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SYNTHESIS OF 2-HYDROXY-1,2,3,4-TETRAHYDROQUINOLINE DERIVATIVES BY A CYCLOCONDENSATION REACTION[§]

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Abstract – The reaction of enolates (**2**) of 1,3-dicarbonyl compounds with *N*-(2-bromomethylphenyl)benzenesulfonamides (**1**) gives *N*-phenylsulfonyl-2-hydroxy-1,2,3,4-tetrahydroquinoline derivatives (**3**) whose structure and stereochemistry were assigned on the basis of analytical and spectroscopic data. Some studies on the chemical behaviour of **3** are also reported.

INTRODUCTION

Functionalized 1,2,3,4-tetrahydro- and 1,4-dihydroquinoline show a wide spectrum of biologically activities[1] and attract interest for their potential pharmaceutical application. In this context and as a part of our studies concerning the synthesis of heterocyclic derivatives, through nucleophilic addition / cyclocondensation reactions, we report the reaction of benzyl bromide (**1**) with carbanions deriving from 1,3-dicarbonyl compounds (**2**). Some our previous results concerned the reaction of sulfonium ylides with 2-(tosylamino)benzyltrimethylammonium halides[2] and *N*-phenylsulfonyl-*o*-amino-benzyl bromides[3] to give indole or 1,2-dihydroindole derivatives respectively.

This paper deals with a simple method for the preparation of substituted 1-phenylsulfonyl-2-hydroxy-1,2,3,4-tetrahydroquinolines, a new class of derivatives of quinoline ring system.

RESULTS AND DISCUSSION

The treatment of benzyl bromide[3] (**1**) with preformed carbanions (**2**) (molar ratio = 1/2), prepared in DMF solution from sodium hydride and 1,3-dicarbonyl compounds, leads to the formation of substituted 2-

§ This paper is dedicated to Dr. Satoshi Omura on the occasion of his 70th birthday.
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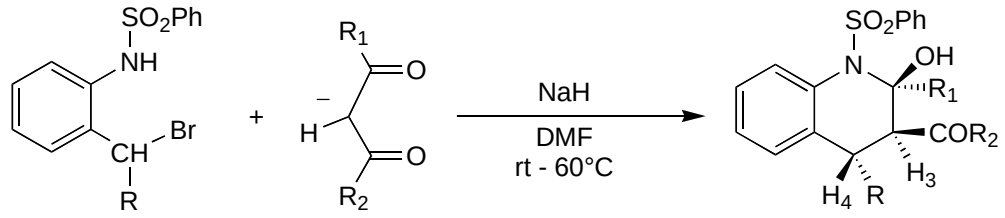
hydroxy-1,2,3,4-tetrahydroquinolines (**3**) (**Scheme 1**).

Scheme 1



1 **2** **3**

1a : R = Me
1b : R = C_6H_5
1c : R = H

2a : R_1 = Me; R_2 = Me
2b : R_1 = Me; R_2 = OMe
2c : R_1 = Me; R_2 = C_6H_5
2d : R_1 = C_6H_5; R_2 = OEt
2e : R_1 = C_6H_5; R_2 = C_6H_5

3a : R = Me; R_1 = Me; R_2 = Me
3b : R = C_6H_5; R_1 = Me; R_2 = Me
3c : R = C_6H_5; R_1 = Me; R_2 = OMe
3d : R = C_6H_5; R_1 = Me; R_2 = C_6H_5
3e : R = C_6H_5; R_1 = C_6H_5; R_2 = C_6H_5
3f : R = C_6H_5; R_1 = C_6H_5; R_2 = OEt
3g : R = H; R_1 = Me; R_2 = Me

