

# Oxidative aromatization and *N*-oxidation of 1,2,3,4-tetrahydroquinoline and -isoquinoline derivatives using sodium tungstate in the presence of activated carbon-molecular oxygen

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## ABSTRACT

1,2,3,4-tetrahydroquinoline and -isoquinoline derivatives were oxidatively aromatized to the corresponding quinolines or isoquinolines and oxygenated to the corresponding quinolines or isoquinoline *N*-oxides in moderate yields using molecular oxygen as an oxidant and sodium tungstate as a catalyst in the presence of activated carbon in MeOH or xylenes. The present oxidation process revealed the importance of activated carbon, without which the oxidation would not proceed. Additionally, it serves as an example of an environmentally benign oxidative process conducted using molecular oxygen in place of harmful metal oxidants like CrO<sub>3</sub>, Pb(OAc)<sub>4</sub>, or Hg(OAc)<sub>2</sub>.

**KEYWORDS:** aromatization, activated carbon, sodium tungstate, oxidation, *N*-oxidation, molecular oxygen, 1,2,3,4-tetrahydroquinoline

## INTRODUCTION

The sodium tungstate (Na<sub>2</sub>WO<sub>4</sub>·2H<sub>2</sub>O)-catalyzed oxidation of 1,2,3,4-tetrahydroquinolines with 30% aqueous hydrogen peroxide solution in methanol gives 1-hydroxy-3,4-dihydroquinolin-2(1*H*)-ones, which have potent biological activities, in good to excellent yields [1]. However, this

oxidation process requires an excess amount of hydrogen peroxide, which is a strong oxidizer, is caustic, and does not give quinolines or quinoline *N*-oxides as oxidation products. Recently, various types of oxidations have been developed using molecular oxygen in the presence of activated carbon [2], which is an environmentally friendly, reusable, and inexpensive substance. Herein we examined the oxidation of 1,2,3,4-tetrahydroquinolines and -isoquinolines using a metal catalyst and molecular oxygen as an oxidant in the presence of activated carbon.

## MATERIALS AND METHODS

Medium-pressure liquid chromatography (MPLC) was carried out with a Yamazen 540 FMI-C pump and a Wakogel FC-40 (20-40 μm, Wako). Darco KB (100 mesh, wet powder, Aldrich) was used as the activated carbon in the present reaction. The spectral data of all products agreed with those of authentic samples.

### General procedure for oxidative aromatization and *N*-oxidation of 1,2,3,4-tetrahydroquinoline or -isoquinoline derivatives using metal catalyst in the presence of activated carbon-molecular oxygen

A mixture of 1,2,3,4-tetrahydroquinoline or -isoquinoline derivative (3.75 mmoles), activated carbon (Darco KB, 50 wt%) and metal catalyst (2 mol% or 6 mol%) was heated with stirring

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while bubbling the molecular oxygen into the solvent according to the reaction conditions described in tables 1 and 2. The resulting solution was filtered and the solvent was evaporated to give the residue, which was worked up in the manner as described below.

#### Work-up of reaction of 1,2,3,4-tetrahydroquinoline derivative

The residue was purified by MPLC to afford the quinoline derivative (with hexane:ethyl acetate = 20:1 or 10:1) and the quinoline *N*-oxide derivative (with ethyl acetate) in the yields shown in tables 1 and 2.

#### Work-up of reaction of 1,2,3,4-tetrahydroisoquinoline

The residue was purified by MPLC to afford isoquinoline and 3,4-dihydroisoquinoline (with hexane:ethyl acetate = 20:1 or 10:1) and

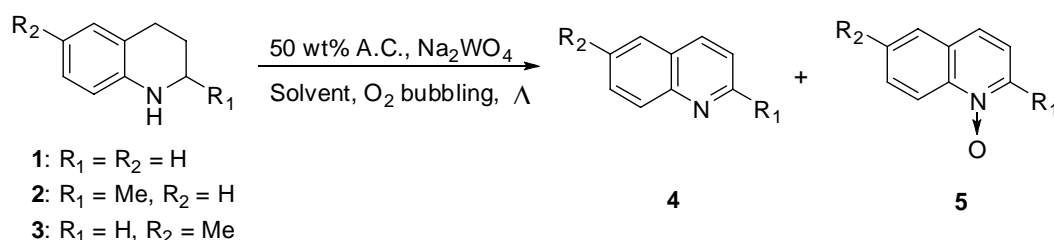
isoquinoline *N*-oxide (with ethyl acetate) in the yields shown in scheme 1.

