Reductive Ring Cleavage of Nonconjugated Δ^2-Isoxazolines to β-Hydroxy Ketones with Aluminum and Copper(II) Chloride

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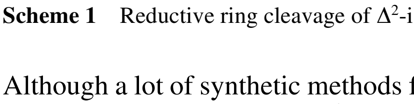
Abstract: A facile, economic, and efficient protocol for the reduction of nonconjugated Δ^2-isoxazolines to the corresponding β-hydroxy ketones using $Al/CuCl_2$ as the reducing agent has been developed. The method is both rapid and complete requiring less than ten minutes to attain total ring cleavage. This is the first example of using an in situ prepared Al/Cu couple in organic synthesis.

Key words: reduction, isoxazolines, β-hydroxyketones, aluminum/copper couple

Δ^2-Isoxazolines constitute of a class of heterocycles that are most commonly assembled by a dipolar cycloaddition reaction of a nitrile oxide and an alkene.[1] Besides being potential pharmaceutical agents,[2] isoxazolines have found numerous applications in synthesis through reductive cleavage of the N–O bond to give 1,3-amino alcohols or β-hydroxy ketones through hydroxyimine intermediates.[3] β-Hydroxy ketones have attracted the scientific interest as useful building blocks in organic synthesis[4] and, moreover, as biologically significant scaffolds.[5] Reduction of isoxazolines can be accomplished using Raney-Ni,[6] $Mo(CO)_6$,[7] SmI_2,[8] Fe/NH_4Cl,[9] $TiCl_3$,[6b,10] EtMgBr/Ti(O*i*-Pr)$_4$,[11] and some other reagents.[12]



Scheme 1 Reductive ring cleavage of Δ^2-isoxazolines

Although a lot of synthetic methods for the preparation of β-hydroxy ketones from Δ^2-isoxazolines are already known, development of fast, economic, and ecological ways are formidable tasks for organic chemists (Scheme 1). Moreover, there is a growing interest in carrying out important synthetic transformations in aqueous media.[13] We report herein a simple and mild procedure for the reduction of Δ^2-isoxazolines using aluminum powder and copper(II) chloride in aqueous methanol, where excellent discrimination between conjugated and nonconjugated isoxazolines has been observed.

During our investigations aimed on the synthesis of biologically important β-hydroxy ketones, we have synthesized various isoxazolines **1a**–**p** using a well-known dipolar cycloaddition method.[1] Having in hand the requisite substrates, we could test their reactivity towards different reduction conditions. The results are shown in Table 1. First of all, we choose isoxazolines **1a** and **1b** as model substrates and tried the recently discovered low-cost reduction method by the Fe/NH_4Cl system (Table 1, entries 1 and 2).[9] The starting materials were consumed completely within four hours; but yields of the desired β-hydroxy ketones **2a**,**b** were moderately low. Moreover, in the case of starting material **1b**, we observed the formation of two side products – 1-phenyl-2-hepten-1-one, formed after the elimination of water and methyl phenyl ketone, formed after the retro-aldol reaction. After these unsatisfactory results, we turned our attention to the possible use of bimetallic systems.

Bimetallic reductive systems such as Fe/Pd, Fe/Cu, Fe/Co, Zn/Cu, Pd/Ag, Pd/Cu, Pt/Cu, Al/Cu, etc. are known as effective catalysts mainly for dechlorination of various chlorinated hydrocarbons, and they were studied particularly for potent groundwater remediation.[14] We chose an in situ preparation of several inexpensive couples such as Fe/Cu, Zn/Cu, and Al/Cu and tested their reactivity towards the reductive cleavage of the isoxazolines.

