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Mesoionic oxides: facile access from triazolium salts or triazolylidene copper precursors, and catalytic relevance†

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Reaction of CsOH with triazolium salts affords mesoionic compounds containing an exocyclic oxygen; the same product is obtained by reaction of the corresponding Cu(I) triazolylidenes with CsOH and represents an unusual reactivity pattern of N-heterocyclic carbene precursors that has implications for carbene copper-catalyzed reactions.

Mesoionic compounds,[1] in particular sydnones (**A**, Fig. 1),[2] are of considerable interest due to their pharmacological relevance, as established *e.g.* in Feprosidnin or Molsidomine.[3] In an attempt to broaden the sydnone family, recent focus has been directed towards aza-versions and specifically towards 1,2,3-triazolium-4-olates as structural analogues (**B**, Fig. 1).[4] Investigation of these mesoionic compounds is thwarted however by their restricted synthetic accessibility.[5] Here we present a short and convenient route to this class of compounds, which involves the reaction of CsOH with either a triazolium salt or the corresponding triazolylidene copper complex. The straightforward access entails an unexpected reaction pathway of heterocyclic azolium salts with a base, providing the oxo-adduct[6] rather than the free N-heterocyclic carbene (NHC).[7] Analysis of the bonding in these mesoionic compounds has direct implications for describing the bonding situation in related free and metal-complexed triazolylidenes.[8]

Compounds **2a–c** were synthesized *via* two different routes, both starting from the corresponding triazolium salts **1a–c** (Scheme 1). Direct reaction with 1 or 2 mol equiv. CsOH afforded compounds **2** as major products (70–90%) together with demethylated 1,4-substituted triazole. After column chromatographic purification of this mixture, analytically pure **2a–c** were isolated in 20–30% yield as white solids. Higher purities and yields (up to 90% overall from **1**) were accomplished when applying an indirect protocol involving first the synthesis of the corresponding triazolylidene copper(I) complex **3** *via* an established transmetalation methodology,[9] followed by treatment of this complex with CsOH (2 mol equiv.).[10] For compound **3c**, which in contrast to **3a,b** is air- and moisture sensitive, a sequential one-pot synthesis from **1c** involving Ag_2O, CuCl and CsOH was found to give pure **2c** in good yields. Notably, decomposition of **3c** in a moist environment in the absence of CsOH gave mixtures of **1c** (major product) and minor quantities of **2c**.

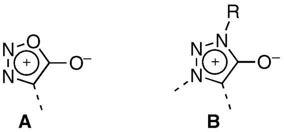
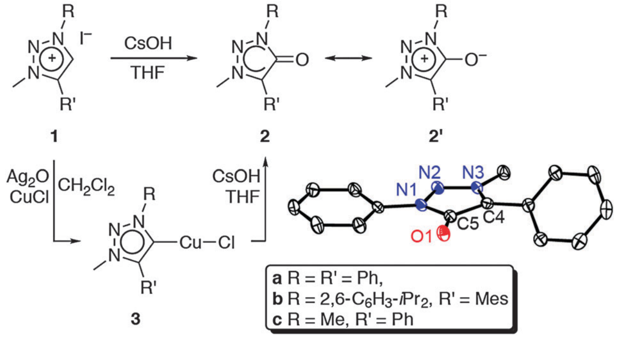


Fig. 1 Generic structure of sydnone **A** and its aza-derivative **B**.



Scheme 1 Direct and indirect syntheses of mesoionic **2** from the triazolium salt **1** and ORTEP representation of **2c** (50% probability).

Unambiguous confirmation of the formation of **2a** was obtained from a single crystal X-ray diffraction analysis (Scheme 1).† The unit cell of **2a** lacks any anion and identifies **2a** as an overall neutral compound. As a key feature, the molecular structure reveals a C–O bond distance of 1.243(2) Å, which is characteristic for a C═O double bond. The heterocycle is essentially planar, indicating charge delocalization as observed in related mesoionic compounds.[11] It is particularly instructive to compare the bond lengths and angles of **2a** with those in related triazolium salts.[12] In the latter, the heterocycle is bound to a hydrogen, representing the extreme case of a C–E single bond of a triazolium adduct, whereas **2a** displays the C═E double bond limit of a triazolylidene fragment. Comparison of these two extremes reveals that the exocyclic double bond induces an elongation of both adjacent heterocyclic bonds C5–N1 and C5–C4.† This diagnostic structural feature allows free and metal-bound triazolylidenes to be classified. Accordingly, the bond elongation in the free carbene is about 70% compared to **2a**

