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One Step Synthesis of 4-Ethoxy-1,2,3,4-Tetrahydroquinoline from Nitroarene and Ethanol: A TiO_2 Mediated Photocatalytic Reaction

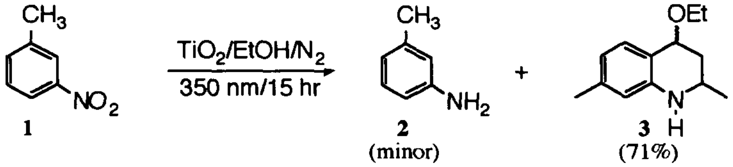
Koon Ha Park,* Hyun Sang Joo, Kyung Il Ahn, and Kun Jun

Department of Chemistry, Chungnam National University
Taejon 305-764, Korea

Abstract: 4-Ethoxy-1,2,3,4-tetrahydroquinoline is formed in a one pot reaction from a heterogeneous solution of nitroarene, ethanol, and TiO_2 by UV light (λ=350 nm).

Titanium(IV) oxide (TiO_2) has attracted much attention since the discovery of the photo Kolbe reaction[1] due to its photocatalytic properties in diverse systems. For instance, TiO_2 is documented to be an efficient catalyst in organic transformations[2] and in detoxification of water contaminated by either surfactants[3] or other organic materials as well.[4] A recent report demonstrates that platinized TiO_2 is a successful catalyst in the selective N-cyclization of Nε-carbamyl-L-lysine into almost optically pure L-pipecolinic acid.[5] In spite of numerous reports relating to TiO_2, however, examples of inducing intermolecular C-C bonding are rather limited in the literature.

Herein, we report a one pot synthesis of 4-ethoxy-1,2,3,4-tetrahydroquinoline from a heterogeneous solution of nitroarene, ethanol, and TiO_2 upon irradiation by UV light (λ=350 nm). A prototype reaction, using 3-nitrotoluene (**1**) as a substrate, is shown below.[6]



Under the reaction conditions specified above, nitroarene **1** is converted smoothly to 2,7-dimethyl-4-ethoxy-1,2,3,4-tetrahydroquinoline **3** with small amounts of a reduced product, m-toluidine **2**. This reaction is applicable to other substrates. Thus, p-nitrotoluene and nitrobezene produce 2,6-dimethyl-4-ethoxy-1,2,3,4-tetrahydroquinoline and 4-ethoxy-2-methyl-1,2,3,4-tetrahydroquinoline[7] respectively with yields of about 70%. Substrates having either oxygen or amino substituents such as m-nitroanisole etc. proceed rather slowly compared to those having alkyl substituent under the same reaction conditions.

In the literature, it is reported that nitroarene is reduced to the aniline derivative in high yield on being irradiated by UV light in the presence of semiconductor powders for 15 min.[8] The reduction of nitroarene to an aniline derivative was confirmed in our reaction also. i.e. when the relative formation of products **2** and **3** were analyzed versus time, it was observed that only **2** accumulated initially until 10% conversion. Afterwards the concentration of **2** remained almost constant. Instead the cyclized product **3** began to form.

At the same time, it was detected by gas chromatography that the reaction mixture contained both acetaldehyde and acetaldehyde diethyl acetal, which obviously were formed photocatalytically, mediated by TiO_2. Without TiO_2 no reaction proceeded. The redox catalysis by TiO_2 upon nitroarene and ethanol is shown below.

$$TiO_2 \xrightarrow{h\nu} TiO_2\,(e^-, h^+)$$

$$\text{Ar-NO}_2 \xrightarrow{e^-} \longrightarrow \text{Ar-NH}_2 \qquad CH_3CH_2OH \xrightarrow{h^+} \longrightarrow CH_3CHO$$

