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Cleavage of acetylenic substituents from camphor-derivatives by copper(I) chloride

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ABSTRACT

Copper(I) chloride was found to be a highly efficient reagent to promote the cleavage of acetylenic substituents from the camphor skeleton of compounds **1** containing two C–C triple bonds as well as from the compounds **6** and **7** containing one. This is a formal reversal of the formation of these compounds by the reaction of acetylides with keto and imino groups in compound **18**. The substituent R at the triple bond modifies the reactivity and regioselectivity. As intermediates in the process we identified complexes of the types $[Cu(L)_{depr}]$ (where $(L)_{depr}$ denotes a deprotonated camphor-derived ligand (L)) and [CuCl(L)]. Quantum mechanical calculations support and rationalize the experimental results.

1. Introduction

The triple bonds of the camphor-derived compounds (**1**, see Fig. 1) can react with a variety of electrophiles including many metal salts with unique reaction patterns such as cyclisations, ring-opening/ring-closure cascades and C–H activations [1–6], leading to peculiar products such as taxol analogues by expansion of a six-membered to an eight-membered ring under platinum(II) catalysis [3,4]. We found that $CuCl_2$ reacts with compound **1c** (R = Ph) under annulation of a five-membered ring to the camphor skeleton accompanied by sulfur reduction [3]. In order to gain insight in the activation of triple bonds by coordination to closed-shell transition metal ions, we studied the reaction of copper(I) chloride with the camphor-derived mono- (compounds **6** and **7**) and di-alkyne species (compounds **1**). Surprisingly, the reaction followed a totally different pathway and led to the cleavage of acetylenic substituents from the camphor skeleton, a formal reversal of the formation of these compounds by the reaction between (3a*S*)-8,8-dimethyl-5,6-dihydro-3*H*-3a,6-methano-2,1-benzisothiazol-7(4*H*)-one 2,2-di-oxide (**18**) and lithium acetylides. We therefore employed quantum mechanical calculations on model compounds in order to rationalize this behaviour.

2. Results and discussion

2.1. Experimental results

The camphor-derived alkynes **1**, **6** and **7** do not react directly with copper(I) chloride, in contrast to $CuCl_2$. To promote their reactivity, it is necessary to deprotonate them. Both sodium amide and triethylamine can serve for this purpose. In the di-alkynes (**1**), potential deprotonation sites are the hydroxy and the sulfonamide groups. A remarkable selectivity is observed in the deprotonation reaction: depending on the substituent R of the triple bonds, either OH (for R = Ph, compound **1c**) or NH (for R = CH_2-Ph, compound **1d**) is deprotonated exclusively. This can easily be followed by ^{1}H NMR spectroscopy. When the corresponding signals of the OH or NH groups have disappeared, a stoichiometric amount of CuCl is added, and the formation of the compounds **4** or **5** starts. However, isolation in pure form was possible only for the ligand **1d** (with the benzyl group at the triple bonds). Although generally precipitation of these complexes from the dichloromethane solution in which they are prepared readily occurs, any attempts of re-dissolution (or prolonged stirring in the mother liquor as well as increasing the amount of solvent) led to the formation of reprotonated complexes which we formulate on the basis of elemental analysis (C, H, N, S) as $[CuCl(\mathbf{1})] \cdot x H_2O$. The presence of water in the analytical data is mainly due to the hygroscopic nature of the compounds since the elemental analyses could not be performed under inert atmosphere. Small amounts of copper(II) chloride readily form in solution that are responsible for in ill-resolved paramagnetic NMR spectra.

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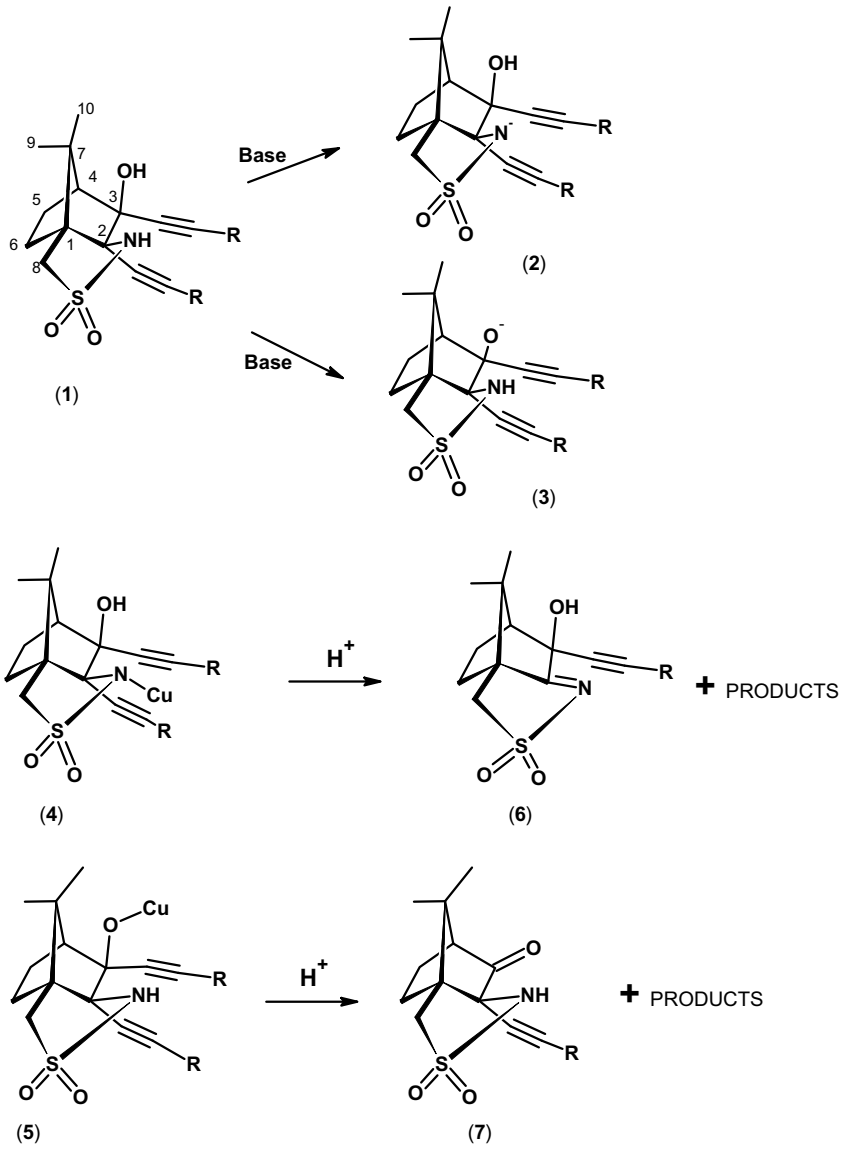

Fig. 1. Site-selective deprotonation and complexation of camphor-derived diynes with copper(I) and dealkynylation by protonation.