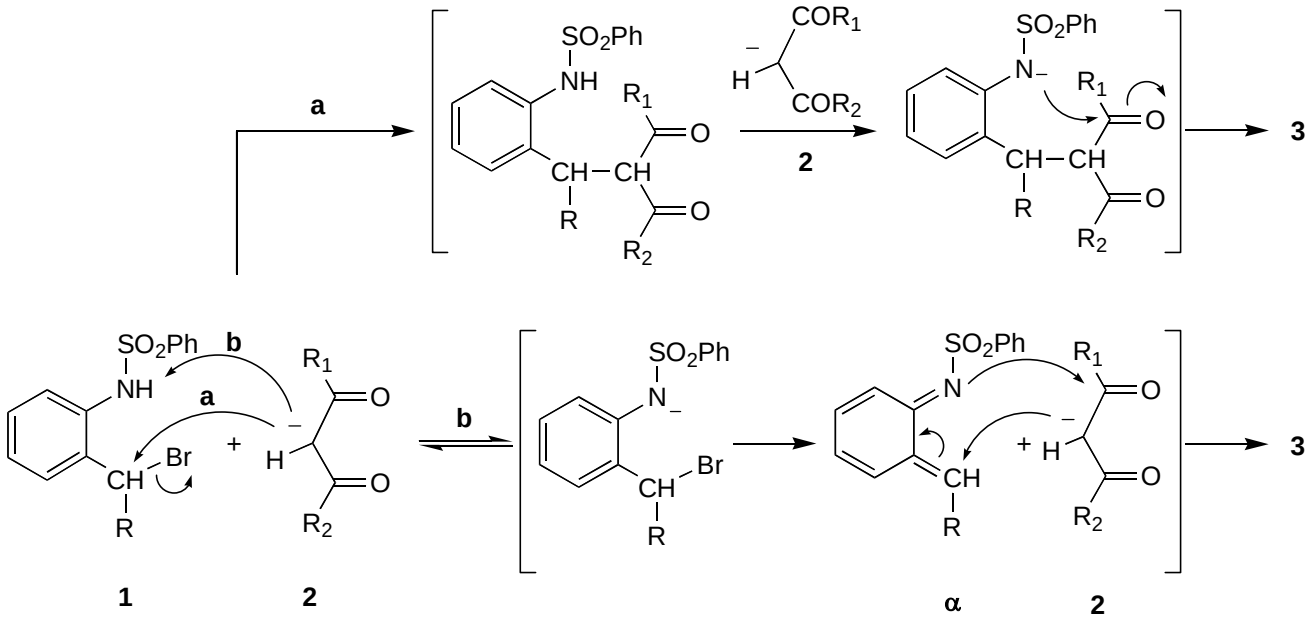
In all cases the reaction proceeds easily between rt and 50°C and gives with good yields and high stereoselectivity compounds (**3**). Occasionally a little part of other diastereoisomers was detected by ^{1}H NMR on the crude reaction mixture but it was impossible to isolate it.

The structure of products (**3**) were assigned on the basis of analytical and spectroscopic data, IR and ^{1}H-NMR. Also the relative configurations of compounds (**3**) were assigned by means of NMR spectroscopic data. First of all the *trans* relationship between H-3 and H-4 was attributed on the basis of their coupling constant value (10.5-12.2 Hz). Moreover NOESY experiments involving compound (**3a**), taken as a model, allowed to assign the other relative configurations: in fact positive effect was observed between the CH_3-4 and the CH_3-2 allowing to assign them a *cis* relationship. A positive effect observed between H-3 and the CH_3-4 confirmed their *cis* relative configuration already attributed.

In the case of 1-phenyl-1,3-butanedione (**2c**), an unsymmetrical substituted 1,3-dicarbonyl compound, a single regioisomer was obtained, namely that derived from ring closure on the acetyl group.

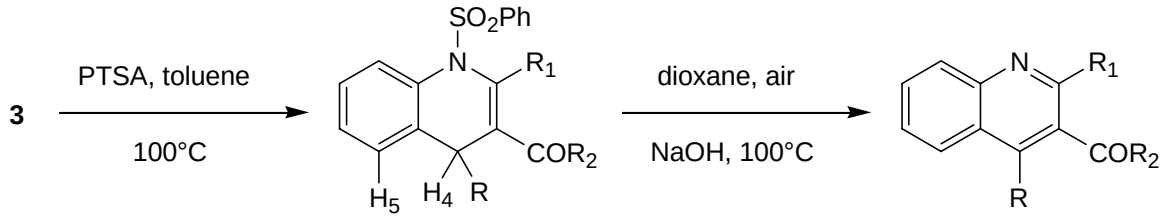
The formation of the products can be rationalized assuming the behaviour of an enolate towards a system, such as the *N*-phenylsulfonyl-*o*-amino-benzylbromides, bearing an electrophilic center and a nucleophilic heteroatom (pathway **a**). Alternatively the dehydrohalogenation of benzylbromides by the enolate to the highly reactive intermediate, *N*-(6-alkylidene-cyclohexa-2,4-dienylidene)benzenesulfonamide (α) cannot be ruled out. Starting from (α) the attack of enolate on the electrophilic carbon atom, followed by an intramolecular nucleophilic addition of nitrogen anion on carbonyl group would give the final products (**3**) (**Scheme 2** – pathway **b**).