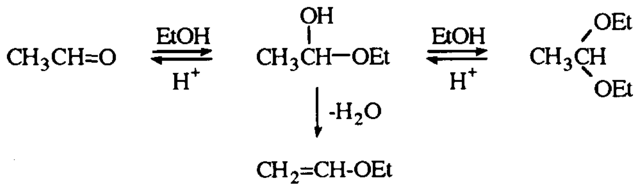
The photocatalytic formation of acetaldehyde from ethanol is consistent with the earlier reports.[9-12] Based on the results, it would be reasonable to suppose that tetrahydroquinoline would be formed by thermal reaction of aniline prepared photocatalytically *in situ* with an intermediate having 4 carbon atoms made photocatalytically from two molecules of ethanol. A first candidate was crotonaldehyde which was supposed to be formed by the aldol condensation of acetaldehyde.[13] However thermal reaction of crotonaldehyde with aniline did not produce any quinoline.

For the formation of tetrahydroquinoline in the reaction of aniline with acetaldehyde, the Doebner-von Miller reaction might be conceived.[14,15] The Doebner-von Miller reaction is generally described to proceed through the condensation of a Schiff's base and an enamine formed from an aniline derivative and acetaldehyde to give 4-hydroxy- or 4-anilino-1,2,3,4-tetrahydroquinoline as intermediates, finally leading to a quinaldine derivative. In this regards, our reaction is unique in obtaining 4-ethoxy-1,2,3,4-tetrahydroquinoline, which has not been reported as one of the intermediates in the Doebner-von Miller reaction.

In order to have more knowledge of our reaction, **1** was reacted in deuterated ethanol (CH_3CH_2OD). After work-up it was found by ^1H NMR that no deuterium was incorporated into the product **3**. This result indicated therefore that the reaction did not proceed via the aldol condensation of acetaldehydes.[13,14] If the α,β–unsaturated aldehyde is an intermediate, at least one deuterium would have been incorporated at the C-3 position of the heterocyclic ring. Therefore it would be reasonable to suppose that the product **3** would be obtained by the intervention of a species consisting of a C_2 unit derived from acetaldehyde.

Among the possible candidates, ethyl vinyl ether which might be formed from either hemiacetal or acetal is believed to be the best one. We tried but were not able to detect it in the reaction. We believe that ethyl vinyl ether would be produced in low concentration and furthermore would be consumed readily. In fact, when ethyl vinyl ether was made to react with N-ethylideneaniline, the reaction was completed within 4 hr. Overall we believe that ethyl vinyl ether would be formed as follows.

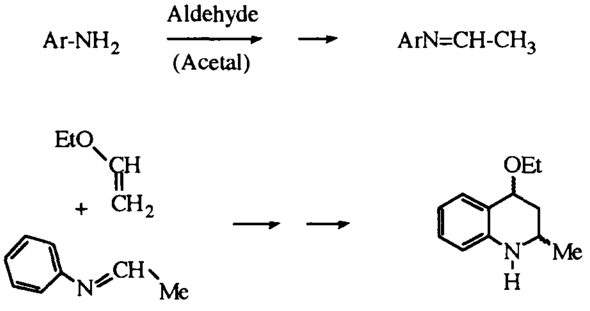
Once the ethyl vinyl ether is available in the reaction mixture, it would react with N-ethylideneaniline to make 4-ethoxy-1,2,3,4-tetrahydroquinoline.



$$CH_3CH{=}O \underset{H^+}{\overset{EtOH}{\rightleftharpoons}} CH_3CH(OH){-}OEt \underset{H^+}{\overset{EtOH}{\rightleftharpoons}} CH_3CH(OEt)_2$$

$$CH_3CH(OH){-}OEt \xrightarrow{-H_2O} CH_2{=}CH{-}OEt$$

A mechanism for the formation of 4-ethoxy-1,2,3,4-tetrahydroquinoline in the photcatalytic reaction of nitrobenzene in ethanol is proposed as follows.



$$Ar{-}NH_2 \xrightarrow[\text{(Acetal)}]{\text{Aldehyde}} \longrightarrow ArN{=}CH{-}CH_3$$

To our knowledge, reports of the synthesis of tetrahydroquinoline derivatives are rare in the literature. Earlier, Povarov reported the reaction of aromatic amines with vinyl alkyl ethers to make 4-ethoxy-1,2,3,4-tetrahydroquinoline in the presence of a Lewis acid.[16]

In conclusion, our procedure provides a method for the synthesis of 4-ethoxy-1,2,3,4-tetrahydroquinoline starting from nitroarene and ethanol just by irradiation in the presence of TiO_2. This work will continue to determine the stereochemistry of the product **3**.