The formation of the complexes [CuCl(**1**)] is surprising since one might expect that they can also be formed directly from CuCl and the camphor-dialkynes **1** which is, however, not the case. The presence of at least one triple bond is confirmed by IR spectroscopy and excludes the known modifications of the compounds **1** which occur with other metals and even with $CuCl_2$ [3].

Similar complexes can be obtained from the camphor-derived mono-alkynes (**6** and **7**) by deprotonation and reaction with CuCl. Species **7c** (R = Ph) behaves similar to **1** in the sense that both the primary product [Cu($\mathbf{7c}$)$_{depr}$] and the reprotonated complex [CuCl(**7c**)] can be obtained, while from **6e** only [CuCl(**6e**)] can be isolated.

A detailed analysis of the organic products which accompany the formation of the [CuCl(**1**)] complexes gave the very surprising result that a reaction with high selectivity had occurred with the formation of the compounds **7c** from **1c** on one hand and **6d** and **6e** from **1d** and **1e** on the other.

The cleavage of an acetylenic substituent is an unprecedented type of reaction in the series of camphor derivatives studied. The regioselectivity of the bond cleavage reflects the selectivity in the deprotonation reaction and suggests that copper coordination preferably occurs at the deprotonated heteroatom.

The yield of the organic species can be greatly increased by adding a few drops of aqueous HCl to the reaction mixture or to a suspension of the isolated complexes [CuCl(**1**)] in dichloromethane, and an excess of CuCl over the stoichiometric amount also helps. When the same technique is applied to the complexes [CuClL] (L: **6e**, **7d** or **7e**) the cleavage of the acetylenic substituent occurs in exactly the same manner leading to 3-oxo-camphorsulfonimine **18**, and is thus a complete reversal of the reaction in which the compounds **1**, **6** and **7** are formed by its reaction with lithium acetylides [1,3,7]. This very different behaviour of copper(I) when compared with other metal salts is not easy to understand. We therefore undertook a series of quantum mechanical calculations in order to obtain further insight in the reaction path.

2.2. Quantum mechanical calculations

2.2.1. Copper coordination site in camphor-derived diynes

Experimentally, there is a surprisingly clear preference for deprotonation of the diyne **1c** at the hydroxy group, in contrast to **1d** and **1e** where the proton at the sulfonamide nitrogen is removed by base. The deprotonation site is important since copper coordination can be expected to occur initially in this position

and trigger the regioselectivity of the final cleavage of the acetylenic substituent. In an attempt to understand better this behaviour, we studied the influence of the substituent R in compounds **1** on the initial deprotonation by theoretical means.

We calculated the compound **1c** (R = Ph) where experimental results exist, **1a** (R = H) as the simplest compound of this type for comparison, and **1b** (R = Me) as a reasonable model for **1d** ($R = CH_2Ph$), in order to limit the size of the calculation. The calculations were done at the HF level using 6-31G* as basis set which seems to be a reasonable compromise between accuracy and computation time.

There are two main reasons that can drive preferential N or O deprotonation: (i) different acidities of the protons (reflected in the calculated partial charges in the neutral molecules **1**), these acidities may have an effect on the deprotonation rate – kinetic argument or (ii) the stability of the monoanions **2** and **3** (Fig. 1) may be different, thus the more stable anion forms – thermodynamic argument.

The relevant results from the calculation made on the neutral compounds **1a–c** are displayed in Table 1. Both Mulliken and Löwdin charges are quoted for the chain of atoms connecting directly the protons under consideration. According to the electronegativity of the participating atoms and groups, the tendency appears reasonable. All charges for a specific atom are very similar for any of the substituents (H: **a**; CH_3: **b**; C_6H_5: **c**) except for the Mulliken charges at the carbon C-1 (neighbour to the oxygen atom) which show a moderate increase in charge with increasing bulkiness of the substituent. There is no obvious connection of those differences with deprotonation at oxygen in **1c** or nitrogen in **1d**.

The thermodynamic stability of the anions **2b** vs. **3b** and **2c** vs. **3c** was compared by calculation of the total energies, neglecting zero-point corrections which are similar for **2** and **3**. For anions **2b** and **3b** (R = Me), it was still possible to include diffuse basis functions at the heteroatoms which is expected to give more reliable results for anions, but this did not change the energy difference significantly (12.6 kcal/mol with diffuse functions vs. 12.4 kcal/mol without).

The N-deprotonated isomer turned out to be more stable by 12.4 kcal/mol ($R = CH_3$) and 11.7 kcal/mol ($R = C_6H_5$) pointing to deprotonation at the nitrogen atom being thermodynamically favoured. The influence of the solvent (dichloromethane) in both cases is unlikely to be very different, so no obvious reason for preferential deprotonation at the oxygen atom in **1c** to form **3c** is found. However, the experimental results show that it occurs and former studies [3–5] indicate that coordination of type **1** camphor ligands to platinum(II) involves the oxygen atom of the OH group. Thus, we decided to check first the possibility of forming copper(I) complexes with propargylic alcohols deprotonated at oxygen both in a linear (**10**) or bent (cyclic) fashion (**11**). In these models, the sterically demanding camphor-derived residue is replaced by a CH_2 group. The results are therefore expected not to reflect possible steric hindrance but rather electronic effects of the R substituents (Fig. 2).

Table 1
Calculated charges (Mulliken and Löwdin method) in the H^1–O–C^1–C^2–N^2–H chain of the camphor-derived diynes

R[a]	1a		1b		1c	
	Mulliken	Löwdin	Mulliken	Löwdin	Mulliken	Löwdin
H^1	0.466	0.379	0.462	0.377	0.465	0.378
O	−0.781	−0.483	−0.785	−0.487	−0.785	−0.486
C^1	0.358	0.169	0.376	0.172	0.396	0.172
C^2	0.012	0.072	0.017	0.075	0.026	0.075
N	−0.843	−0.539	−0.842	−0.540	−0.840	−0.539
H^2	0.434	0.315	0.432	0.314	0.434	0.315

[a] **1a** (R = H), **1b** (R = CH_3), **1c** (R = C_6H_5).

For calculations of copper-containing compounds an ECP basis set appeared appropriate, and we decided to include electron correlation by a DFT method (PBE0) (see Section 4). Only closed-shell copper(I) complexes of propargylic alcohols were studied since it is well known that terminal alkynes undergo Glaser coupling in the presence of copper(II) [8–10]. We also decided to calculate monomers only since in the real systems the camphor moiety introduces a considerable steric bulkiness that should make oligomerisation difficult although copper–organic compounds are known to form polymers or oligomers [11–13].

