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Dual role of 2-tosylaminomethylaniline as a ligand and a nucleophile in the copper-mediated oxidation of methanol†

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Some reactivity in the oxidation of methanol to formaldehyde has been spectroscopically detected on the methanolic mother liquors of a copper(II) complex of a Schiff base ligand derived from the condensation of 8-hydroxyquinoline-2-carboxaldehyde and 2-tosylaminomethylaniline. An investigation has shown that 2-tosylaminomethylaniline (HA^{TS}) plays a dual role in the oxidative process acting as a N-donor ligand and reacting *in situ* with formaldehyde, which leads to 3-tosyl-1,2,3,4-tetrahydroquinazoline (**1**). This was characterized by using both spectroscopic and X-ray diffraction techniques. The influence of 8-hydroxyquinoline derivatives, water and ligand stoichiometry on the yield of **1** was studied.

Introduction

Copper homogeneous catalysts have exhibited good reactivity in the aerobic oxidation of alcohols.[1–7] Key findings in sound studies[8] for these conversions include: (1) mono- or bidentate N-donor ligands in combination with co-catalysts such as TEMPO, DBAD, DMAP, *etc.* are necessary for efficient catalysis, and (2) a metal–ligand bond must dissociate to allow alcohol binding and/or β-hydride elimination. For example, Sheldon and co-workers showed that $CuBr_2$ in the presence of bipy and TEMPO as ligands led to excellent conversion of several primary alcohols with air at room temperature.[9–11] The authors postulated a copper mediated dehydrogenation mechanism, in which TEMPO acts as a hydrogen acceptor and is able to regenerate the active Cu^{2+} species (Fig. 1).

Recently, we have reported[11] the sensitivity of a Schiff base/tetrahydroquinazoline (H_2L_{SB}/H_2L_{TQ}) system to a copper-mediated oxidation (Fig. 2). This results in the obtainment of a dinuclear copper complex $Cu_2(L_A)(L_Q)(MeOH)\cdot 2MeOH$, which contains a coordinated methanol molecule and two ligand derivatives. The reaction of the tetrahydroquinazoline ligand H_2L_{TQ} with $Cu(OAc)_2\cdot H_2O$ in a 1 : 1 molar ratio under reflux gave $Cu_2(L_{SB})_2$ (main product) as well as *p*-toluenesulfonic acid and $Cu_2(L_A)(L_Q)(MeOH)\cdot 2MeOH$ (by-products). This revealed the existence of both hydrolytic and oxidative processes on the methanolic mother liquors of $Cu_2(L_{SB})_2$. Now,

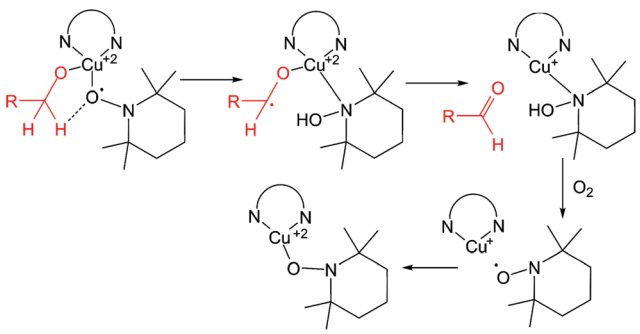

Fig. 1 Proposed role of TEMPO (2,2,6,6-tetramethyl-1-piperidine-*N*-oxyl) and bipy (2,2′-bipyridine) ligands on the copper-mediated oxidation of primary alcohols.

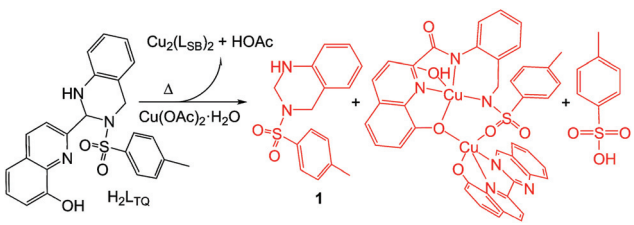

Fig. 2 Main and by-products (highlighted in red colour) resulting from the reaction of 2-(3-tosyl-1,2,3,4-tetrahydroquinazolin-2-yl)quinolin-8-ol (H_2L_{TQ}) with $Cu(OAc)_2\cdot H_2O$.

