Copper-mediated aerobic synthesis of 3-tosyl-1,2,3,4-tetrahydroquinazoline from 2-tosylaminomethylaniline and methanol

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Abstract

An investigation has shown that 2-tosylaminomethylaniline plays a dual role in the oxidative process of methanol to formaldehyde acting as N-donor ligand and nucleophile, which leads to 3-tosyl-1,2,3,4-tetrahydroquinazoline (**1**). This was characterized by using both spectroscopic and X-ray diffraction techniques.

Keywords

Tetrahydroquinazoline / Methanol oxidation / 2-Tosylaminomethylaniline / Copper

Introduction

1,2,3,4-Tetrahydroquinazolines substituted by aryl groups at the 2-position are accessible in almost quantitative yield *via* reaction of 2-aminobenzylamine and benzaldehyde derivatives in a similar manner used for the synthesis of aromatic Schiff bases [1]. In fact, it is known that 2-aryl-1,2,3,4-tetrahydroquinazolines are in tautomeric equilibrium with the corresponding aromatic Schiff bases, which are most quickly formed [2].

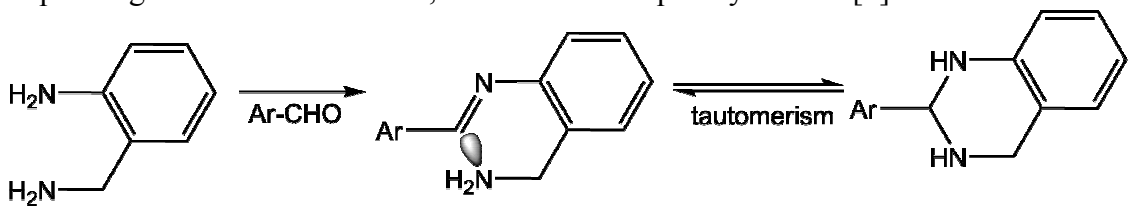

Fig. 1. Synthetic approach to 2-aryl-1,2,3,4-tetrahydroquinazolines: imine condensation followed by intramolecular nucleophilic addition of the amino $N^{-\delta}$ atom to the electrophilic sp^2-hybridized imino $C^{+\delta}$ atom associated with hydrogen atom migration.

Since copper homogeneous catalysts have exhibited good reactivity in the aerobic oxidation of alcohols to aldehydes [3,4], we have considered that perhaps a 1,2,3,4-tetrahydroquinazoline could be obtained from a 2-aminobenzylamine derivative and methanol. With this in mind, we have investigated the copper-mediated aerobic synthesis of 3-tosyl-1,2,3,4-tetrahydroquinazoline (**1**) from methanol and 2-tosylaminomethylaniline [5] as nucleophile.

Experimental

Synthesis of 3-tosyl-1,2,3,4-tetrahydroquinazoline (1). Since the obtaining of this compound was the goal of two experiments, the experimental details of each one of them stated below.

Experiment 1: Compound **1** was obtained from a methanol solution (1 mL) of 2-tosylaminomethylaniline (0.03 g, 0.10 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.01 g, 0.05 mmol), which was heated under reflux for 24 h. Alternatively, the reaction solvent was methanol-^{13}C. Filtration of the resulting suspensions yielded filtrates that then were concentrated under vacuum to remove solvents. Separation of compound **1** from the crude mixture was performed by flash chromatography eluting with diethyl ether:hexane (50:50).

Experiment 2: Three methanol solutions (2 mL) of 2-tosylaminomethylaniline (0.06 g, 0.20 mmol) were heated under reflux for 24 h, one of them in absence of any metal salt and upon the other two solutions $Ni(OAc)_2 \cdot 4H_2O$ (0.02 g, 0.10 mmol) and $Zn(OAc)_2 \cdot 2H_2O$ (0.02 g, 0.10 mmol) were added.