The results of these calculations are presented in more detail in the Supplementary material (available online).

In the linear model no interaction between copper and the triple bond is possible whereas in the bent (cyclic) isomers the interaction of copper with the triple bond is possible as well as the interaction with the R substituent (Table 2).

Energetically, the bent structures **11** are favoured by 6–7 kcal/mol over the linear ones for R = H, CH_3 and C_6H_5 and considerably more favoured for benzyl and aminomethyl substituents due to additional interactions of copper with the phenyl group or the nitrogen atom, respectively. π-Coordination of the triple bond to the copper atom is accompanied by longer Cu–O distances and lower ν(C≡C) frequencies (by 50–200 cm^{-1}, Table 2). For the benzyl-substituted compound **11d**, the Cu–C2, Cu–C3 and Cu–C1 bond distances are all in the same range. Since C-1 coordination does not occur, there can hardly be any interaction between copper and the triple bond. The high stability of **11d** (bent) compared with**10d** (linear) is therefore mainly due to the η^2-coordination of copper to the phenyl group (Cu–CPh: 2.098 and 2.167 Å, respectively). We also find that in the aminomethyl-substituted compound **11e** copper coordinates directly to the nitrogen atom (Cu–N: 1.975 Å and angle N–Cu–O 154.4°) and the interaction with the triple bond is weak.

Besides the linear and cyclic structures **10** and **11**, no other minima on the potential hypersurface were detected. We therefore conclude that bonding in complexes of camphor-derived diynes should resemble model **11**, with copper coordinating to the triple bond in a degree which depends strongly on the nature of the substituent R.

In fact, by reaction of CuCl with **1d** a reasonably stable compound formulated as [Cu(**1d**)$_{depr}$] was obtained while no analogous products could be isolated from **1c** or **1e** under the same reaction conditions; in contrast, protonated species [CuCl(**1**)] are formed.

2.2.2. Protonation of copper(I) model complexes of propargylic alcohols

Following by ^{1}H NMR the reaction of **1c** with CuCl, there is some evidence for formation of a complex of type **5**, although it is not stable enough to be isolated and further reacts to the dealkynylated camphor derivatives **7**. The process is highly sensitive to proton concentration (even moisture fastens the process).

To get some insight into the protonation process that prompts dealkynylation we used the model systems **8** (Fig. 2) where the expected final products are formaldehyde, a terminal alkyne, and Cu^+ (**9**, Fig. 2) or their isomeric ensembles where copper remains coordinated to the two organic products. The possible sites for proton attack (at model molecules **10** or **11**) are oxygen, the carbon atoms of the triple bond and amino nitrogen for **11e**.

In the simplest case (R = H, **10a** and **11a**) we found seven minima on the potential hypersurface together with a transition state (**12TS**, Fig. 3). Protonation at oxygen is straightforward and leads to **12A** from **10a** or **12E** from **11a** where the structure of the starting complexes is almost maintained. As for the neutral compounds, the cyclic isomer is more stable than the linear (ΔE = 15.5 kcal/mol).

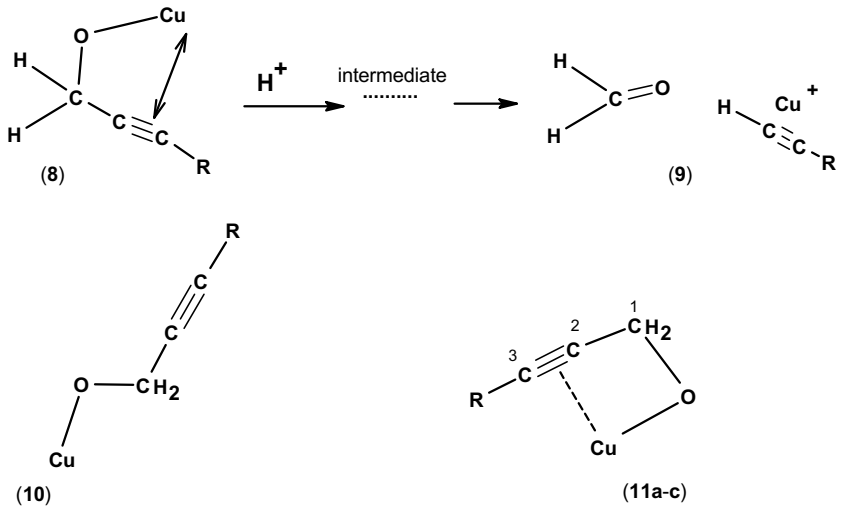

Fig. 2. Modelling the cleavage of acetylenic substituents from camphor derivatives with neutral copper(I) complexes (**8**) of propargylic alcohols. Open (**10**) and ring-closed (**11a–c**) structures used in the calculations. R = H: **a**; R = CH_3: **b**; R = C_6H_5: **c**; R = $CH_2C_6H_5$: **d**; R = CH_2NH_2: **e**.

Table 2
Calculated bond distances (Å), angles (°) and frequencies ($\nu_{C\equiv C}$; cm^{-1}) for cyclic neutral Cu(I) complexes (**11**)

	Cu–O	Cu–C1	Cu–C2	Cu–C3	C≡C	C1–C2–C3	C2–C3–R	ν(C≡C)
11a	1.930	2.486	2.054	2.167	1.276	164.0	157.8	1951
11b	1.925	2.475	2.066	2.235	1.273	166.1	162.5	2110
11c	1.911	2.498	2.125	2.371	1.265	169.7	173.1	2158
11d	1.832	2.812	2.816	3.066	1.251	163.6	162.6	2253
11e	1.859	2.708	2.539	2.614	1.253	158.8	154.7	2218

See Fig. 2 for numbering.