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the presence of 3-tosyl-1,2,3,4-tetrahydroquinazoline (**1**) was additionally detected. Since this finding can be a sign of the copper-mediated aerobic oxidation of methanol to formaldehyde, it deserves further investigation.

Results and discussion

The ^{1}H NMR spectrum of the residual mixture obtained by concentration of the methanolic mother liquors of $Cu_2(L_{SB})_2$ revealed the formation of 3-tosyl-1,2,3,4-tetrahydroquinazoline (**1**), which was chromatographically purified and spectroscopically characterized (see ESI†), involving about 2% yield. 3-Tosyl-1,2,3,4-tetrahydroquinazoline, which is represented in Fig. 3 with the labeling scheme for ^{1}H NMR, shows four non-aromatic proton signals at about 2.3, 4.4, 4.6 and 5.3 ppm corresponding to methyl, methylene at the 2-position, methylene at the 4-position and amino groups, respectively. The ^{13}C NMR spectrum of **1** (see ESI†) shows two characteristic non-aromatic carbon signals at about 58.5 and 47.9 ppm corresponding to methylene groups (at 2- and 4-position of the tetrahydroquinazoline ring, respectively). Two-dimensional H–H (COSY and NOESY experiments) and H–C (HSQC and HMBC experiments) NMR correlation spectra have been used to a complete assignment of the spectra of **1**.

Working hypothesis to explain the formation of 1 on the mother liquors of $Cu_2(L_{SB})_2$

The concurrence of both hydrolytic and oxidative processes on the methanolic mother liquors of $Cu_2(L_{SB})_2$, which becomes evident in $Cu_2(L_A)(L_Q)(MeOH)\cdot 2MeOH$,[12] seems to be crucial for obtaining **1**. It must be noted that the pH of the reaction medium is about 5.5 because of acetic acid that is formed during the course of the reaction illustrated in Fig. 2. Besides, it may be that the coordination of the azomethine group to the metal ion, which could act as a focus for Lewis acid activity, and the use of a protic solvent like methanol encourage the hydrolysis[13,14] of the Schiff base in $Cu_2(L_{SB})_2$. Under the described conditions, a proton catalyzed attack of water on the $C^{\delta+}$ atom of the coordinated imino group can occur in $Cu_2(L_{SB})_2$ and thus a retro-Schiff base reaction would be initialized.[15] The imine hydrolysis would lead to a copper complex of two monoanionic ligands, one of them carrying an amine group (2-tosylaminomethylaniline, HA^{Ts}) and the other one an aldehyde group (8-hydroxyquinoline-2-carboxaldehyde, HQ), $Cu(A^{Ts})(Q)$. Subsequent access to the copper coordination sphere of a methanol molecule would afford a Cu-methanolate complex that lead to a Cu-formaldehyde complex *via* β-hydride elimination. Then, formaldehyde will suffer a nucleophilic attack by 2-tosylaminomethylaniline to produce **1** (3-tosyl-1,2,3,4-tetrahydroquinazoline, TQ). The global chemical equation could be written as $2H_2L_{SB} + Cu(OAc)_2 + 2MeOH + O_2 \rightarrow 2TQ\ (\mathbf{1}) + Cu(Q)_2 + 2HOAc + 2H_2O$. Accordingly, we have used as a basis for further research that 8-hydroxyquinoline-2-carboxaldehyde is not necessary for the formation of **1**, while 2-tosylaminomethylaniline is an essential species.