## RESULTS AND DISCUSSION

The general procedure of the present reaction is as follows. A mixture of 1,2,3,4-tetrahydroquinoline (3.75 mmol), activated carbon (Darco KB, 50 wt%) and Na<sub>2</sub>WO<sub>4</sub>·2H<sub>2</sub>O (2 mol%) was heated with stirring for 24 h while bubbling the molecular oxygen into the solvent. After filtration, the usual work-up of solvent evaporation and SiO<sub>2</sub>-purification gave quinolines and quinoline 1-oxides in the yields shown in table 1.

Similarly, the oxidation of the parent 1,2,3,4-tetrahydroisoquinoline in xylenes using sodium tungstate and molecular oxygen in the presence of activated carbon gave 3,4-dihydroisoquinoline [5] (68%), isoquinoline (12%) and isoquinoline *N*-oxide (4%) (Scheme 1).

**Table 1.** Oxidation of 1,2,3,4-tetrahydroquinolines using Na<sub>2</sub>WO<sub>4</sub> and O<sub>2</sub> in the presence of A.C.



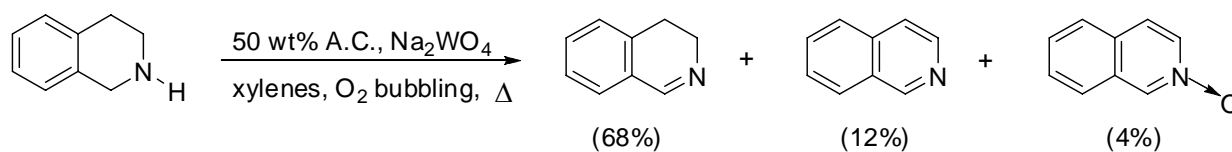
| Reactant | Solvent            | A.C. <sup>a</sup> | Na <sub>2</sub> WO <sub>4</sub> <sup>b</sup> | O <sub>2</sub>      | Temp. (°C) | Time (h) | Yield of 4 (%)  | Yield of 5 (%)  |
|----------|--------------------|-------------------|--|---------------------|------------|----------|-----------------|-----------------|
| 1        | MeOH               | 50 wt%            | 2 mol%                                       | atm. <sup>c</sup>   | reflux     | 24       | trace           | -               |
|          | MeOH               | 50 wt%            | 2 mol%                                       | bubbl. <sup>d</sup> | reflux     | 24       | 17 <sup>e</sup> | 57 <sup>e</sup> |
|          | MeOH               | 50 wt%            | -  | bubbl.              | reflux     | 24       | 52              | -               |
|          | MeOH               | -                 | 2 mol%                                       | bubbl.              | reflux     | 24       | -               | -               |
|          | xylenes            | 50 wt%            | 2 mol%                                       | bubbl.              | 130        | 24       | 78              | 18              |
|          | xylenes            | 50 wt%            | 6 mol%                                       | bubbl.              | 130        | 24       | 73              | 24              |
|          | CH <sub>3</sub> CN | 50 wt%            | 2 mol%                                       | bubbl.              | reflux     | 24       | 34              | 4               |
|          | dioxane            | 50 wt%            | 2 mol%                                       | bubbl.              | reflux     | 24       | 31              | trace           |
| 2        | MeOH               | 50 wt%            | 2 mol%                                       | bubbl.              | reflux     | 24       | 12 <sup>e</sup> | 20 <sup>f</sup> |
| 3        | MeOH               | 50 wt%            | 2 mol%                                       | bubbl.              | reflux     | 24       | 33 <sup>e</sup> | 44 <sup>g</sup> |

<sup>a</sup>A.C.: activated carbon; <sup>b</sup>Na<sub>2</sub>WO<sub>4</sub>·2H<sub>2</sub>O: sodium tungstate(VI) dihydrate; <sup>c</sup>atm.: atmosphere; <sup>d</sup>bubbl.: bubbling; <sup>e</sup>commercially available from Aldrich Co.; <sup>f</sup>Reference [3]; <sup>g</sup>Reference [4].

