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Copper-promoted rearrangement of 1,3-cyclohexadiene-acylnitroso cycloadducts

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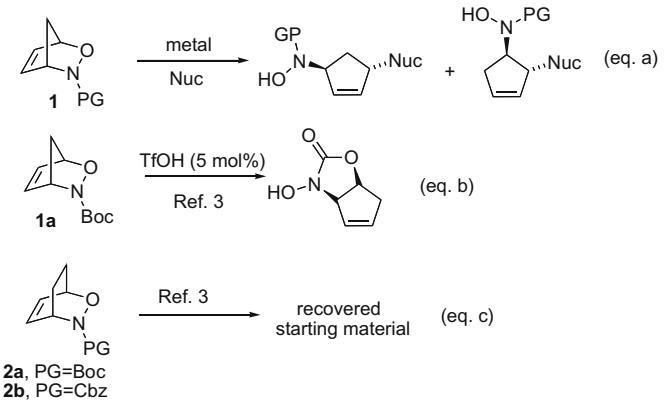
ABSTRACT

The ring opening of [2.2.2]-acylnitroso cycloadducts was obtained for the first time by means of a cationic rearrangement promoted by $Cu(OTf)_2$–PPh_3 under homogeneous and polymer-supported conditions.

Cyclopentadiene-derived bicyclic oxazines **1**, derived from acylnitroso hetero-Diels–Alder reactions, are important intermediates in the synthesis of natural products and biologically active molecules.[1] Very recently, a lot of efforts have been devoted to the metal-catalyzed nucleophilic ring opening of these compounds by the cleavage of the C–O bond giving access to a large variety of cyclopentene derivatives (Eq. a, Scheme 1).[2] In particular, an unusual bicyclic hydroxamate resulted from C–O bond cleavage when *N*-Boc-protected **1a** was treated with catalytic Brønsted acid under anhydrous conditions was reported by Miller and Bodnar (Eq. b).[3] However, this protocol turned out to be completely uneffective with less strained [2.2.2]-acylnitroso derivatives **2** (Eq. c).

In general, the ring opening of [2.2.2]-acylnitroso adducts would be important because it is able to generate valuable nitrogen-substituted cyclohexenes from compounds easily available in gram scale from the Diels–Alder reaction of 1,3-cyclohexadiene with acylnitroso derivatives. So far, most reactions of these bicyclic systems dealt with the reductive N–O bond cleavage affording cyclohexenyl amino alcohols.[4,2g,1] On the other hand, the nucleophilic ring opening by C–O cleavage to give cyclohexenyl hydroxylamine derivatives is known to be difficult, and realized only with heteronucleophiles (alcohols, water) in Lewis acid-catalyzed solvolytic conditions.[5] A rearrangement-type reaction of [2.2.2]-bicyclic cycloadducts has not yet been described. This Letter describes the first successful metal-promoted rearrangement of 1,3-cyclohexadiene acylnitroso cycloadduct to give new cyclohexenyl hydroxylamine derivatives.



Scheme 1. State of the art of C–O bond cleavage of acylnitroso cycloadducts.

Recent findings by Lautens and our group have shown that simple copper(II) catalysts promote the rearrangement of *N*-Boc [2.2.1]-bicyclic hydrazines to give bicyclic carbazates.[6] In the preliminary experiments using 12 mol % of $Cu(OTf)_2$/(±)-binap complex as catalysts in CH_2Cl_2,[6b] the starting material **2a** was recovered from the reaction unchanged. In order to address the scarce reactivity of [2.2.2]-acylnitroso cycloadduct **2a** and **2b**, we screened a variety of conditions using copper and other Lewis acid as catalysts or promoters to effect the rearrangement of the above-

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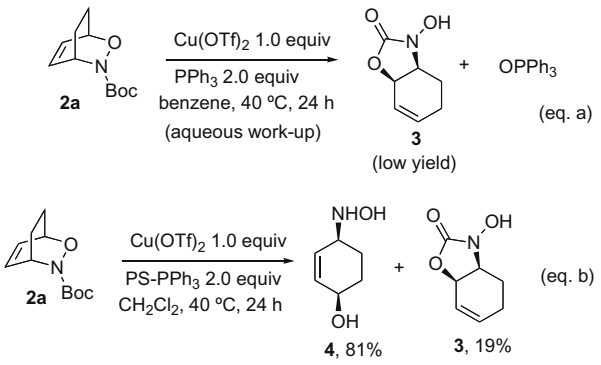
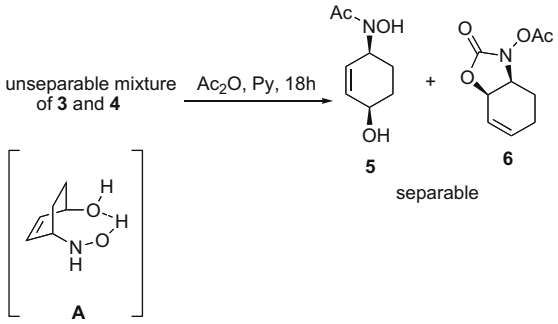


Scheme 2. Copper-triphenylphosphine-promoted rearrangement of acylnitroso cycloadduct **2a**.