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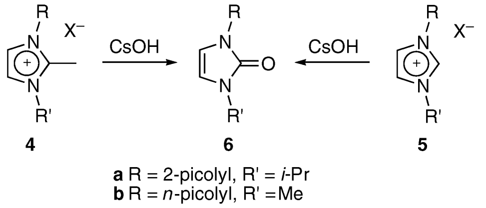
and thus in full agreement with the mesoionic assignment.[12a] The heterocyclic bonds in the triazolylidene metal complexes are typically similar,[8,9a] which suggests partial M=C double bond character in these complexes.

The ^{1}H and ^{13}C NMR data of compounds **2a–c** are remarkably similar to those of the corresponding copper complexes **3a–c**. For example the carbonyl resonance in **2a** was observed at 155.6 ppm, a mere 5 ppm upfield compared to the resonance in **3a** (δ_{C-Cu} 161.3 ppm).[9a] In the ^{1}H NMR spectrum, the most characteristic shift pertains to the N–CH$_3$ group, which appears at δ_H 4.12 ppm in **2a** and at 4.21 ppm in **3a**, and to *para*-positioned aryl protons. All other signals differ by less than 0.05 ppm and are thus not diagnostic for distinguishing **2** from **3**.[13]

The pertinent IR data reveal a stretch vibration around 1640 cm^{-1} (CHCl$_3$) and thus provide unambiguous spectroscopic evidence for the presence of a carbonyl unit in **2**. The wavelength of this vibration is slightly solvent dependent and shifts between 1660 cm^{-1} (Et$_2$O, ε_r = 4.42) and 1640 cm^{-1} (CH$_2$Cl$_2$, ε_r = 9.02), though the shift does not correlate with the relative permittivity of the solvent (*cf.* ν_{CO} = 1641 cm^{-1} in MeCN, ε_r = 35.94).† This independence suggests that the crystallographically identified keto resonance form of **2** prevails in solution. In contrast, solid state IR measurements in KBr with a substantially higher polarity lowers the energy of the C–O bond to 1603 cm^{-1}, in line with a larger enolate resonance contribution (*cf.* **2′** in Scheme 1).

Related oxo-adducts of NHCs have recently been observed as thermally induced decomposition products from imidazol-2-ylidene copper complexes,[14] and from direct interaction of an imidazolinium salt with Cu$_2$O, affording cyclic urea.[13] In the former case, elegant work provided direct evidence for O$_2$ as the oxygen source. The methodology presented here appears to be complementary, since the copper complex **3a** is air-stable within the timeframe of the reaction (24 h). **3a** decomposes only very gradually and after 3 days, a mixture of **1a** and the mesoionic compound **2a** (40% and 32% by ^{1}H NMR integration, respectively) were observed together with unreacted **3a** (28%). In the presence of CsOH and under an atmosphere of dry N$_2$, exclusive formation of the mesoionic compound **2a** in high yields was observed without any thermal induction (RT, 24 h), perhaps *via* CuCl dissociation involving the transient formation of a free carbene,[15] or more likely by a redox pathway comprising a Cu(II)–OH intermediate that undergoes reductive C–O bond formation.[16] These observations suggest that CsOH rather than O$_2$ or water is initiating the formation of **2**.