Scheme 2



The 2-hydroxy-1,2,3,4-tetrahydroquinolines can be considered useful intermediates for the preparation of 1,4-dihydroquinolines by a dehydration process. With this purpose we treated some derivatives (**3**) in toluene solution, at 100°C in the presence of PTSA and observed their complete transformation in **4** (**Scheme 3**).

Scheme 3



4a : R = Me; R_1 = Me; R_2 = Me
4b : R = C_6H_5; R_1 = Me; R_2 = Me
4c : R = C_6H_5; R_1 = Me; R_2 = OMe
4d : R = C_6H_5; R_1 = Me; R_2 = C_6H_5

5b : R = C_6H_5; R_1 = Me; R_2 = Me
5c : R = C_6H_5; R_1 = Me; R_2 = OH

The position of the double bond in compounds (**4**) was confirmed by means of NOESY experiments on compound (**4a**): in fact either the H-4 and the CH_3-4 showed positive effect with the aromatic H-5.

According to the known behaviour of *N*-phenylsulfonyl protected heterocycles under basic conditions, it is possible to eliminate the protective group and to obtain quinoline derivatives (**5**) performing the reaction in presence of oxygen to gain aromaticity.

In conclusion we have developed a simple and efficient protocol for the preparation of 2-hydroxy-1,2,3,4-tetrahydroquinoline derivatives.

EXPERIMENTAL

Melting points were determined on a *Büchi* B-540 apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the Department. ^{1}H NMR spectra were recorded in $CDCl_3$ solution using a *Bruker AC 300 MHz* spectrometer, and chemical shifts are given in ppm relative to TMS. IR spectroscopy was performed using a *Perkin-Elmer 1725X FT-IR* spectrometer.

Benzyl bromide (**1a-c**) were prepared according to the reported procedure[3]. 1,3-dicarbonyl compounds (**2a-d**) are commercially available.

Synthesis of products (3a-g): general procedure.

To a suspension of NaH (6.0 mmol) in DMF (10 mL), 1,3-dicarbonyl compound (**2a-d**) (6.0 mmol) was added dropwise and the mixture was stirred until gas evolution ceased. The temperature was brought to 5°C and benzyl bromide (**1a-c**) (3.0 mmol) was added portion-wise. The mixture was stirred 4h at rt and 2h at 60°C. The addition of water (20 mL) caused the precipitation of product which was recovered by extraction with AcOEt (50 mL). The organic layer was separated, washed with aq. Na_2CO_3 (10%, 25 mL) to remove the excess of β-dicarbonyl compound, dried (Na_2SO_4), filtered and the solvent was evaporated off. The residue was purified by recrystallization. In this way were prepared:

3-Acetyl-2-hydroxy-2,4-dimethyl-1-phenylsulfonyl-1,2,3,4-tetrahydroquinoline (3a): Solid, mp 125-127°C (*i*-Pr_2O). Yield 95%. ^{1}H NMR δ: 0.61 (d, 3H, *J* = 6.8 Hz, CH_3-4); 1.91 (s, 3H, CH_3CO); 2.20 (s, 3H, CH_3-2); 3.45 (m, 1H, *J* = 6.8, 11.2 Hz, H-4); 3.80 (d, 1H, *J* = 11.2 Hz, H-3); 7.00-8.00 (m, 10H, Ar, OH). IR (*nujol*, cm^{-1}): 3280 (OH), 1713 (CO). *Anal.* Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.52; H, 6.09; N, 4.05.