Scheme 3. Result of the acetylation of the mixture of compounds **3** and **4**.

mentioned compounds. Unfortunately, in most of the cases we obtained only the degradation of the cycloadducts or the formation of complex reaction mixtures. After extensive examination of the reaction conditions, we found that stoichiometric amounts of $Cu(OTf)_2$ in combination with 2 equiv of PPh_3 in benzene at 40 °C could effect the rearrangement of *N*-Boc-protected derivative **1a** (>95% conversion). The use of benzene as the reaction solvent at the temperature of 40 °C was crucial to obtain complete conversion of **1a** and to minimize by-products. On the other hand, the Cbz-adduct **1b** always afforded complex mixtures of products that were not purified. Interestingly, the same reaction of **1a** carried out without the phosphine ligand afforded only the degradation of the cycloadduct indicating a positive role for the copper–phosphine complex. After an aqueous work-up, the ^1H NMR examination of the crude mixture showed the presence of [5,6]-bicyclic hydroxamate **3** together with large amounts of PPh_3 and $OPPh_3$ (Eq. a, Scheme 2). Unfortunately, every attempt to purify hydroxamate **3** by chromatographic purification was unsuccessful and only $OPPh_3$ was recovered. Using iron-free silica gel,[2f] it was possible to isolate compound **3** but always this was obtained in very low yields in mixture with $OPPh_3$, which is known to be a very strong hydrogen bond acceptor.[7] It was interesting to find that omitting the aqueous work-up, just filtrating on a pad of Celite and evaporating under vacuum, the reaction outcome changed considerably. In this case, the ^1H NMR examination of the crude mixture showed a ca. 80:20 mixture of *cis*-allylic hydroxylamine **4** and [5,6]-bicyclic hydroxamate **3** (Scheme 2). Of particular importance is the direct access to an unprotected primary allylic hydroxylamine, such as **4**, which cannot be obtained by other means considering its reactive and oxidatively labile stage.[8]

The formation of stoichiometric amounts of triphenylphosphine oxide under this reaction condition complicated the purification of allylic hydroxylamine **4** and cyclic hydroxamate **3**. To try to obviate this problem, the rearrangement was carried out using a polymer-bound PPh_3 (Eq. b). In this case the best results were obtained in refluxing CH_2Cl_2 even if benzene was also a suitable solvent for the reaction. A simple filtration allowed the obtainment of compounds **4** (81%) and **3** (19%) free from triphenylphosphine oxide. The formation of polymer-bound triphenylphosphine oxide was detected by solid-state ^{31}P NMR of the residual resin (broad peak at +33.1 ppm).[9] A simple acetylation of the mixture of **3** and **4**, using an excess of acetic anhydride in anhydrous pyridine afforded a mixture of the corresponding *N*-acetates **5** and **6**, which were separated by chromatographic purification (Scheme 3). Interestingly, we were unable to acetylate the allylic alcohol moiety, probably due to the strong hydrogen bond which is formed between the two hydroxylic functionalities, as tentatively shown in **A** (Scheme 3).

The polymerization of THF when used as the reaction solvent suggested a stepwise mechanism with the involvement of open cationic species (Scheme 4). Probably, the copper-triphenylphosphine catalyst promotes the C–O cleavage to give an allylic carbocation which undergoes intramolecular cyclization by the former carbonyl oxygen with concomitant loss of isobutylene. When the cyclization occurs at the distal position (path *a*) the cyclic 1,4-hydroxamate intermediate **B** decarbonylates under the reaction conditions affording the allylic hydroxylamine **4**. The direct observation by FT-IR of the benzene solution used as the reaction medium of a strong $\nu(CO)$ at 1956 cm^{-1} supported the proposed mechanism.[10] In fact, this absorption is typical of a bridging CO ligand with Cu(I),[11] and might explain the decarbonylation of intermediate **B** to give the final main product **4**. The alternative cyclization pathway is a formal [3,4]-sigmatropic rearrangement (path *b*) and affords cyclic hydroxamate **3** as the minor product (Scheme 4).