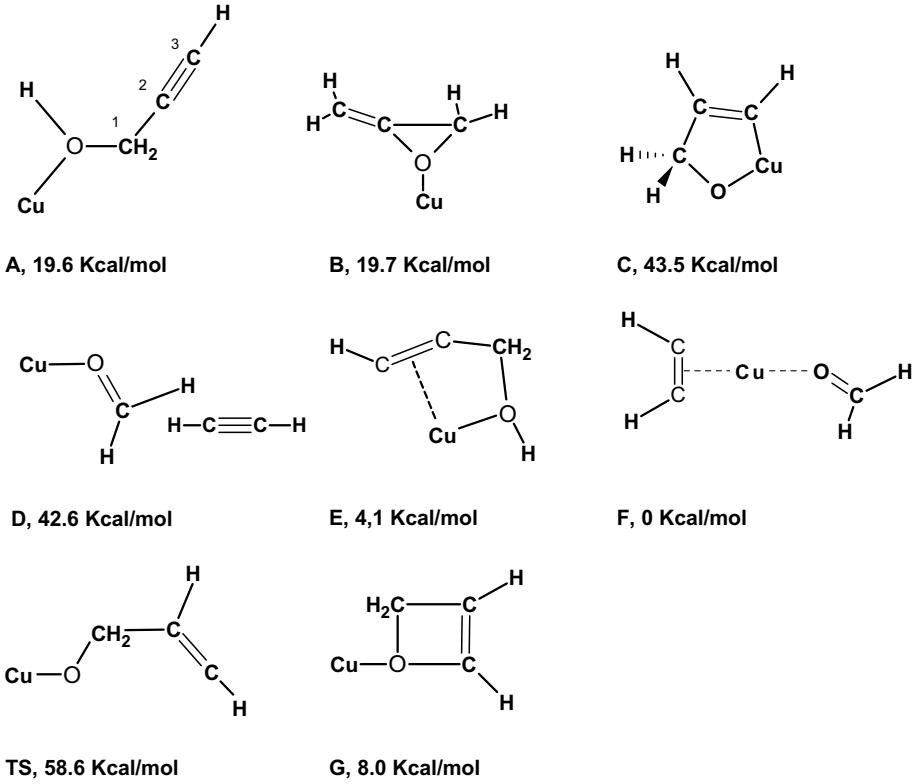

Fig. 3. Calculated structures (and energies) of protonated Cu(I) complexes (**12**, R = H). The (often delocalized) positive charge is not shown.

Protonation at C3 produces the compounds **12A** and **12B** and protonation at C2 leads to the compounds **12C** and **12G** from the bent isomer. A slightly different starting geometry leads to C–C bond rupture and the formation of a cationic copper complex **12F** where both acetylene and formaldehyde coordinate. This is the most stable point detected on the potential hypersurface. Protonation at C-2 in **10a** (linear isomer) also leads to C–C bond rupture but to a situation where only formaldehyde coordinates to copper (**12D**, Fig. 3). This is of course a computational artifact since in a real system the acetylene is mobile and can easily adopt a position where it can coordinate to copper. Albeit at high energy, the transition state **12TS** connects the oxeten **12G** with **12D** (Fig. 3) as shown by an IRC (intrinsic reaction path) calculation on this reaction. Although the oxeten is considerably more stable than the ensemble **12D**, it is less stable by 8.0 kcal/mol than the isomeric ensemble **12F** which can easily form from **12D** by acetylene diffusion. This reaction path shows therefore a potential reaction mechanism for the cleavage of the camphor-derived diynes **5** (or even **4**, if the properties of the ketone and imine groups were similar) to the ketone **7** (Fig. 1), although we cannot exclude other transition states (possibly with lower energy) which may lead to the same cleaved products. The proposed reaction mechanism seems to be almost an inversion of that suggested for the formation of propargylic amines from terminal alkynes and imines under catalysis by copper(I) [13].

Information about bond distances of the isomeric molecules **12** can be found in Table 3, and a more detailed description including the protonated copper(I) complexes of substituted propargylic alcohols (with R = Me (**13**), Ph (**14**), CH_2Ph (**15**) and CH_2NH_2 (**16**)) is given in the Supplementary material. As shown in Table 3, bonding and stability of the protonated copper(I) complexes of these derivatives generally follows the patterns observed with the neutral complexes **10** and **11**, i.e., additional stabilization is achieved by coordination of the phenyl (η^2-coordination) or amino group to copper.

2.2.3. Copper(I) compounds using mono-deprotonated derivatives of N-[(3S,4R)-3-hydroxy-1,5-hexadiyn-4-yl]methanesulfonamide as model ligands

Propargylic alcohols were used as models in a first attempt to rationalize the reaction of di-alkyne species (**1**) with CuCl. The process is not straightforward and the reactivity most probably is not only controlled by the site of deprotonation. It appeared possible that not only the substituent R at the triple bonds but also the sulfonamide group has an influence on the course of the reaction. Thus, we decided to go a step forward and use mono-deprotonated derivatives of *N*-[(3*S*, 4*R*)-3-hydroxy-1,5-hexadiyn-4-yl]methanesulfonamide (R = H (**17**), CH_3 (**19**), Ph (**20**), CH_2Ph (**21**), CH_2–NH_2 (**22**), Fig. 4) instead of propargylic alcohols as models for coordination to Cu(I).

Both deprotonation at N and O were considered, and copper(I) complexes were calculated from different starting geometries in order to find most of the minima on the potential hypersurface. Since rotation around the C3–C4 bond (Fig. 4, for numbering) is inhibited in the camphor-derived diynes we mimicked this behaviour by fixing the dihedral angle (H–C3–C4–H) to zero. The disadvantage of this procedure is that the resulting constrained minima are not true minima on the unconstrained potential hypersurface, and therefore the Hessian calculation always gives imaginary frequencies. The calculated stretching frequencies for the C≡C bonds should thus be considered as estimates.

The introduction of the sulfonamide group in the models for coordination of **1** to copper(I) considerably changes the bonding situation compared to propargylic alcohols. Now, the copper ion can coordinate to almost any nucleophilic atom or group (excluding the nitrogen atom of the sulfonamide when it is not deprotonated) allowing a variety of coordination modes with different stabilities. The principal aim of the calculations was therefore to

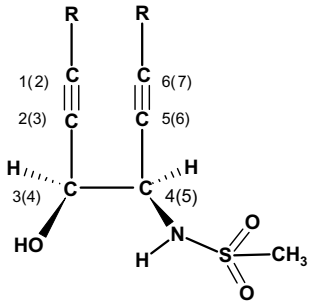

Fig. 4. Scheme for *N*-[(3*S*, 4*R*)-3-hydroxy-1,5-hexadiyn-4-yl]methanesulfonamide (**17**); *N*-[(4*S*, 5*R*)-4-hydroxy-2,6-octadiyn-5-yl]methanesulfonamide (**19**); *N*-[(3*S*, 4*R*)-3-hydroxy-1,6-diphenyl-1,5-hexadiyn-4-l]methanesulfonamide, (**20**); and *N*-[(4*S*,5*R*)-4-hydroxy-1,8-diphenyl-2,6-octadiyn-5-yl]methanesulfonamide (**21**) used as models.