^1H NMR (500 MHz, acetone-d_6): 7.69 (d, J = 8.2 Hz, 2H, 2xH-2'), 7.23 (d, J = 8.2 Hz, 2H, 2xH-3'), 6.91 (d, 1H, H-5), 6.88 (t, 1H, H-7), 6.61 (dt, J = 7.5 and 1.1 Hz, 1H, H-6), 6.42 (dd, J = 8.5 and 1.1 Hz, 1H, H-8), 5.32 (br, 1H, NH), 4.62 (br, 2H, CH_2-2), 4.42 (s, 2H, CH_2-4) and 2.30 (s, 3H, CH_3) ppm. ^{13}C NMR (125 MHz, acetone-d_6) d: 144.2 (C4'), 143.2 (C8a), 136.9 (C1'), 130.1 (2xC3'), 128.5 (2xC2'), 128.0 (C5), 127.6 (C7), 119.1 (C6), 118.7 (C4a), 116.9 (C8), 58.5 (CH_2-2), 47.9 (CH_2-4) and 21.6 (CH_3) ppm. FT-IR (KBr): 3361(s) ν(NH) cm^{-1}, 1604(m) $\nu(C{=}N_{quin})$, 1342(s) $\nu_{as}(SO_2)$, 1165(vs) $\nu_s(SO_2)$. HRMS found, 311.0829 *m/z* $[M+Na]^+$, calcd for $C_{15}H_{16}N_2NaO_2S$: 311.0825. Elemental analysis found: C 62.7; H 5.5; N 9.5 %; calcd for $C_{15}H_{16}N_2O_2S$: C 62.5; H 5.6; N 9.7%.

Crystal structure data. Diffraction data for **1** were collected at 100(2) K, using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) from a fine focus sealed tube. Some significant crystal parameters and refinement data are summarized in Table 1. Data were processed and corrected for Lorentz and polarization effects. Multi-scan absorption corrections were performed using the SADABS routine [6,7]. The structure was solved by standard direct methods [8] and then refined by full matrix least squares on F^2 [9]. All non-hydrogen atoms were anisotropically refined. Hydrogen atoms were included in the structure factor calculation in geometrically idealized positions, with thermal parameters depending of the parent atom, by using a riding model.

Table 1. Diffraction data for **1**

Formula	$C_{15}H_{16}N_2O_2S$	**Z**	4
M_r	288.36	**D_c (g/cm^3)**	1.421 Mg/m^3
Crystal system	Monoclinic	**μ (mm^{-1})**	0.243 mm^{-1}
Space group	$P2_1/c$ (Nº 14)	**F(000)**	608
Unit cell	a = 15.9574(4) Å	**θ range (º)**	2.73 to 31.205 º (99.5)
	b = 6.0364(1)	**Ref. col. / Ref. Ind**	72839 / 5158
	c = 14.9838(3) Å	**R_{int}**	0.0525
	α = 90 º	**Data / restr./param.**	5158 / 0 / 187
	β = 110.936(1) º	**R_1, wR_2 [I > 2σ(I)]**	R_1=0.0382, wR_2=0.0537
	γ = 90 º	**R_1, wR_2 (all data)**	R_1=0.0961, wR_2=0.1042
Volume (Å^3)	1348.03(5) Å^3	**Residuals (e.Å^{-3})**	0.551, -0.468 e.A^{-3}

Results and discussion

With the aim of studying the copper-mediated aerobic synthesis of 3-tosyl-1,2,3,4-tetrahydroquinazoline, we have used $Cu(OAc)_2 \cdot H_2O$ and 2-tosylaminomethylaniline as

starting reagents. This latter species plays a crucial role serving two purposes: as N-donor ligand to stabilize the copper alcoholate complex moduling the redox properties of the metal ion and as a base to facilitate an intramolecular deprotonation of the Cu-bound alcohol. Besides, the alcohol oxidation usually leads to the reduction of Cu(II) and therefore air is needed to oxidize the Cu(I) complex back to Cu(II). The reactions were carried out in methanol and alternatively in methanol-^{13}C (*experiment 1*). After 24 h in refluxing, compound **1** was formed, but in the ^{13}C NMR spectrum obtained from methanol 99 atom% ^{13}C, the intensity of the signal at about 59 ppm has enhanced extremely if is compared with the same signal in the spectrum obtained from non-labelled methanol. This carbon signal emerges as a singlet, indicating the isotopic labelling at 2-position of 3-tosyl-1,2,3,4-tetrahydroquinazoline. Since the methylene group at the 2-position of 3-tosyl-1,2,3,4-tetrahydroquinazoline comes from the methanol used as solvent, results point out to the oxidation of methanol to formaldehyde. On a subsequent reaction step, following a similar pathway to the reported for the synthesis of 1,2,3,4-tetrahydroquinazolines [1], 3-tosyl-1,2,3,4-tetrahydroquinazoline would be produced from nucleophilic addition of 2-tosylaminomethylaniline to formaldehyde. Fig. 2 schematizes the two reaction processes and shows the ^{13}C NMR spectra of 3-tosyl-1,2,3,4-tetrahydroquinazoline obtained from non-isotopically labelled methanol and methanol-^{13}C.