Further investigation on methanol oxidation to 1

Convinced that 2-tosylaminomethylaniline (HA^{Ts}) rather than 8-hydroxyquinoline-2-carboxaldehyde (HQ) plays a critical role on the methanol oxidation leading to **1**, we have used isotope labelling as a tool to check the formation of **1** in the absence of HQ (*experiment 1*). The experiment consists of two reactions using HA^{Ts} and $Cu(OAc)_2\cdot H_2O$ as starting reagents, the first one was carried out in non-deuterated methanol and the second one in methanol-d_4. After 24 h in refluxing, **1** was formed in both cases, but in the ^{1}H NMR spectrum obtained from methanol-d_4 complete deuteration at the 2-position of the tetrahydroquinazoline ring has occurred, preventing the observation of this methylene signal. Fig. 4 schematizes the

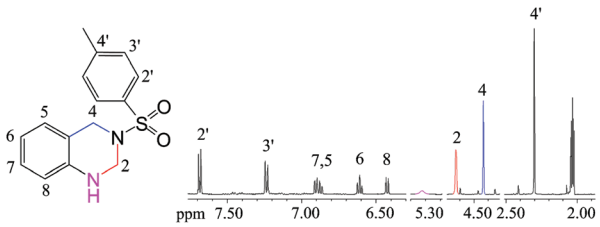

Fig. 3 ^{1}H NMR spectrum of **1** (in acetone-d_6) obtained by concentration of the methanolic mother liquors of $Cu_2(L_{SB})_2$. The most characteristic signals of the tetrahydroquinazoline were highlighted using a colour code: magenta for amino group, red for methylene group at 2-position and blue for methylene group at 4-position of the ring.

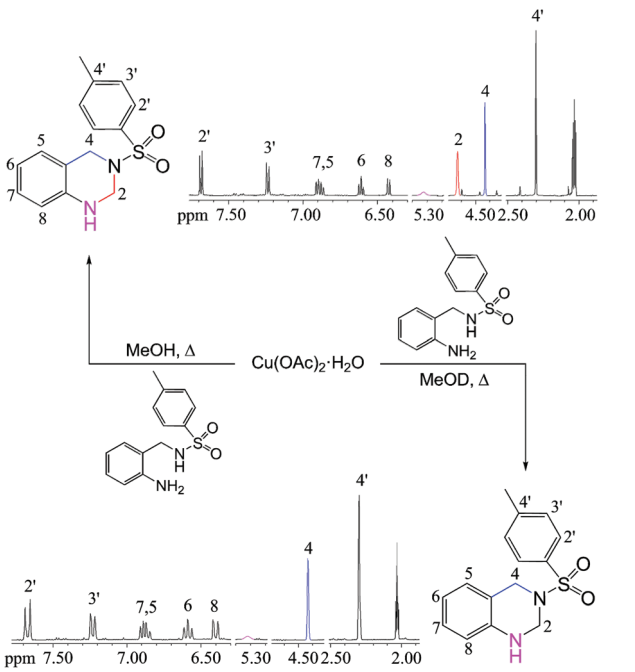

Fig. 4 Reactions used to establish the role of 2-tosylaminomethylaniline as nucleophile upon the oxidation of methanol. ^{1}H NMR spectra (in acetone-d_6) of **1** obtained from both non-deuterated methanol (top) and methanol-d_4 (bottom) solutions. The signal of the methylene group at 2-position of non-deuterated **1** is highlighted in red colour.

two reaction processes and shows the NMR spectra of **1** obtained from non-deuterated methanol and methanol-d_4. This is a sign that the origin of the methylene located at the 2-position of the tetrahydroquinazoline ring is the methanol used as a solvent.

We have performed an additional isotopic labelling experiment that supports the latter statement. This was carried out in methanol-^{13}C by using HA^{Ts} and $Cu(OAc)_2{\cdot}H_2O$ as starting reagents. After 24 h in refluxing, **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 when compared with the same signal in the spectrum obtained from non-labelled methanol (see ESI†). This carbon signal emerges as a singlet, indicating the isotopic labelling at the 2-position of **1**. Since the methylene group at the 2-position of **1** comes from the methanol used as a solvent, results point out to the oxidation of methanol to formaldehyde. On a subsequent reaction step, following a similar pathway to that reported for the synthesis of 1,2,3,4-tetrahydroquinazolines,[16] **1** would be produced from nucleophilic addition of 2-tosylaminomethylaniline to formaldehyde.