3-Acetyl-2-hydroxy-2-methyl-4-phenyl-1-phenylsulfonyl-1,2,3,4-tetrahydroquinoline (3b): Solid, mp 161-163°C (*i*-Pr_2O). Yield 92%. ^{1}H NMR δ: 1.91 (s, 3H, CH_3-2); 1.96 (s, 3H, CH_3CO); 4.62 (d, 1H, *J* = 12.2 Hz, H-3); 4.96 (d, 1H, *J* = 12.2 Hz, H-4); 7.00-8.00 (m, 15H, Ar, OH). IR (*nujol*, cm^{-1}): 3275 (OH), 1705 (CO). *Anal.* Calcd for $C_{24}H_{23}NO_4S$: C, 68.39; H, 5.50; N, 3.32. Found: C, 68.66; H, 5.39; N, 3.26.

2-Hydroxy-3-methoxycarbonyl-2-methyl-4-phenyl-1-phenylsulfonyl-1,2,3,4-tetrahydroquinoline (3c): Solid, mp 160-162°C (EtOH). Yield 85%. ^{1}H NMR δ: 2.12 (s, 3H, CH_3-2); 3.56 (s, 3H, CH_3O); 4.42 (d, 1H, *J* = 11.3 Hz, H-3); 4.88 (d, 1H, *J* = 11.3 Hz, H-4); 6.80-8.00 (m, 15H, Ar, OH). IR (*nujol*, cm^{-1}): 3278 (OH) , 1710 (CO). *Anal.* Calcd for $C_{24}H_{23}NO_5S$: C, 65.89; H, 5.30; N, 3.20. Found: C, 65.85; H, 5.20; N, 3.17.

3-Benzoyl-2-hydroxy-2-methyl-4-phenyl-1-phenylsulfonyl-1,2,3,4-tetrahydroquinoline (3d): Solid, mp 170-172°C (EtOH). Yield 95%. ^{1}H NMR δ: 2.00 (s, 3H, CH_3-2); 5.17 (d, 1H, *J* = 11.8 Hz, H-3); 5.49 (d, 1H, *J* = 11.8 Hz, H-4); 6.80-8.00 (m, 20H, Ar, OH). IR (*nujol*, cm^{-1}): 3285 (OH) , 1690 (CO). *Anal.* Calcd for $C_{29}H_{25}NO_4S$: C, 72.03; H, 5.20; N, 2.90. Found: C, 72.24; H, 5.21; N, 2.93.

3-Benzoyl-2-hydroxy-2,4-diphenyl-1-phenylsulfonyl-1,2,3,4-tetrahydroquinoline (3e): Solid, mp 204-205°C (EtOH). Yield 85%. ^{1}H NMR δ: 5.32 (d, 1H, *J* = 11.2 Hz Hz, H-4); 6.31 (d, 1H, *J* = 11.2 Hz, H-3); 6.80-8.00 (m, 25H, Ar, OH). IR (*nujol*, *cm*$^{-1}$): 3290 (OH) , 1698 (CO). *Anal.* Calcd for $C_{34}H_{27}NO_4S$: C, 74.84; H, 4.99; N, 2.57. Found: C, 75.08; H, 4.72; N, 2.50.

3-Ethoxycarbonyl-2-hydroxy-2,4-diphenyl-1-phenylsulfonyl-1,2,3,4-tetrahydroquinoline (3f): Solid, mp 173-174°C (EtOH). Yield 94%. ^{1}H NMR δ: 1.00 (t, 3H, *J* = 7.1 Hz, CH_3); 4.00 (q, 2H, *J* = 7.1 Hz, CH_2); 5.15 (d, 1H, *J* = 10.5 Hz, H-4); 5.31 (d, 1H, *J* = 10.5 Hz, H-3); 6.60-8.00 (m, 20H, Ar, OH). IR (*nujol*, *cm*$^{-1}$): 3280 (OH) , 1700 (CO). *Anal.* Calcd for $C_{30}H_{27}NO_5S$: C, 70.16; H, 5.30; N, 2.73. Found: C, 70.11; H, 5.21; N, 2.68.