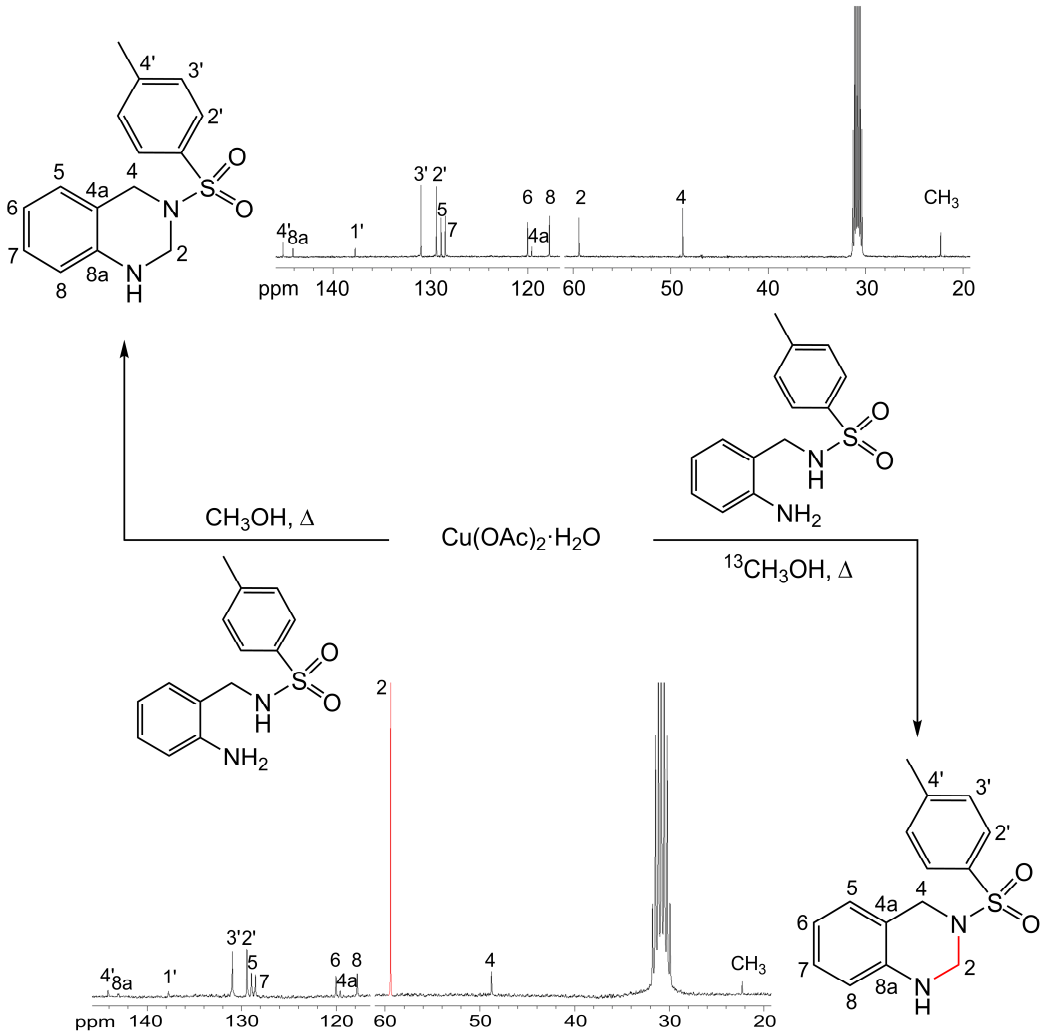

Fig. 2. Reactions used to establish the role of 2-tosylaminomethylaniline as nucleophile upon the oxidation of methanol. ^{13}C NMR spectra (in acetone-d_6) of **1** obtained from both non-isotopically labelled methanol (top) and methanol-^{13}C (bottom) solutions. The signal of the methylene group at 2-position of isotopically labelled **1** is highlighted in red colour.