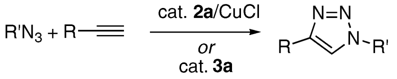
The direct formation of **2** from the triazolium salt **1** in the absence of copper lends further support to a hydroxide-mediated pathway. A putative mechanism may entail either triazolium deprotonation and subsequent nucleophilic–electrophilic interaction of the free carbene with water,[6a] or nucleophilic addition of hydroxide to the C5 position followed by (formal) H$_2$ elimination.[17] While our data do not allow to confidently discard one of these pathways, experiments have been performed to better understand this reaction. Reaction of **1** with overstoichiometric quantities of CsOH (2–8 mol equiv.) led, in addition to some formation of mesoionic **2**, to partial N–CH$_3$ bond cleavage (Hoffman elimination) of the triazolium salt as a competitive process and afforded the corresponding 1,4-disubstituted triazole as a further product.[18] Demethylation increased with higher CsOH, and was more pronounced with **1c** than with the aryl-substituted triazolium salts **1a**,**b**. Substitution of Cs$^+$ by K$^+$ produced **2c** but the yield is lower, probably due to the limited solubility of KOH in THF. With Bu$_4$NOH as a base, **1c** gave a mixture of products and only traces of **2c**. Ag$_2$O represents a special case; in CH$_2$Cl$_2$, **1** affords selectively the corresponding silver carbene complex, while in THF, exclusive formation of the mesoionic compound **2** was observed, presumably mediated by transiently formed Ag(OH). Hence, appropriate solvatization of the M(I) salt, a critical parameter for stabilizing free carbenes,[19] is also pivotal for generating mesoionic **2**. Attempts to isolate the free carbene to further support this hypothesis have been unsuccessful thus far.



Scheme 2 Expansion of CsOH mediated oxidation to C2-alkylated and unsubstituted imidazolium salts.

The scope of this oxygenation reaction was probed with the imidazolium salts **4** and **5** comprised of a methyl-functionalized and an unsubstituted C2 position, respectively (Scheme 2). When treated with CsOH, both types of imidazolium salts formed the cyclic urea **6**. While the reactivity patterns of the unsubstituted imidazolium salts **5** and the triazolium salts **1** are probably mutually related and may involve a Cs-stabilized carbene, the C2-demethylation of **4** is less trivial. Formation of a mesoionic compound analogous to **2** may be prevented because of the pK_a mismatch between the C4/5-bound proton (pK_a around 30) and CsOH. Such C2–C$_{alkyl}$ bond cleavage has been observed previously with Ag$_2$O in an oxidative process,[20] though the drastic difference in standard redox potentials of Ag^I and Cs^I (0.80 V *vs.* 2.92 V) tends to suggest that methyl group dissociation may be related to the observed demethylation of **1** in the presence of a large excess of CsOH.

The mesoionic compounds **2** are excellent ligands for CuCl, and the corresponding complexes catalyze the [3 + 2] dipolar cycloaddition of alkynes and azides ('click' reaction). Thus, addition of catalytic quantities of **2a** and CuCl to a mixture of phenylacetylene and benzyl azide (3% catalyst loading) afforded, after 30 min, the corresponding 1-benzyl-4-phenyl-triazole in essentially quantitative yield (eqn (1)).† In the absence of added CuCl, **2a** is catalytically silent in this cycloaddition reaction. It is interesting to note that copper complexes comprising bulky carbene ligands (1,2,3-triazol-5-ylidenes akin to **3** or imidazol-2-ylidenes) were reported to show excellent catalytic activity in this reaction.[9a,21] Indeed, when using complex **3a** as catalyst precursor, full conversion was observed with the same time frame as for the **2a**–CuCl mixture. In light of these results we are not confident in attributing the catalytic activity to the carbene complex **3a**. Instead, the catalytically active species may ensue from a coordination compound **2a**·CuCl that readily forms *in situ* from **3** as detailed above. Similar decomposition or indeed catalyst activation pathways may also be relevant in related carbene copper-catalyzed reactions that involve a base.



(1)

In summary, we have disclosed a rapid synthesis of mesoionic compounds starting from synthetically versatile triazolium salts and CsOH. Identical products are formed while treating the corresponding triazolylidene cuprous salt with CsOH. Formation of the mesoionic compound directly from the triazolium salt likely involves the transient formation of a free carbene, while the reaction from the copper complex presumably occurs *via* reductive carbene hydroxide elimination from a putative [Cu(triazolylidene)(OH)] intermediate. The low stability of this latter complex, *e.g.* when compared to the analogous normal imidazole-derived NHC congeners, provides further support for a more reactive $M–C_{carbene}$ bond in mesoionic complexes.[22] The smooth oxygen transfer may have direct implications in using Cu-triazolylidene complexes as catalysts. Perhaps more relevant, the synthetic methodology is remarkably general and provides facile access to a wide range of mesoionic compounds that have potential in their own right, *e.g.* as new structural motifs in active pharmacological ingredients, and also as a new class of ligands with a high degree of electronic flexibility (*cf.* limiting resonance structures of **2**).

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