Table 3
Structures of protonated Cu(I) complexes[a] of substituted propargylic alcohols HO–C^1H_2–C^2≡C^3–R

	ΔE	Cu–O	Cu–C1	Cu–C2	Cu–C3	C2–C3	ν(C≡C)	Other
12A	0	1.891	3.072	4.271	5.390	1.248	2175	Cu–H(O): 2.556
12B	+0.1	1.881	3.296	3.203	4.041	1.342	1856	
12C	+23.9	1.764	2.758	2.767	1.917	1.369	1563	
12E	−15.5	2.096	2.703	2.108	2.211	1.259	2071	
12G	−11.6	1.876	3.197	3.979	3.114	1.359	1608	
12TS	+39.0	1.821	2.912	4.207	4.346	1.300	1679	
13A	0	1.816	2.981	3.903	4.935	1.290	1953	
13B	−16.4	1.879	3.262	3.180	4.018	1.344	1876	
13C	−0.9	1.753	2.787	2.759	1.909	1.357	1707	Cu–CH_3: 2.589
14A	0	1.806	2.874	4.167	4.460	1.320	1919	
14B	−19.2	2.039	3.600	2.941	3.259	1.350	1828	Cu–C_{Ph}: 2.070, 2.484
14C	−6.2	1.787	2.763	2.742	1.919	1.352	1776	Cu–C_{Ph}: 2.305
15A	0	1.814	2.965	3.921	4.958	1.294	1921	
15B	−52.6	1.944	3.430	3.095	3.810	1.349	1859	Cu–C_{Ph}: 2.727 (subst), 2.518, 2.228, 2.150, 2.413, 2.689
15C	−34.8	1.750	2.773	2.758	1.940	1.360	1689	Cu–C_{Ph}: 2.287 (subst), 2.131,
15X	+10.7	1.831	2.681	1.898	3.048	1.446	–	C^3–CH_2: 1.391, Cu–C_{Ph}: 1.846
16A	0	1.815	2.971	3.879	4.933	1.298	1892	
16B	−47.1	1.753	2.787	2.759	1.909	1.357	1707	Cu–CH_2: 2.589 Cu–N: 2.382

Energies relative to acyclic structure **12A** (kcal/mol), bond distances (Å), C≡C stretching frequency (cm^{-1}).
[a] **12**: R = H; **13**: R = CH_3; **14**: R = C_6H_5; **15**: R = CH_2–C_6H_5; **16**: R = CH_2NH_2.

Table 4
Calculated data for copper(I) complexes of deprotonated *N*-[(3*S*,4*R*)-3-hydroxy-1,5-hexadiyn-4-yl]methanesulfonamide

Compound	ΔE (kcal/mol)	Site		ν(C≡C) (cm^{-1})
		Deprotonated	Cu Coordination	
17a	0	N	O(S), C≡C	2140, 2008
17b	9.4	O	O^-, O(S)	2168, 2146
17c	10.4	N	N^-, OH, O(S)	2166, 2158
17d	20.7	O	O^-, C≡C	2162, 1963

identify the most stable species which might give hints to the structures of the copper complexes obtained experimentally with the camphor-derived ligands **1**, **6** or **7** (Fig. 1).

In these models, the coordination of copper to one of the oxygen atoms of the SO_2 group becomes highly relevant for the stability (Table 4). Simultaneous coordination of copper to the triple bond at C4 and to other nucleophilic centres is unflavored by the constraint and does not occur. A detailed discussion of bonding and stability in the substituted derivatives is given in the Supplementary material.

A typical coordination pattern involves copper bonding to N^-, OH and one of the oxygen atoms of the SO_2 group (**17c**, see the Supplementary material for figures). Energetically it occupies a medium position in the isomeric series. Another common arrangement is the simultaneous coordination to copper of the oxygen anion and the triple bond (at C3, **17d**). Lacking the stabilizing effect of the oxygen atom of the SO_2 group this isomer has always the highest energy.

2.2.4. Protonation of copper(I) complexes of deprotonated N-[(3S,4R)-3-hydroxy-1,5-hexadiyn-4-yl]methanesulfonamide

From the experiment and the results of the calculations on the copper complexes of propargylic alcohols, protonation seems to be a crucial step in the cleavage of the acetylide residue from the camphor skeleton. We therefore attempted protonation of the constrained complexes **17**. Since in these multi-functional molecules there are many potential sites for protonation, the final position of the proton after geometry optimisation may be different from the initial situation and even rearrangements with migration of the acetylenic groups may occur which, however, were not found experimentally. For details, see the Supplementary material.

Proceeding from R = H (**17**) to R = Me (**19**), R = Ph (**20**) or R = CH_2Ph (**21**) and CH_2NH_2 (**22**), the influence of the functional groups on the structure of the copper complexes was studied. The general behaviour of the compounds with terminal hydrogen (**17**) is maintained throughout, particularly the stabilization of structures by coordination of an oxygen atom of the SO_2 group to copper. Thus, we observe for both the methyl and phenyl substituents that the three structures containing this bonding element are clearly more stable (11–13 kcal/mol) than the one which does not. In both the methyl and the phenyl series, it is the simultaneous coordination of a triple bond and the oxygen atom of the SO_2 group which leads to the most stable isomers. The close analogy in the stability ranking of the compounds **17**, **19** and **20** shows that simple alkyl and aryl substituents do not have a significant influence on the structures of the species and probably also not on their reactivity.

A very different situation was found for benzyl-substituted ligands where the phenyl group can interact with the metal ion. The two most stable isomers correspond to a situation where η^2-coordination of copper to the phenyl ring (*ortho*/*meta* position) occurs (see Supplementary material). This stabilizing effect corresponds to ca. 14 kcal/mol. Once more the model accounts for the relevance of the R group in the process as experimentally observed.

Another special case is the aminomethyl ($-CH_2NH_2$) group which is much more nucleophilic than any of the other R groups discussed till now, and it is therefore not surprising that coordina-

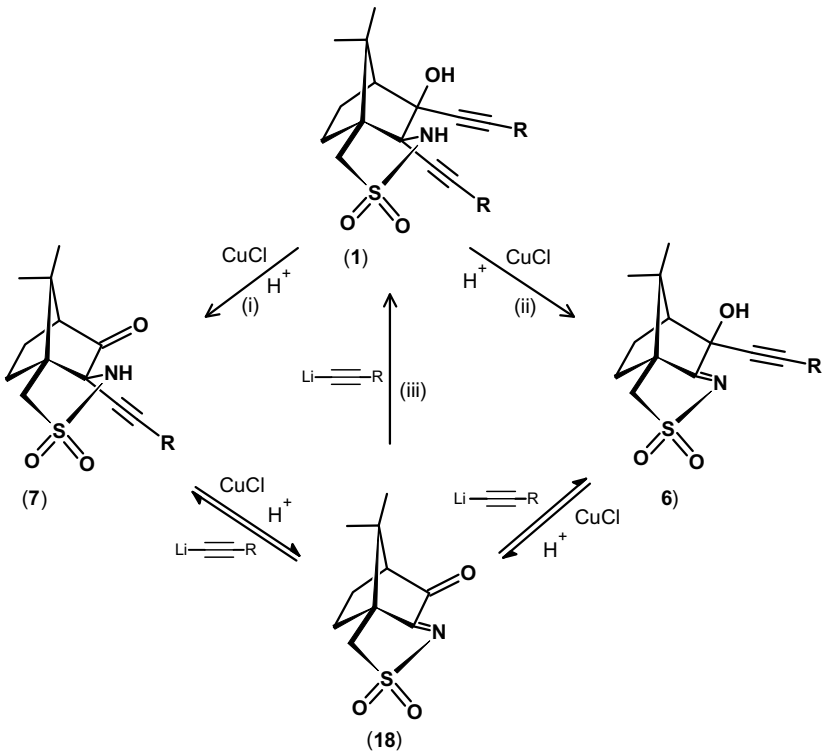

Fig. 5. Formation of camphor-derived diynes (**1**) or camphor-derived monoynes (**6**) or (**7**) from 3-oxo-camphorsulfonylimine (**18**), and its reversal by reaction with copper(I) chloride.