In order to verify the critical role of Cu^{2+} in the methanol oxidation leading to **1**, we have performed an experiment to check the formation of **1** in the absence of copper. The experiment consists of three reactions by heating under reflux the corresponding methanolic solutions of HA^{Ts}, the first one was carried out without addition of any metal ion, and to the other two solutions Ni^{2+} and Zn^{2+} were added (*experiment 2*). After 24 h, the results showed that **1** was not formed, revealing the copper-mediated oxidation of methanol to formaldehyde. The global chemical equation could be written as HA^{Ts} + MeOH + $\frac{1}{2}O_2$ → TQ (**1**) + $2H_2O$.

With the aim of verifying the role of HA^{Ts} as a nucleophile, we have performed an additional experiment that starts with a THF solution of 2-tosylaminomethylaniline and formaldehyde in a 1 : 1 molar ratio (*experiment 3*). After 2 h under reflux, **1** is formed, which supports the interpretation of the results of experiment 1. The obtained crude product was purified by flash chromatography, and then recrystallized in methanol. The 3-tosyl-1,2,3,4-tetrahydroquinazoline (**1**), which is represented in Fig. 5 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 1.

We have already demonstrated that 8-hydroxyquinoline-2-carboxaldehyde is not essential for the formation of **1**; however, it could be that its presence in the reaction medium influences in some way the yield of **1**. In order to clarify this point we have performed an experiment to check the yield of **1** in the presence of two 8-hydroxyquinoline derivatives: 8-hydroxyquinoline-2-carboxaldehyde and 2-(aminomethyl)quinolin-8-ol (*experiment 4*). After 24 h under reflux, both methanol solutions containing HA^{Ts} and $Cu(OAc)_2{\cdot}H_2O$, one of them adding 8-hydroxyquinoline-2-carboxaldehyde and the other one adding 2-(aminomethyl)quinolin-8-ol, lead virtually to the same amount of **1** (8%), which match up with the

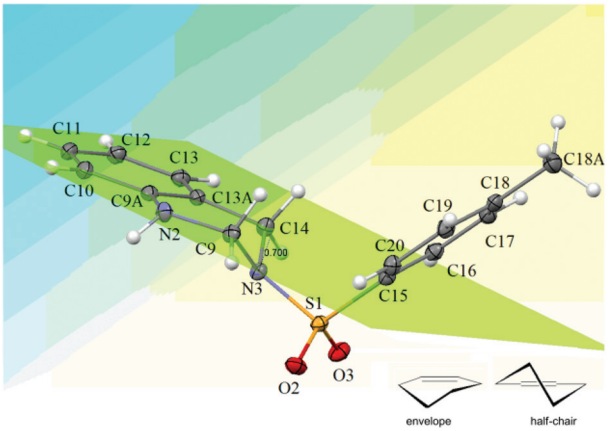

Fig. 5 Molecular structure of 3-tosyl-1,2,3,4-tetrahydroquinazoline (**1**) showing the envelope configuration in the tetrahydroquinazoline framework (the deviation from the mean plane being 0.7 Å). Ellipsoids have been represented at 50% probability level.

Table 1 Main bond lengths and angles of **1**

Atoms	Distances (Å)	Atoms	Angles (°)
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)		

percentage obtained in the absence of 8-hydroxyquinoline derivatives.

As water is involved in the oxidation of methanol mediated by $Cu_2(L_{SB})_2$, it seems particularly important to study the influence of water in the obtainment of **1** from 2-tosylaminomethylaniline. We have performed an experiment by heating under reflux two methanol solutions of HA^{Ts} and $Cu(OAc)_2{\cdot}H_2O$, one of them with the addition of water and the other one without the addition of water (*experiment 5*). The results showed that when we added water to the reaction medium, **1** was not formed after 24 h, which could be a sign of water and methanol competing with each other in the access to the copper coordination sphere. In contrast, without the addition of water, the formation of **1** is evident after 24 h (about 8% yield).