**Table 2.** Oxidation of 1,2,3,4-tetrahydroquinoline using a variety of catalysts and O<sub>2</sub> in the presence of A.C.

| Run | Catalyst <sup>a</sup>                       | Solvent | A.C.   | O <sub>2</sub> | Temp. (°C) | Time (h) | Yield of 4 (%) | Yield of 5 (%) |
|-----|---|---------|--------|----------------|------------|----------|----------------|----------------|
| 1   | Na <sub>2</sub> WO <sub>4</sub>             | MeOH    | 50 wt% | bubbl.         | reflux     | 24       | 17             | 57             |
| 2   | Re <sub>2</sub> O <sub>7</sub> <sup>b</sup> | MeOH    | 50 wt% | bubbl.         | reflux     | 24       | 31             | Trace          |
| 3   | MTO <sup>c</sup>                            | MeOH    | 50 wt% | bubbl.         | reflux     | 24       | 31             | Trace          |
| 4   | VO(acac) <sub>2</sub> <sup>d</sup>          | MeOH    | 50 wt% | bubbl.         | reflux     | 24       | 38             | 0              |

<sup>a</sup>2 mol% was used; <sup>b</sup>Re<sub>2</sub>O<sub>7</sub>: rhenium(VII) oxide; <sup>c</sup>MTO: methyltrioxorhenium(VII); <sup>d</sup>VO(acac)<sub>2</sub>: vanadium(IV)-oxy acetylacetonate.

**Scheme 1.** Oxidation of 1,2,3,4-tetrahydroisoquinoline using Na<sub>2</sub>WO<sub>4</sub> and O<sub>2</sub> in the presence of A.C.

As can be seen from table 1 and scheme 1, in place of the expected 1-hydroxy-3,4-dihydroquinolin-2(1*H*)-ones [1] and 3,4-dihydroisoquinoline *N*-oxides [6] as the reaction products, quinolines, isoquinolines and their *N*-oxides were obtained as the result of oxidative aromatization and *N*-oxidation. Table 1 also indicates the following: 1) direct bubbling of O<sub>2</sub> into the solvent is more effective than atmospheric O<sub>2</sub> reaction; 2) Na<sub>2</sub>WO<sub>4</sub>·2H<sub>2</sub>O as a catalyst is essential to give rise to *N*-oxidation; 3) no reaction proceeded without activated carbon, which plays a very important role in this reaction; 4) the reaction using xylenes as a solvent at 130 °C proceeded smoothly to afford quinoline and quinoline *N*-oxide, without recovery of the starting material; and 5) MeOH is the most appropriate solvent for *N*-oxidation among the present solvents. The biological importance of heterocyclic *N*-oxides is well documented [7].

It is very interesting to compare the suitability of Na<sub>2</sub>WO<sub>4</sub>·2H<sub>2</sub>O as a catalyst for *N*-oxidation with other catalysts such as Re<sub>2</sub>O<sub>7</sub> [8], MTO [8] and VO(acac)<sub>2</sub> [9], which are well known as catalysts for *N*-oxidation. The general procedure shown in table 1 was carried out using the respective catalysts in place of Na<sub>2</sub>WO<sub>4</sub>·2H<sub>2</sub>O (Table 2).

## CONCLUSION

As can be seen from table 2, Na<sub>2</sub>WO<sub>4</sub>·2H<sub>2</sub>O is the most appropriate catalyst for *N*-oxidation among the catalysts studied. The oxidation of quinoline under the above-mentioned reaction conditions resulted in the complete recovery of quinoline. This indicates that quinoline *N*-oxide does not form *via* quinoline under the present oxidation conditions but *via* some other reaction path. As a new, environmentally friendly method of *N*-oxidation that does not use peracids such as 3-chloroperoxybenzoic acid or peroxyacetic acid [3], our activated carbon-Na<sub>2</sub>WO<sub>4</sub>-molecular oxygen system would be advantageous for oxidative aromatization [10] and *N*-oxidation [11] of compounds containing groups sensitive to peracids. Application to other *N*-heterocycles and the improvement [12] of reaction conditions to increase the yield are currently underway in our laboratory.

## CONFLICT OF INTEREST STATEMENT

The authors confirm that the article content has no conflicts of interest.

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