In conclusion, we successfully found a solution to address the scarce reactivity of 1,3-cyclohexadiene-acylnitroso cycloadducts in the rearrangement reactions to give an easy access to new cyclohexenyl-derived hydroxylamine derivatives.[12]

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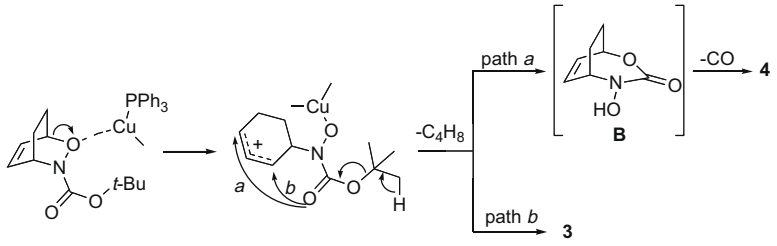

Scheme 4. Proposed mechanism for the rearrangement of acylnitroso cycloadduct **2a**.

versity of Pisa. We gratefully thank Dr. Silvia Barsocchi and Dr. Marco Geppi (Dipartimento di Chimica e Chimica Industriale of the University of Pisa) for performing solid-state ^{31}P NMR.

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12. *Experimental procedure for the polymer-supported rearrangement* (Scheme 2, Eq. b): a 50 mL dried Schlenk tube was charged, under argon protection, with $Cu(OTf)_2$ (362 mg, 1.0 mmol), PS-PPh_3 (667 mg, 2.0 mmol. 3.0 mmol/g loading) in CH_2Cl_2 (5 mL) and the mixture was stirred for 15 min at room temperature. Cycloadduct **2a** (210 mg, 1.0 mmol) in CH_2Cl_2 (5.0 mL) was added and the mixture was stirred at 40 °C. After 24 h, the reaction mixture was filtered on a sintered glass Büchner funnel washing with minimal amounts of CH_2Cl_2 and AcOEt. After evaporation of the solvent under vacuum a crude greenish oil (300 mg) containing a mixture of compounds **3** (19%) and **4** (81%) was obtained. Compound **4**: ^1H NMR (250 MHz, CD_3CN): δ = 1.51–1.65 (m, 2H); 2.13–2.41 (m, 2H); 4.60–4.67 (m, 1H, C*H*OH); 4.99–5.06 (m, 1H, C*H*N); 6.59–6.66 (m, 1H); 6.91 (dddd, 1H, J = 0.9, 1.5, 2.5, 5.8 Hz); 9.38 (br s, 1H); 10.21, (br s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 19.5, 20.2, 49.8, 71.7, 128.3, 136.2. Compound **3**: IR ν 3504, 1739 cm^{-1}. ^1H NMR (250 MHz, CD_3CN): δ = 1.82–2.13 (m, 2H), 2.15–2.32 (m, 2H); 3.75–3.94 (m, 1H, C*H*O); 4.67–4.69 (m, 1H, C*H*N); 5.83–5.94 (m, 1H); 6.15–6.24 (m, 1H). ^{13}C NMR (62.5 MHz, CD_3CN): δ = 19.5, 26.1, 57.3, 69.5, 122.1, 134.6, 159.9.
N-Hydroxy-N-((1S,4R*)-4-hydroxycyclohex-2-enyl)acetamide* (**5**). In a 25 mL flask, the above-mentioned crude mixture of **3** and **4** was dissolved in anhydrous pyridine (4.0 mL). After cooling at 0 °C, Ac_2O (2.0 mL) was added dropwise. The reaction mixture was allowed to react for 16 h at room temperature, then it was diluted with Et_2O (20 mL), treated with ice and with aqueous $NaHCO_3$ (5 ml). The dried ($MgSO_4$) organic phase gave after evaporation a crude oily mixture that was purified by column chromatography eluting with hexanes/AcOEt 6:4 to give as the second eluting fractions the title compound (117 mg, 65% yield starting from **2a**) as an oil. IR ν 3472, 1656 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 1.43–1.59 (m, 2H); 1.91 (s, 3H); 1.93–2.09 (m, 2H); 4.79–4.83 (m, 1H); 5.11–5.19 (m, 1H); 6.52–6.70 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 20.9, 21.1, 23.5, 46.2, 71.8, 131.2, 133.0, 170.3. ESI-MS for $C_8H_{13}NO_3$: 194.07 ($M+Na^+$). The first eluting fractions gave 24 mg (12% from **2a**) of *(3aS*,7aR*)-2-oxo-4,5-dihydrobenzo[d]oxazol-3(2H,3aH,7aH)-yl acetate* (**6**). IR ν 1762, 1674 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 1.71–1.94 (m, 2H); 2.24 (s, 3H); 2.38–2.49 (m, 2H); 4.19–4.28 (m, 2H); 4.91–5.01 (m, 1H); 5.75–5.83 (m, 1H); 6.13–6.29 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 20.1, 21.8, 29.7, 57.2, 69.7, 121.4, 135.0, 157.1, 167.8. ESI-MS for $C_9H_{11}NO_4$: 197.10.