In order to gain some insight into the methanol oxidation pathway, we have separated an aliquot from the latter reaction medium after 1 h of the start. Evaporation of the latter aliquot left a brown powder, which was identified as $Cu(OAc)_2(H_2O)(MeOH)_2(HA^{TS})$ by a combination of mass and infrared spectrometries. As this compound could be involved in the oxidation of methanol to formaldehyde, we have checked the formation of **1** after 24 h under reflux of a methanolic solution of $Cu(OAc)_2(H_2O)(MeOH)_2(HA^{TS})$, which was previously obtained by the following reaction: HA^{Ts} + $Cu(OAc)_2{\cdot}H_2O$ + 2MeOH → $Cu(OAc)_2(H_2O)(MeOH)_2(HA^{TS})$ (*experiment 6*). The NMR spectroscopic detection of **1** in the residual mixture obtained by concentration of the methanolic solution supports that

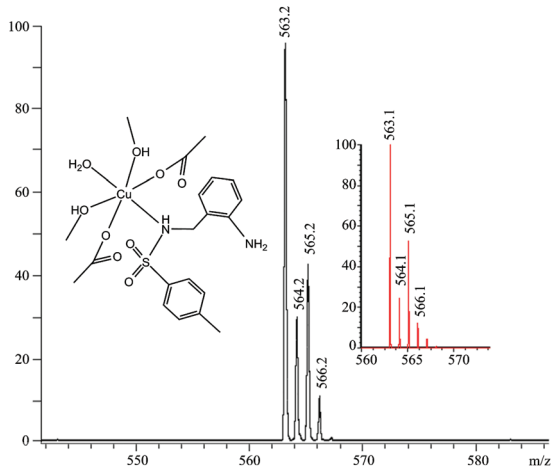

Fig. 6 Partial view of the mass spectrum of $Cu(OAc)_2(H_2O)(MeOH)_2$-(HA^{TS}) showing the calculated isotopic profile (inset) of the molecular ion $[M + Na]^+$.

$Cu(OAc)_2(H_2O)(MeOH)_2(HA^{TS})$ is involved in the methanol oxidation process.

The isotopic profile of the molecular ion $[M + Na]^+$, which matches up with the calculated one (Fig. 6), clearly shows the mononuclear nature of $Cu(OAc)_2(H_2O)(MeOH)_2(HA^{TS})$. The infrared spectrum supports the formation of the copper complex of acetate and 2-tosylaminomethylaniline. The presence of water and methanol as ligands in $Cu(OAc)_2(H_2O)$-$(MeOH)_2(HA^{TS})$ supports that water and methanol compete with each other in the access to the copper coordination sphere. Besides, the characterization of the latter copper complex has revealed that a 1 : 1 molar ratio (HA^{Ts} : Cu^{2+}) could be adequate for the oxidation of methanol to formaldehyde.

With the aim of studying the influence of the ligand stoichiometry on the yield of **1**, we have performed an experiment (Fig. 7) by heating under reflux two methanol solutions of HA^{Ts} and $Cu(OAc)_2{\cdot}H_2O$, one of them with reactants in a 2 : 1 molar ratio and the other one in a 1 : 1 molar ratio (*experiment 7*). The results showed that when a 1 : 1 molar ratio was used the yield of **1** was about 22% after 24 h under reflux. In contrast, when a 2 : 1 molar ratio was used the yield of **1** on the residual mixture obtained by concentration of the methanolic solution was about 8% (Fig. 7). This supports that a 1 : 1 molar ratio (HA^{Ts} : Cu^{2+}) is adequate for the oxidation of methanol to formaldehyde as it was deduced from the stoichiometry of $Cu(OAc)_2(H_2O)(MeOH)_2(HA^{TS})$.

Common to reported mechanisms[17–20] for Cu-imine catalysed reactions is that no oxidation is observed without a base, which is needed for the deprotonation of the alcohol. Besides, the alcohol oxidation usually leads to the reduction of Cu(II) and therefore oxygen is needed to oxidize the Cu(I) complex back to Cu(II). Based on the latter, the oxidation of methanol to formaldehyde would involve the formation of a Cu-methanolate complex which would lead to a Cu-formaldehyde complex by 2-tosylaminomethylaniline assisted deprotonation (Fig. 8). On a subsequent reaction step, the experimentally