3-Acetyl-2-hydroxy-2-methyl-1-phenylsulfonyl-1,2,3,4-tetrahydroquinoline (3g): Solid, mp 76-78°C (*i*-Pr_2O). Yield 80%. ^{1}H NMR δ: 1.90 (s, 3H, CH_3CO); 2.20 (s, 3H, CH_3-2); 2.65 (d, 2H, *J* = 8.2 Hz, H-4); 3.50 (m, 1H, *J* = 8.2 Hz, H-3); 7.00-8.00 (m, 10H, Ar, OH). IR (*nujol*, *cm*$^{-1}$): 3292 (OH) , 1707 (CO). *Anal.* Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.57; H, 5.46; N, 3.95.

Preparation of 1,4-dihydroquinolines (4a-d): general procedure.

A mixture of **3** (1.5 mmol) and catalytic amount of PTSA in toluene (15 mL) was heated to 105°C for 6-8h. The reaction mixture was cooled to rt and washed with $NaHCO_3$ 5% solution. The organic phase was dried (Na_2SO_4), filtered and the solvent evaporated off. The residue was purified by crystallization. In this way were prepared:

3-Acetyl-2,4-dimethyl-1-phenylsulfonyl-1,4-dihydroquinoline (4a): Solid, mp 72-74°C (hexane). Yield 82%. ^{1}H NMR δ: 0.60 (d, 3H, *J* = 7.2 Hz, CH_3-4); 2.30 (s, 3H, CH_3CO); 2.50 (s, 3H, CH_3-3); 3.50 (t, 1H, *J* = 7.2 Hz, H-4); 7.00-7.80 (m, 9H, Ar). IR (*nujol*, *cm*$^{-1}$): 1661 (CO). *Anal.* Calcd for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.97; H, 5.81; N, 4.15.

3-Acetyl-2-methyl-4-phenyl-1-phenylsulfonyl-1,4-dihydroquinoline (4b): Solid, mp 191-192°C (EtOH). Yield 85%. ^{1}H NMR δ: 1.96 (s, 3H, CH_3CO); 2.55 (s, 3H, CH_3-2); 3.72 (s, 1H, CH); 6.65-7.80 (m, 14H, Ar). IR (*nujol*, *cm*$^{-1}$): 1689 (CO). *Anal.* Calcd for $C_{24}H_{21}NO_3S$: C, 71.44; H, 5.25; N, 3.47. Found: C, 71.47; H, 5.25; N, 3.39.

3-Methoxycarbonyl-2-methyl-4-phenyl-1-phenylsulfonyl-1,4-dihydroquinoline (4c): Solid, mp 170-171°C (EtOH). Yield 73%. ^{1}H NMR δ: 2.68 (s, 3H, CH_3-2); 3.64 (s, 3H, CH_3); 4.40 (s, 1H, CH); 6.90-7.80 (m, 14H, Ar). IR (*nujol*, *cm*$^{-1}$): 1714 (CO). *Anal.* Calcd for $C_{24}H_{21}NO_4S$: C, 68.72; H, 5.05; N, 3.34. Found: C, 68.77 H, 4.95; N, 3.30.

3-Benzoyl-2,4-diphenyl-1-phenylsulfonyl-1,4-dihydroquinoline (4d): Solid, mp 135-136°C (*i*-Pr_2O). Yield 70%. ^{1}H NMR δ: 2.31 (s, 3H, CH_3); 3.95 (s, 3H, H-4); 6.80-7.80 (m, 19H, Ar). IR (*nujol*, *cm*$^{-1}$): 1685 (CO). *Anal.* Calcd for $C_{29}H_{23}NO_3S$: C, 74.81; H, 4.98; N, 3.01. Found: C, 74.65 H, 4.95; N, 3.15.

Preparation of products (5b-c): general procedure.

A solution of **4** (1.0 mmol) in dioxane (20 mL) was treated with NaOH (2.0 mmol) in H_2O (0.5 mL) and heated at 100°C for 6h in current of air. The solvent was evaporated and the residue taken up with water, the pH adjusted ad 6.5 with acetic acid and the product extracted with toluene. The organic layer was dried (Na_2SO_4) and the solvent was removed. The residue was purified by crystallization. In this way were prepared:

3-Acetyl-2-methyl-4-phenylquinoline (5b): Solid, mp 110-112°C (EtOH). Lit.[4], mp 112-114°C.

2-Methyl-4-phenyl-3-quinolinecarboxylic acid (5c): Solid, mp 265-267°C (CH_3COOH). Lit.[4], mp 267-268°C.

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