In order to verify the critical role of Cu^{2+} upon the methanol oxidation leading to 3-tosyl-1,2,3,4-tetrahydroquinazoline, we have performed an experiment to check the formation of compound **1** in absence of copper. The experiment consists in three reactions by heating under reflux the corresponding methanolic solutions of 2-tosylaminomethylaniline, the first one was carried out without addition of any metal ion, and upon the other two solutions Ni^{2+} and Zn^{2+} were added (*experiment 2*). After 24 h, the results showed that 3-tosyl-1,2,3,4-tetrahydroquinazoline was not formed, revealing the copper-mediated oxidation of methanol to formaldehyde.

3-Tosyl-1,2,3,4-tetrahydroquinazoline (**1**), which is represented in Fig. 3 with the labelling scheme, crystallizes in the spatial group $P2_1/c$ and shows an envelope configuration in the tetrahydroquinazoline framework. The main angles and bond distances of 1 are collected in Table 2.

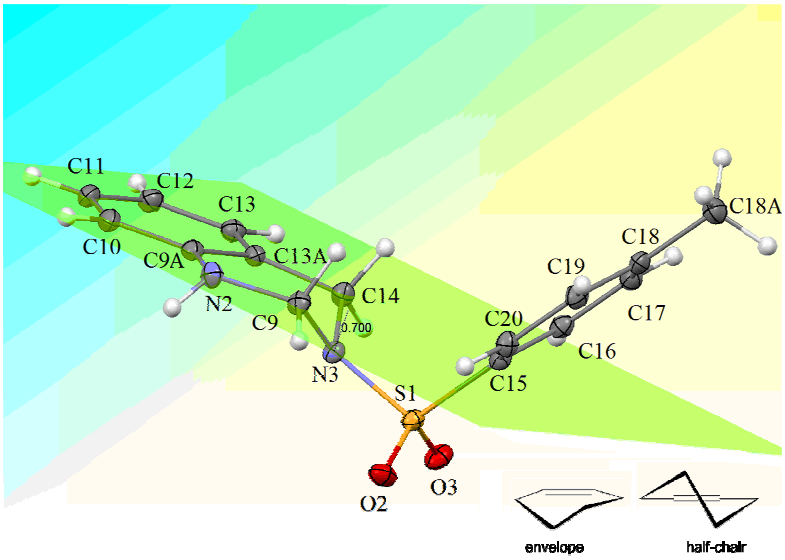

Fig. 3. Molecular structure of 3-tosyl-1,2,3,4-tetrahydroquinazoline showing the envelope configuration in the tetrhahydroquinazoline framework (the deviation from the mean plane being 0.7 Å). Ellipsoids have been represented at 50% probability level.

Table 1. Main bond lengths and angles of 3-tosyl-1,2,3,4-tetrahydroquinazoline.

Atoms	Distances (Å)	Atoms	Angles (º)
C(9)-N(2)	1.4423(15)	C(9A)-N(2)-C(9)	117.33(9)
C(9)-N(3)	1.4813(14)	C(9)-N(3)-C(14)	110.22(8)
N(2)-C(9A)	1.4027(15)	C(9)-N(3)-S(1)	116.44(7)
C(14)-N(3)	1.4734(14)	C(14)-N(3)-S(1)	110.22(8)
N(3)-S(1)	1.6373(9)	N(3)-S(1)-C(15)	107.60(5)
S(1)-C(15)	1.7596(11)		

Conclusions

The methanol oxidation by the Cu^{2+}/2-tosylaminomethylaniline system is very attractive because with this improved methodology a variety of useful tetrahydroquinazoline derivatives would be readily available by using as starting materials alcohols instead of the corresponding aldehydes.

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