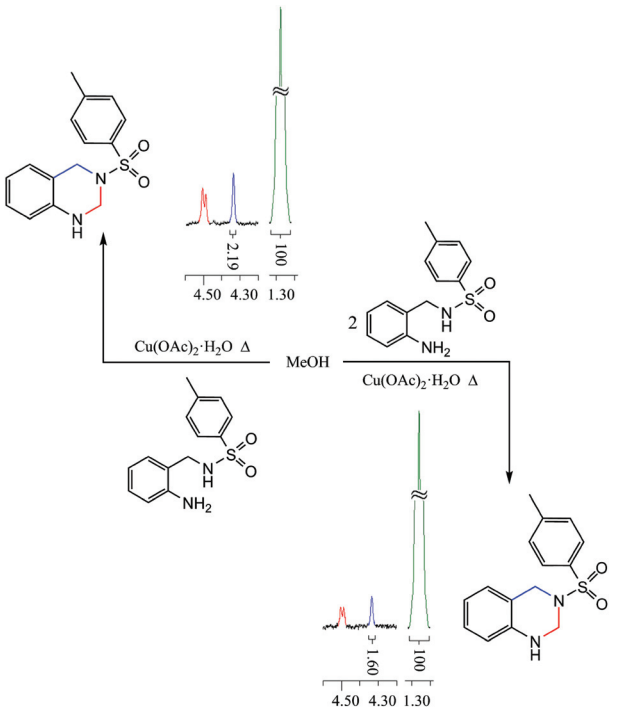

Fig. 7 Reactions used to study the influence of 1 : 1 and 2 : 1 molar ratios (HA^{Ts} : Cu^{2+}) on the yield of **1**. Partial views of the ^1H NMR spectra (in dmso-d_6) of the residual mixtures obtained by concentration of the methanolic mother liquors of these reactions are also shown. The signals corresponding to the protons at 2- and 4-positions of the tetrahydroquinazoline ring have been highlighted in red and blue colours, respectively. The yield of **1** was determined by integration of the methylene signal at 4-position (highlighted in blue color) against the internal standard 1,3,5-tri-*tert*-butylbenzene (**ttbb**). The integration value for the methyl signal of **ttbb** (at 1.35 ppm, highlighted in brown colour) was considered as 100 for ease of comparison.

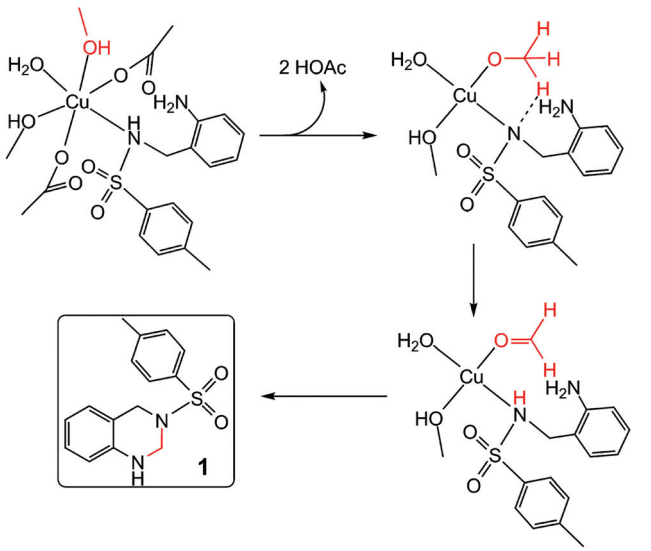

Fig. 8 Proposed pathway for obtaining **1** from $Cu(OAc)_2(H_2O)(MeOH)_2(HA^{TS})$.

obtained tetrahydroquinazoline **1** would be produced from the nucleophilic addition of 2-tosylaminomethylaniline to the carbon atom of formaldehyde.

Conclusions

The concurrence of both hydrolytic and oxidative processes on the methanolic mother liquors of $Cu_2(L_{SB})_2$ explains the obtainment of 3-tosyl-1,2,3,4-tetrahydroquinazoline (**1**), which is a sign of the copper-mediated aerobic oxidation of methanol to formaldehyde.