tion to copper occurs readily leading to the most stable isomers of the series (see Supplementary material). However, simultaneous coordination of one triple bond and the oxygen atom of the SO_2 group leads to an isomer of similar energy (the corresponding structure is also lowest in energy with the methyl and phenyl substituents). Thus, there is no safe way to predict if the presence of the aminomethyl group will have an influence on the course of reactions between copper(I) and the species **1**.

3. Conclusions

Deprotonated camphor-derived mono- and di-alkynes (L = **6**, **7** and**1**), react with CuCl to form complexes of the type $[Cu(L)_{depr}]$ where $(L)_{depr}$ denotes deprotonated (L). Under slightly basic conditions (before removal of unreacted base) it is possible to isolate these complexes for L = **1d** and **7c**. In contrast, under slightly acidic conditions only the protonated species [CuCl(L)] were detected. An unprecedented cleavage of one alkyne substituent from the ligands was observed on addition of excess HCl to the complexes to form the mono-alkynes (**6d**, **6e**, and **7c**, respectively) from the di-alkynes (**1**) in high yields. This process can already be started by adventitious water, e.g., from the solvents used for workup, making the purification of the complexes difficult. The formation of a small amount of a copper(II) compound accompanies this bond cleavage. The oxidation of copper(I) to copper(II) cannot occur in an initial stage of the reaction since it is well known that $CuCl_2$ reacts with alkynes **1** to form products of ring annulation and sulfur reduction [3]. The final product of repeated CC bond rupture is the compound **18** from which ligands **1** were originally obtained (Fig. 5). The model calculations on copper complexes of propargylic alcohols represent some features of the activation of the triple bonds towards cleavage. A transition state was found which connects the cleaved products with a cyclic precursor. There is a clear relation between this model and the experimental behaviour of compound **1c**. On the other hand, the calculations on the complexes of the model ligand *N*-[(3*S*,4*R*)-3-hydroxy-1,5-hexadiyne-4-yl]methanesulfonamide represent better the behaviour of the other camphor-derived ligands (**1d**, **1e**, **6e**, **7c**). They clearly show the importance of the coordination of copper to one oxygen atom of the sulfonamide group. A successful search for transition states of this model would certainly help to elucidate the reaction mechanism in more detail.

4. Experimental

4.1. Computational methods

All calculation were performed with Pc Gamess, version 7.1 [14], which is based on Gamess (US) [15,16]. For the camphor-derived diynes, 6-31G* was used as basis set at the HF level. The inclusion of diffuse basis function for the anions did not change the relative energies significantly. We employed the ECP basis set SBKJC [17–19] for all atoms in the calculations of the copper-containing model systems, in combination with the DFT functional PBE0 [20]. For all copper complexes of the model compounds containing the sulfonamide group, we constrained the dihedral angle H–C(O)–C(N)–H to 0° in accord with the situation in the camphor derivatives **1**. Since in these cases the optimized geometries do not correspond to minima on the unconstrained potential hypersurface, imaginary frequencies were observed in the Hessian calculations. The IR frequencies quoted were calculated from the Hessian matrix with a scaling factor of 0.975 which was derived from a calculation of 1,2-dicyanobenzene by comparison with the experimental value of the C≡N stretching frequency in a KBr pellet. For visualization and analysis of the results, the program MOLDEN [21] was used.

4.2. Synthesis

The experiments involving CuCl or $LiBu^n$ were carried out under inert atmosphere by using vacuum and the Schlenk techniques. Camphor di-alkyne (R = Ph, **1c**; CH_2Ph, **1d**) species were prepared by published methods [3,7]. CuCl was synthesised from $CuCl_2$ by reduction with sodium sulphite [22]. Solvents were purchased from Fluka or Panreac purified by conventional techniques and distilled before use.

NMR spectra (^1H, ^{13}C, DEPT, HSQC HMBC) were obtained in $CDCl_3$ or DMSO-d_6 using Bruker 300 or 400 MHz Avance II$^+$ Spectrometers; TMS ($\delta = 0$ ppm) was used as internal reference. The numbering of the carbon and attached hydrogen atoms in the NMR spectra of compounds **1**, **6**, and **7** is shown in Fig. 1. IR spectra were obtained in a JASCO FTIR 430 spectrometer. FAB mass spectra, was obtained in a Trio 2000 mass spectrometer using nitrobenzylic alcohol as matrix.

4.3. Organic species

The species were prepared from 3-oxo-camphorsulfonimide **18** by reaction with the appropriate lithiated alkyne, typically following the procedure below:

4.3.1. (1aS3aS,7R)-7-Hydroxy-1a,7-bis[3-(N,N-diethylamino)propyn-1-yl]-8,8-dimethyl-1,1a,4,5,6,7-hexahydro-3H-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (*1e*)