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6. A similar procedure as Mahdavi's was adopted except the concentration of substrate: A heterogeneous solution of ethanol (200 mL), m-nitrotoluene (2 mmol) and TiO_2 (0.5 g, Junsei Chemical Co.) in a 500 mL Pyrex round-bottomed flask was flushed with nitrogen for 30 min. After the flask was sealed with a rubber septum, the reaction mixture was stirred and irradiated in a Rayonet photochemical reactor (model # RPR-100) equipped with 16 lamps (RPR-3500A) for 10 hrs. After irradiation, TiO_2 was filtered off and the filtrate was subjected to HPLC for the determination of the yield (70%). The isolation was performed by column chromatography on a silica gel column by eluting with a co-solvent of hexane and ethyl acetate (volume ratio;8:2).
7. 2,7-Dimethyl-4-ethoxy-1,2,3,4-tetrahydroquinoline **3**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.15-1.21(m, 6 H), 1.38-1.44 (td, 1 H, J=12.0, 3.0), 2.00-2.04 (dt, 1 H, J=13.40, 2.6), 2.20 (s, 3 H), 3.51-3.58 (m, 3 H), 3.75 (s, br., 1 H), 4.22 (t, 1 H, J=2.9), 6.28 (s, 1 H), 6.42-6.43 (dd, 1 H, J=7.6, 1.1), 6.95-6.97 (d, 1 H, J=7.6); ^{13}C NMR (500 MHz, $CDCl_3$) δ 15.4, 21.0, 21.9, 35.5, 41.9, 62.7, 72.4, 115.6, 116.4, 130.7, 131.7, 138.5, 144.6. 2,6-Dimethyl-4-ethoxy-1,2,3,4-tetrahydroquinoline: ^1H NMR (500 MHz, $CDCl_3$) δ 1.19-1.23 (m, 6 H), 1.41-1.47 (td, 1 H, J=12.8, 3.1), 2.04-2.08 (dt, 1 H, J=13.4, 2.6), 2.21 (s, 3 H), 3.53-3.62 (m, 4 H), 4.23-4.25 (t, 1 H, J=2.8), 6.43-6.44 (d, 1 H, J=8.2), 6.86-6.88 (dd, 1 H, J=8.1), 6.92 (s, 1 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 15.6, 20.3, 22.1, 35.5, 42.1, 63.0, 72.8, 114.5, 119.9, 125.5, 129.7, 131.1, 142.6. 4-Ethoxy-2-methyl-1,2,3,4-tetrahydroquinoline : ^1H NMR (500 MHz, Acetone-d_6) δ 1.11-1.13 (t, 3 H, J=7.0), 1.18-1.20 (d, 3 H, J=6.4), 1.33-1.39 (td, 1 H, J=11.8, 3.1), 2.03-2.05 (m, 1 H),.3.50-3.56 (m, 3 H), 4.23-4.24 (t, 1 H, J=2.9), 6.49 (td, 1 H, J=7.3, 1.1), 6.54 (dt, 1 H, J=8.1, 0.5), 6.96 (m, 1 H), 7.03 (dd, 1 H, J=7.3, 1.1), ^{13}C NMR (500 MHz, $CDCl_3$) δ 15.9, 22.2, 36.4, 42.5, 63.3, 73.8, 114.8, 115.8, 120.3, 129.4, 131.6, 146.5.
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