Further investigation on methanol oxidation has shown that among the species originated by imine hydrolysis 2-tosylaminomethylaniline (HA^{Ts}) and 8-hydroxyquinoline-2-carboxaldehyde, the latter one does not influence the yield of **1**, while the first plays a dual role acting as a ligand and a nucleophile. Besides, we have isolated and spectroscopically characterized $Cu(OAc)_2(H_2O)(MeOH)_2(HA^{TS})$, which is a key to understand the formation of **1** from HA^{Ts} and $Cu(OAc)_2{\cdot}H_2O$ as well as the inhibition of the methanol oxidation by the addition of water. We have observed that a 1 : 1 molar ratio (HA^{Ts} : Cu^{2+}) is more adequate than a 2 : 1 molar ratio for the obtainment of **1** (22% *vs.* 8%), and therefore the oxidation of methanol to formaldehyde.

The methanol oxidation by the Cu^{2+}/HA^{Ts} 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.

Experimental

General

Excluding 2-tosylaminomethylaniline (HA^{Ts}),[21] all starting materials and reagents were commercially available and were used without further purification. ^{1}H NMR spectra (500 MHz) and ^{13}C NMR spectra (125 MHz) were measured in deuterated solvents. *J* values are given in hertz. NMR assignments were carried out by a combination of COSY, NOESY, HSQC and HMBC experiments. Infrared spectra were recorded as KBr pellets using a Jasco FT/IR-410 spectrophotometer in the range 4000–600 cm^{-1}. Elemental analyses were performed using a Carlo Erba EA 1108 analyzer. Electrospray mass spectra were recorded using a Bruker Microtof spectrometer. MALDI-TOF mass spectra were recorded using a Bruker Ultraflex III TOF/TOF using methanol as a solvent and DCTB as a matrix.

Crystal structure analysis 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 2.

Data were processed and corrected for Lorentz and polarization effects. Multi-scan absorption corrections were performed using the SADABS routine.[22,23] The structure was solved by standard direct methods[24] and then refined by full matrix least squares on F^2.[25] All non-hydrogen atoms were anisotropically refined. Hydrogen atoms were included in the structure factor calculation in geometrically idealized positions, with thermal parameters depending on the parent atom, by using a riding model.

CCDC 939751 contains the supplementary crystallographic data for this paper.

Table 2 Diffraction data for **1**

Formula	$C_{15}H_{16}N_2O_2S$
M_r	288.36
Crystal system	Monoclinic
Space group	$P2_1/c$ (No 14)
Unit cell	a = 15.9574(4) Å
	b = 6.0364(1)
	c = 14.9838(3) Å
	α = 90°
	β = 110.936(1)°
	γ = 90°
Volume (Å^3)	1348.03(5) Å^3
Z	4
D_c (g cm^{-3})	1.421 Mg m^{-3}
μ (mm^{-1})	0.243 mm^{-1}
F(000)	608
θ range (°)	2.73 to 31.205° (99.5)
Ref. col./Ref. Ind	72 839/5158
R_{int}	0.0525
Data/restr./param.	5158/0/187
R_1, wR_2 [$I > 2\sigma(I)$]	R_1 = 0.0382, wR_2 = 0.0537
R_1, wR_2 (all data)	R_1 = 0.0961, wR_2 = 0.1042
Residuals (e Å^{-3})	0.551, −0.468 e A^{-3}

Synthesis of compounds

$Cu(Q)_2{\cdot}2H_2O$. This compound was separated from the methanolic mother liquors of $Cu_2(L_{SB})_2$ by flash chromatography eluting with diethyl ether–hexane (50 : 50).

MS (MALDI-TOF, DCTB) 408.5 *m*/*z* (100%) $[M]^+$. FT-IR (KBr): 3444(br,m) ν(O_w–H), 1705(m), ν(C=O); 1475(m) ν(C=N_{quin}) cm^{-1}. Elemental analysis found: C 54.4; H 3.6; N 6.5%; calcd for $C_{20}H_{16}CuN_2O_6$: C, 54.1; H, 3.6; N, 6.3%.

3-Tosyl-1,2,3,4-tetrahydroquinazoline (1). Since the obtainment of this compound was the goal of five experiments, the experimental details of each of them are stated below.