$LiBu^n$ (2.4 mL, 4.8 mmol of a solution 2 M in hexane) was further diluted in 10 mL of Et_2O and slowly added (under nitrogen) to a solution of *N*,*N*-diethylpropargylamine (0.65 mL; 4.5 mmol) in Et_2O (30 mL) and the mixture stirred for 3 h upon which solid 3-oxo-camphorsulfonimine (**18**, Fig. 5) (0.35 g; 1.5 mmol) was added and the stirring kept for ca. 24 h. Addition of H_2O (10 mL) stopped the reaction. The two phases were separated and the organic layer dried over $MgSO_4$. The aqueous solution was further extracted with four portions of CH_2Cl_2 (4 × 50 mL) and the organic phase dried over $MgSO_4$. After filtration the combined organic layers afforded pale yellow micro crystals of **1e**, 1.25 g; 68%. Anal. Calc. for $C_{24}H_{39}N_3O_3S$ $1/8CH_2Cl_2$: C, 62.7; H, 8.5; N 9.1; S, 6.9. Found: C, 62.9; H, 8.8; N, 9.0; S, 7.1. $\nu_{OH} = 3444$, $\nu_{NH} = 3196$ cm^{-1}, $\nu_{C\equiv C}$ not observable, $\nu_{SO_2} = 1298$; 1123 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 3.51$ (2d, 2H, $J = 3.0$ Hz, CH_2NEt_2), 3.46 (s, 2H, CH_2NEt_2), 3.25 (s, 2H, H-8), 2.56 (quintet, $J = 6.9$ Hz, 8H, NCH_2CH_3), 2.25–1.60 (m, 4H, CH_2, H-5,6), 2.03 (d, 1H, $J = 4.5$ Hz, H-4), 1.43, 0.98 (s, 6H, CH_3, H-9,10), 1.05, 1.06 (2t, 12H, $J = 7.0$ Hz, NCH_2CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 85.5$, 85.0, 83.4, 83.0 (C≡C), 81.5 (C-3), 72.3 (C-2), 62.3 (C-1), 56.6 (C-4), 51.3 (C-8), 48.8 (C-7), 47.3, 47.2 (CH_2CH_3), 41.2, 41.1 (CH_2N), 28.3, 23.8 (C5,6), 24.1, 23.6 (C9,10), 12.7, 12.4 (CH_2CH_3) ppm.

4.3.2. (1aS,3aS)-8,8-Dimethyl-1a-(2-phenylethyn-1-yl)-1,1a,4,5,6,7-hexahydro-3H-3a,6-methano-7-oxo-2,1-benzisothiazole 2,2-dioxide (*7c*)

$LiBu^n$ (5.2 mL of a 2 M solution in hexane, 10.4 mmol) was diluted in Et_2O (70 mL) and slowly added (under nitrogen) to a solution of ethynylbenzene (1 mL, 10.0 mmol). The mixture was stirred overnight affording a deep red solution that was slowly added to a solution of 3-oxo-camphorsulfonimide (**18**, Fig. 5) (2.16 g; 9.5 mmol) in Et_2O (60 mL) and stirred for 1 day. The reaction was stopped by addition of H_2O. Separation of the organic and aqueous phases followed by extraction of the aqueous layer with CH_2Cl_2 (3 × 50 mL) and drying over $MgSO_4$ afforded **7c**, 1.6 g, 51%. Anal. Calc. for $C_{18}H_{19}NO_3S \cdot H_2O$: C, 62.2; H, 6.0; N, 4.0; S, 9.2. Found: C, 62.4; H, 5.6; N, 4.3; S, 9.5. $\nu_{NH} = 3237$; $\nu_{C\equiv C} = 2222$, $\nu_{CO} = 1762$ cm^{-1}, $\nu_{SO_2} = 1314$; 1159 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 7.4$–7.2 (m, 5H, C_6H_5), 4.88 (s, 1H, NH), 3.44 (d, 2H, $J = 4.4$ Hz,

H-8), 2.5-1.9 (m, 5H, H-4, H-5,6), 1.29; 1.10 (s, 6H, CH_3, H-9,10) ppm; ^{13}C NMR ($CDCl_3$): δ = 205.2 (C-3), 132.0, 129.2, 128.3 (Ph), 121.3 (C_{ipso}-Ph), 89.8, 84.0 (C≡C), 65.3 (C-2), 57.2 (C-1), 58.4 (C-4), 49.6 (C-8), 45.1 (C-7), 29.1, 21.7 (C5,6), 22.6, 19.7 (C9,10).

*4.3.3. (1aS,3aS)-1a-[3-(N,N-Diethylamino)propyn-1-yl]-8,8-dimethyl-1,1a,4,5,6,7-hexahydro-3H-3a,6-methano-7-oxo-2,1-benzisothiazole 2,2-dioxide (**7e**)*

A procedure similar to that for **7c** led to pale yellow micro crystals of **7e**, yield: ca. <10%. Anal. Calc. for $C_{17}H_{26}N_2O_3S$: C, 60.3; H, 7.7; N, 8.3; S, 9.5. Found: C, 60.4; H, 8.0; N, 8.1; S, 9.3. ν_{CO} = 1762 cm^{-1}, ν_{SO_2} = 1308; 1141 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.50 (s, 2H, CH_2NEt_2), 3.33 (s, 2H, H-8), 2.50 (q, 4H, J = 7.2 Hz, NCH_2CH_3), 2.40 (d, 1H, J = 5.1 Hz, H-4), 1.7–2.4 (m, 4H, CH_2, H-5,6), 1.23; 1.05 (s, 6H, CH_3, H-9,10), 0.99–1.3 (m, 6H, NCH_2CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 205.4 (C-3), 85.6, 80.4 (C≡C), 65.0 (C-2), 56.8 (C-1), 58.4 (C-4), 49.6 (C-8), 47.4 (CH_2NEt_2), 45.0 (C-7), 40.8 (CH_2NEt_2), 29.1, 21.7 (C5,6), 22.6, 19.7 (C9,10), 12.6 (NCH_2CH_3) ppm.

*4.3.4. (3aS,7R)-7-[3-(N,N-Diethylamino)propyn-1-yl]-7-hydroxy-8,8-dimethyl-4,5,6,7-tetrahydro-3H-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (**6e**)*

A similar procedure to that used for **7c** led to **6e** in 49% yield. Anal. Calc. for $C_{17}H_{26}N_2O_3S$: C, 60.4; H, 7.7; N, 8.3; S, 9.5. Found: C, 60.9; H, 8.4; N, 8.2; S, 9.1. ν_{OH} = 3410, ν_{CN} = 1654 cm^{-1}, ν_{SO_2} = 1342; 1156 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.51 (s, 2H, CH_2NEt_2), 3.21, 3.09 (2d, 2H, J = 13.5 Hz, H-8), 2.52 (quartet, 4H, J = 7.0 Hz, NCH_2CH_3), 2.22 (d, 1H, J = 3.6 Hz, H-4), 1.7–2.2 (m, CH_2, H-5,6), 1.07; 1.04 (s, 6H, CH_3, H-9,10), 1.08–1.02 (m, 6H, NCH_2CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 194.4 (C-2), 84.5, 82.5 (C≡C), 72.8 (C-3), 64.1 (C-1), 55.8 (C-4), 50.1 (C-8), 47.1, 47.2 (NCH_2CH_3), 47.4 (C-7), 41.1 (CH_2NEt_2), 28.0, 23.9 (C5,6), 21.1, 21.0 (C9,10), 12.2 (NCH_2CH_3) ppm.

