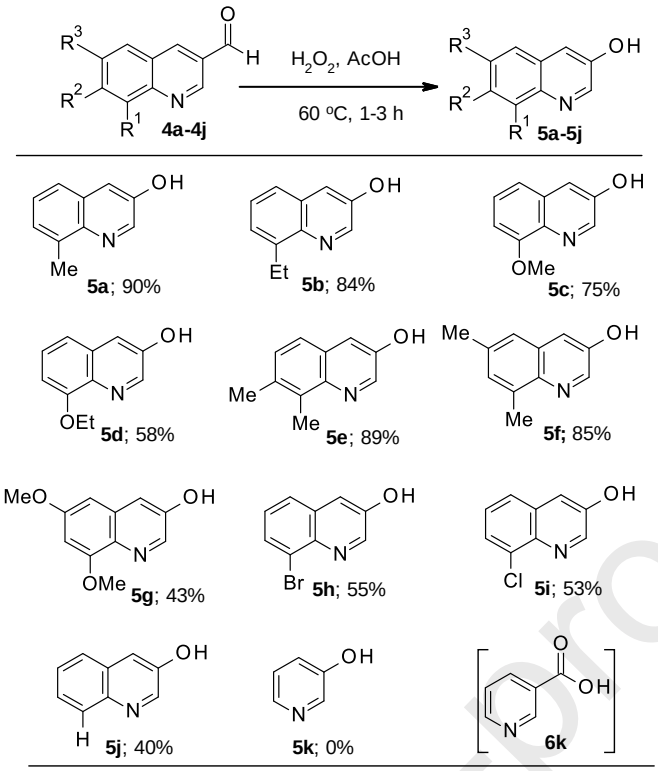
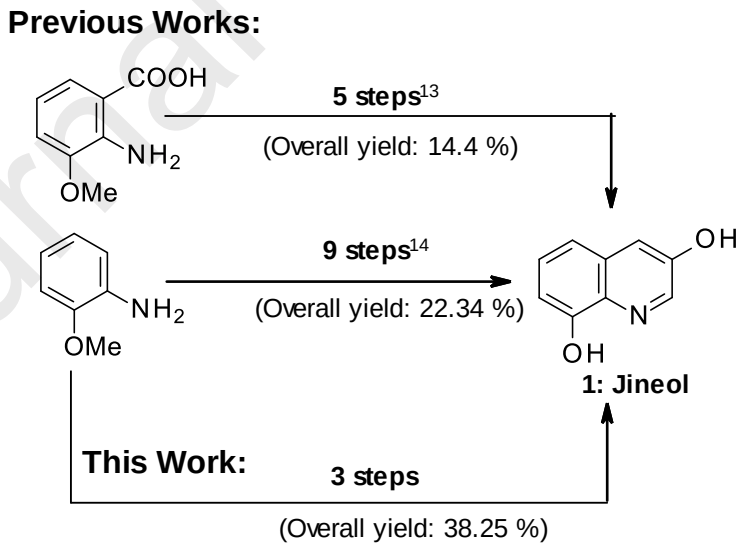


Table 1. Scope of Dakin oxidation of quinoline-3-carboxaldehydes to 3-hydroxyquinolines.

To determine scope of the reaction, a brief array of quinoline-3-carboxyldehydes (**Table 1**, **4a-4j**) was subjected under the optimized condition. Obtained results indicate that both the steric bulk at 8-position of quinoline-3-carboxldehydes as well as electronic nature of the substituents in quinoline ring play important role for the success of the desired Dakin reaction. Quinoline-3-carboxaldehyde having methyl (**4a**) or methoxy (**4c**) at 8-position afforded higher yield than quinoline-3-carboxaldehyde have ethyl (**4b**) or ethoxy (**4d**) at 8-position (**Table 1**, **5a-5d**) could be due to higher steric bulk of methyl and methoxy. All the 8-substituted quinoline-3-carboxaldehydes afforded desired hydroxyl product (**Table 1**, **5a-5i**) in good to excellent yield. On the other hand, under same reaction condition yield for non-substituted quinoline-3-carbaxldehyde found to be low (**Table 1**, **5j**) and major by-product obtained was the quinoline-3-carbaxlic acid. This is probably due to less steric bulk of hydrogen at 8-position compare to methyl or ethyl substitution. The analogy was further confirmed with the reaction of pyridine-3-carboxldehydes. Unlike quinoline-3-carboxaldehyde, pyridine-3-carboxaldehyde has no steric bulk near the nitrogen and under same condition it failed to give any desired hydroxyl product (**5k**) instead it afforded pyridine-3-carboxylic acid (**6k**) as the sole product. Presence of highly electron donating substituents (OMe or OEt) at 8-position afforded lower yield (**Table 1**, **5c** and **5d**); which is contrary to the yield in Dakin reaction. Presence of electron donating moiety is known to facilitate the formation of Dakin oxidation product in

benzaldehyde system. However, when the products in these reactions were analysed, it was found that the starting aldehydes were fully consumed, and the major by-product formed is *N*-oxide of the desired 3-hydroxy quinolines. This could be due to increase in electron density in the *N*-containing ring of quinoline 3-carboxaldehyde, which is expected to increase the reactivity towards formation of Dakin oxidation product as well as *N*-oxide product. The same trend was observed in the reaction of 6, 8-dimethoxy 3-carboxaldehyde (**4g**), which is even more electron rich than 8-mono alkoxide quinoline 3-carboxaldehydes and afforded lower yield of hydroxyl product (**5g**) along with more of corresponding *N*-oxide product. These results indicate that too much enrichment of the electron density in the ring is not suitable for the reaction. However, both the di-methyl substituted quinoline 3-carboxaldehydes afforded similar yield (**Table 1**, **5e, 5f**) as mono methyl substituted quinoline 3-carboxaldehyde (**5a**). Probably the mild electron donating property of one extra methyl in **4e** or **4f** is not enough to increase electron density in *N*-containing ring to form considerable amount *N*-oxide by-product, therefore, there is no significant impact on the yield of desired **5e** or **5f**. Presence of electron withdrawing group at 8-position of quinoline-3-carboxaldehyde (**Table 1**, **5h, 5i**) also participated in desired Dakin oxidation though in low yields.