Experiment 1: Compound **1** was obtained from a non-deuterated 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 solvents were methanol-d_4 and methanol-^{13}C. Filtration of the resulting suspensions yielded filtrates that were then 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 the absence of any metal salt and to 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.

Experiment 3: A solution of 2-tosylaminomethylaniline (0.02 g, 0.07 mmol) and formaldehyde (0.005 mL, 0.07 mmol) in THF (2 mL) was heated under reflux for 2 h. Yield = 69%.

Experiment 4: A solution of 2-tosylaminomethylaniline (0.06 g, 0.2 mmol), 2-(aminomethyl)quinolin-8-ol (0.01 g, 0.06 mmol) or 8-hydroxyquinoline-2-carboxaldehyde (0.01 g, 0.06 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (0.02 g, 0.1 mmol) in methanol (2.5 mL) was heated under reflux for 24 h. Alternatively, the reaction was performed in the absence of 8-hydroxyquinoline residues. In all the cases the yield of **1** was about 8%. The yield of the obtained crude product was determined by integration of the methylene signal at the 4-position against the internal standard 1,3,5-tri-*tert*-butylbenzene (0.009 g, 0.035 mmol).

Experiment 5: A solution of 2-tosylaminomethylaniline (0.10 g, 0.36 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (0.04 g, 0.18 mmol) in methanol (25 mL) was heated under reflux for 24 h. The yield (8%) of **1** in the obtained crude product was determined by integration of the methylene signal at the 4-position against the internal standard 1,3,5-tri-*tert*-butylbenzene (0.02 g, 0.07 mmol). The formation of **1** was prevented by addition of water (5 mL) to the reaction medium.

Experiment 6: A solution of $Cu(OAc)_2(H_2O)(MeOH)_2(HA^{TS})$ (0.10 g, 0.18 mmol) in methanol (25 mL) was heated under reflux for 24 h. The yield (about 20%) of **1** in the obtained crude product was determined by integration of the methylene signal at the 4-position against the internal standard 1,3,5-tri-*tert*-butylbenzene (0.02 g, 0.07 mmol).

Experiment 7: Compound **1** was obtained from a methanol solution (2 mL) of 2-tosylaminomethylaniline (0.03 g, 0.10 mmol or alternatively 0.06 g, 0.20 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (0.02 g, 0.10 mmol), which was heated under reflux for 24 h. Filtration of resulting suspensions yielded filtrates, which were then concentrated under vacuum to remove methanol. When a 1 : 1 molar ratio ($HA^{Ts} : Cu^{2+}$) was used the yield of **1** was about 22%, but when a 2 : 1 molar ratio ($HA^{Ts} : Cu^{2+}$) was used the yield of **1** was about 8%. The yield of the obtained crude product was determined by integration of the methylene signal at the 4-position against the internal standard 1,3,5-tri-*tert*-butylbenzene (0.02 g, 0.07 mmol).

^{1}H 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) ν(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%.

$Cu(H_2O)(MeOH)(HA^{TS})(OAc)_2$. An aliquot was separated from the reaction medium of the experiment 4 after 1 h of the start. Evaporation of the latter aliquot leads to an oily residue. Stirring of the obtained oil with diethyl ether gave a brown powder. Alternatively, the complex was obtained from a methanol solution (40 mL) of 2-tosylaminomethylaniline (0.15 g, 0.50 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (0.10 g, 0.50 mmol), which was heated under reflux for 1 h. Filtration of the resulting suspension yielded a filtrate, which was then concentrated under vacuum to remove methanol.

MS (MALDI-TOF, DCTB) 563.1 m/z (100%) $[M + Na]^+$ FT-IR (KBr): 1576(vs), ν_a(COO); 1431(vs) ν_s(COO), 1324(s) ν_s(SO); 1158(s) ν_{as}(SO) cm^{-1}. Elemental analysis found: C 44.4; H 5.6; N 5.5; S 5.8%; calcd for $C_{20}H_{33}N_2O_9SCu$: C, 44.5; H, 6.0; N, 5.2; S, 5.9%.

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