Camphor-derivatives **7c**, **6d**, **6e** were obtained, respectively, from [CuCl(**1c**)], [CuCl(**1d**)], [CuCl(**1e**)] by addition of concentrated HCl (2 mL) to the suspension of the complex (0.10 g) in of CH_2Cl_2 (10 mL). The aqueous and organic layers were separated and the last one dried over $MgSO_4$ and filtered. The organic species **7c**, **6d**, **6e** were obtained by solvent evaporation. Compound (**23**) was obtained in a similar way from [CuCl(**7c**)] or [CuCl(**6e**)].

4.4. Complexes

$[Cu(L)_{depr}]$ (L = **1d**; **7c**) or [CuClL]\xH_2O (L = **1c**; **1d**; **1e**; **7c**; **6e**) were prepared from the corresponding camphor-derived deprotonated ligand by reaction with CuCl. A typical procedure is as follows:

*4.4.1. [Cu(**1d**)$_{depr}$]*

$NaNH_2$ (0.020 g, 0.51 mmol) was added to a solution of **1d** (0.23 g, 0.50 mmol) in CH_2Cl_2 (20 mL) and the solution was stirred for 1/2 h. Then, CuCl (0.050 g, 0.51 mmol) was added and the mixture stirred overnight. The suspension was filtered and *n*-hexane added to the yellow solution. The yellowish precipitate was filtered affording the title complex, ca. 15% yield. Anal. Calc. for $Cu(C_{28}H_{28}NO_3S)\cdot H_2O$: C, 62.3; H, 5.6; N, 2.6; S, 5.9. Found: C, 62.7; H, 6.5; N, 2.7; S, 6.8. ν_{OH} = 3425 cm^{-1}, $\nu_{C\equiv C}$ = 2231 cm^{-1}, ν_{SO_2} = multiple signals in the range 1334–1118 cm^{-1}.

By using a larger excess of solvent (3×) under prolonged stirring (3 days) a different compound is isolated [CuCl(**1d**)]. Yield, 31%. Anal. Calc. for $CuCl(C_{28}H_{29}NO_3S)\cdot 2H_2O\cdot 1/2CH_2Cl_2$: C, 53.7; H, 5.3; N, 2.2; S, 5.0. Found: C, 53.7; H, 4.6; N, 2.4; S, 5.0. $\nu_{C\equiv C}$ = 2231 cm^{-1}, ν_{SO_2} = 1109 cm^{-1}.

*4.4.2. [CuCl(**1c**)]·2H$_2$O*

$NaNH_2$ (0.023 g, 0.59 mmol) was added to a solution of **1c** (0.25 g, 0.58 mmol) in CH_2Cl_2 (60 mL) and the mixture stirred for 1/2 h. Addition of CuCl (0.057 g, 0.58 mmol) and stirring overnight afforded a greenish suspension that was filtered to separate traces of a non-identified bright yellow precipitate. By partial evaporation of the solvent and addition of Et_2O a green precipitate forms that upon filtration afforded the complex (M/z + 23 = 588): 0.10 g, 0.18 mmol. Yield, 31%. Anal. Calc. for $CuCl(C_{26}H_{25}NO_3S)\cdot 2H_2O$: C, 55.1; H, 5.1; N, 2.5; S, 5.7. Found: C, 55.0; H, 4.2; N, 2.4; S, 5.7. $\nu_{C\equiv C}$ = 2215 cm^{-1}, ν_{SO_2} = 1102 cm^{-1}.

*4.4.3. [CuCl(**1e**)]·H$_2$O*

$NaNH_2$ (0.011 g, 0.28 mmol) was added to a solution of **1e** (0.12 g, 0.27 mmol) in CH_2Cl_2 (35 mL) and the mixture stirred for 1/2 h. Then CuCl (0.026 g, 0.26 mmol) was added and the mixture stirred overnight. Upon filtration the title compound was obtained: 0.046 g, 0.077 mmol, 30% yield. Anal. Calc. for $CuCl(C_{24}H_{36}N_3O_3S)\cdot H_2O\cdot 1/10CH_2Cl_2$: C, 50.7; H, 6.7; N, 7.3; S, 5.6. Found: C, 50.7; H, 6.7; N, 6.9; S, 5.5. ν_{SO_2} = 1145; 1104 cm^{-1}.

*4.4.4. [Cu(**7c**)]*

$NaNH_2$ (0.027 g, 0.68 mmol) was added to a solution of **7c** (0.20 g, 0.61 mmol) in CH_2Cl_2 (60 mL) and CuCl (0.065 g, 0.66 mmol) added. The mixture was stirred for 3 days. Upon filtration to separate unreacted CuCl, evaporation of the solvent and washing of the solid residue with Et_2O (ca. 50 mL) the title compound was obtained: 0.085 g, 0.18 mmol, 30% yield. Anal. Calc. for $Cu(C_{18}H_{18}NO_3S)\backslash 1/4CH_2Cl_2$: C, 52.8; H, 4.5; N, 3.4; S, 7.7. Found: C, 52.8; H, 4.4; N, 3.7; S, 7.7. $\nu_{C\equiv C}$ = 2217, ν_{CO} = 1756 cm^{-1}, ν_{SO_2} = multiple signals in the range 1315–1102 cm^{-1}.

*4.4.5. [CuCl(**7c**)]\2H$_2$O*

$NaNH_2$ (0.024 g, 0.61 mmol) was added to a solution of **7c** (0.20 g, 0.61 mmol) in CH_2Cl_2 (55 mL) then CuCl (0.133 g, 1.34 mmol) was added and the mixture stirred for 2 weeks. Upon filtration of a yellow impurity the title compound was obtained: 0.100 g, 0.23 mmol, 18% yield. Anal. Calc. for $CuCl(C_{18}H_{19}NO_3S)\cdot 2H_2O\cdot 1/2CH_2Cl_2$: C, 43.8; H, 4.7; N, 2.7; S, 6.3. Found: C, 43.4; H, 3.5; N, 2.8; S, 6.5. $\nu_{C\equiv C}$ = 2212, ν_{CO} = 1755 cm^{-1}, ν_{SO_2} = 1103 cm^{-1}.

*4.4.6. [CuCl(**6e**)]·2H$_2$O*

$NaNH_2$ (0.008 g, 0.21 mmol) was added to a solution of **6e** (0.073 g, 0.22 mmol) in CH_2Cl_2 (25 mL), CuCl (0.022 g, 0.22 mmol) and the mixture stirred overnight. The precipitate was filtered affording the title compound (0.032 g, 0.068 mmol, 31% yield). Anal. Calc. for $CuCl(C_{17}H_{26}N_2O_3S)\cdot 2H_2O$: C, 43.1; H, 6.3; N, 5.9; S, 5.9. Found: C, 43.5; H, 5.5; N, 5.9; S, 5.6. $\nu_{C\equiv C}$ = 2077, ν_{CN} = 1634 cm^{-1}, ν_{SO_2} = 1162 cm^{-1}.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2008.06.004.

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