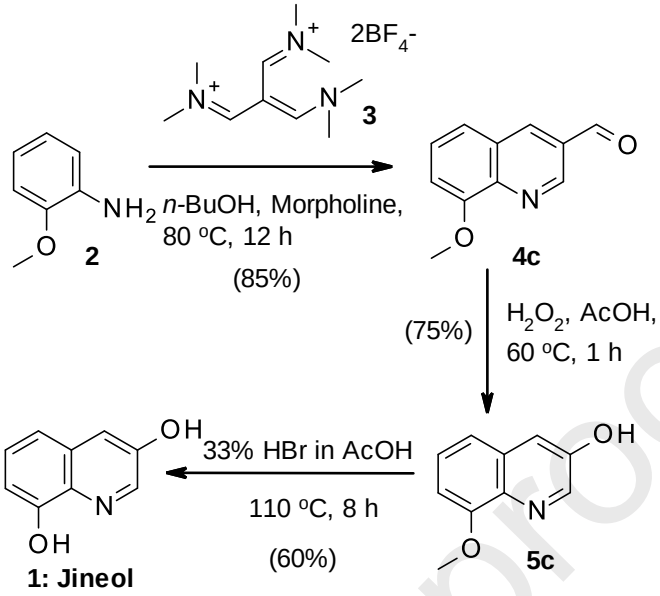
Having a general methodology for the synthesis of 3-hydroxy quinoline in hand, we wanted to implement the same for the synthesis of 3-hydroxyquinoline alkaloid Jineol (**1)**.



Scheme 2. Synthesis of Jineol (**1**) from aniline derivatives in the context of present work.

So far, there are three reports known for the synthesis of Jineol (**1)**. One of them are direct hydroxylation of pre-functionalized quinoline moiety.[12] Two other reports starts from aniline derivatives, which involve multi-step sequences and poor overall yields (**Scheme 2**).[13,

[14] In our strategy, we proposed a short synthesis starting from 2-methoxy aniline (**2**) via synthesis of quinoline carboxaldehyde **4c** followed by Dakin oxidation and de-methylation.



Scheme 3. Synthesis of Jineol (**1**) via Dakin oxidation.

Our initial attempts for the synthesis of quinoline carboxaldehyde **4c** from 2-methoxy aniline (**2**) with the reaction of vinamidinium salt **3** in EtOH or AcOH[6] found to be low yielding. However, when the reaction was performed in *n*-BuOH in the presence of morpholine (3.0 equiv.) at 80 °C, desired 8-methoxy quinoline-3-carboxaldehyde (**4c**) was obtained in 85% yield (**Scheme 3**). To our gratification, 8-methoxyquinoline-3-carboxaldehyde was nicely converted to the desired hydroxy intermediate **5c** in 75% yield under previously optimized condition. The de-methylation of **5c** was found to be critical and low yielding. After careful examination of the reagents (e.g. BBr_3, TMSI, Py.HCl, HI, $MgBr_2$ etc.) 33% HBr in acetic acid found to be the best for de-methylation and afforded desired Jineol (**1**) in 60% yield. The structure of synthesized Jineol (**1**) was confirmed by complete spectral (IR, ^1H, ^{13}C and HRMS) analysis. The melting points and spectral data were in excellent agreement with the reported values.[13]

In summary, we have introduced a convenient and simple methodology for the synthesis of 3-hydroxy quinolines via unprecedented Dakin oxidation of quinoline-3-carboxaldehydes. The methodology proved to be useful in achieving a short and high yielding total synthesis of Jineol (**1**). Efforts are currently underway in our research group to apply this method to the synthesis of natural products having 3-hydroxyquinoline moiety and other potentially valuable organic molecules.

Acknowledgments

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10. Detailed outcome of the screening of oxidizing reagents and solvents are presented in the experimental section.
11. **General procedure for the synthesis of 3-Hydroxyquinolines 5a-5j:** To a stirred solution of quinoline-3-carboxaldehyde derivative **4a-4j** (0.01 mol) in acetic acid (5 mL) at r.t. was added H_2O_2 solution (30 % in water) (3 equiv., 0.03 mol). The reaction mixture was heated at 60°C for 1-3 h under N_2 atmosphere. After the consumption of starting material, the reaction mixture was concentrated under reduced pressure, quenched with 5% aq. sodium metabisulphite solution (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine solution (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by CombiFlash chromatography (silica-gel; cyclohexane-EtOAc) to afford the desired 3-hydroxyquinoline derivatives **5a-5j**.

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Highlights:

- Simple methodology for the synthesis of 3-hydroxy quinolines.
- Unprecedented Dakin oxidation of quinoline-3-carboxaldehydes.
- Substituted quinoline-3-carboxaldehydes are more suitable for Dakin oxidation.
- Efficient total synthesis of quinoline alkaloid Jineol via Dakin oxidation.