The reductive systems Al/Cu, Zn/Cu and Fe/Cu were prepared in situ by adding an aqueous solution of copper(II) salts to mixtures of starting isoxazolines and the corresponding metal in methanol. No reaction was observed by TLC when we tried to use aluminum cuttings and copper(II) sulfate (Table 1, entry 3). Addition of sodium chloride to the reaction mixture solved this problem probably by destroying of the aluminum oxide layer. So the complete consumption of starting material was reached in five minutes (Table 1, entry 4). Using copper(II) chloride instead of the combination $CuSO_4$/NaCl slightly increased the yield of the product (Table 1, entries 5, 6) and, logically, the use of aluminum dust gave a better result in comparison to aluminum cuttings. However, using the Zn/Cu system was not so effective – the conversion of **1a** was only 25% (Table 1, entry 7) and, moreover, the couple Fe/Cu was inactive at all (Table 1, entry 8). It should be noted that 5-butyl-3-phenyl-4,5-dihydroisoxazole (**1b**) was recovered unchanged after the treatment with $Al/CuCl_2$ or $Zn/CuCl_2$ systems (Table 1, entries 9, 10). So it is possible to conclude that the Al (dust)/$CuCl_2$ system in methanol–aqueous media is the best reaction condition for the reductive cleavage of nonconjugated isoxazolines.

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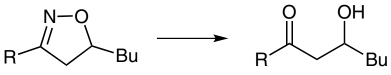
Table 1 Reaction Conditions for the Reductive Cleavage of 3-Substituted 5-Butyl-4,5-dihydroisoxazoles **1a**,**b**



1a,**b** **2a**,**b**

1a, **2a**: R = Hex
1b, **2b**: R = Ph

Entry	Starting material	Reaction conditions	Conv. (%)	Yield of **2** (%)
1	**1a**	Fe/NH_4Cl, EtOH–H_2O, 80 °C	100	50
2	**1b**	Fe/NH_4Cl, EtOH–H_2O, 80 °C	100	36
3	**1a**	Al (cuttings), $CuSO_4{\cdot}5H_2O$, MeOH–H_2O, r.t.	0	–
4	**1a**	Al (cuttings), $CuSO_4{\cdot}5H_2O$, NaCl, MeOH–H_2O, r.t.	100	73
5	**1a**	Al (cuttings), $CuCl_2{\cdot}2H_2O$, MeOH–H_2O, r.t.	100	76
6	**1a**	Al (dust), $CuCl_2{\cdot}2H_2O$, MeOH–H_2O, r.t.	100	82
7	**1a**	Zn (dust), $CuCl_2{\cdot}2H_2O$, MeOH–H_2O, r.t.	25[a]	18[b]
8	**1a**	Fe, $CuCl_2{\cdot}2H_2O$, MeOH-H_2O, r.t.	0	–
9	**1b**	Al (dust), $CuCl_2{\cdot}2H_2O$, MeOH–H_2O, r.t.	5[a]	–
10	**1b**	Zn (dust), $CuCl_2{\cdot}2H_2O$, MeOH–H_2O, r.t.	0	–

[a] Conversions determined from NMR of crude mixtures.
[b] Yield of pure product.

Encouraged by these results we decided to perform the synthesis of various β-hydroxy ketones according to the presented method. The results are summarized in Table 2. All nonconjugated starting izoxazolines underwent smooth reductive ring cleavage (Table 2, entries 1, 3–9). When 5-hydroxymethyl Δ^2-isoxazoline **1g** was subjected to the reductive conditions, the reaction occurred smoothly and cleanly, as observed by TLC (Table 2, entry 7). However, the corresponding product **2g** was not stable, and about 15% of it underwent hydroxy elimination and subsequent condensation to form 2-hexylfuran during the workup and purification procedure. In the case of 5-*tert*-butyl-3-(1-propenyl)-4,5-dihydroisoxazole (**1l**), the reduction of the C=C bond was also observed (Table 2, entry 10). But, on the other hand, 5-*tert*-butyl-3-(2-phenylethenyl)-4,5-dihydroisoxazole (**1m**) remained unaffected during the reaction (Table 2, entry 11). As it was observed earlier, the starting materials bearing aryl moiety in the 3-position of the isoxazoline ring were unreactive towards the reaction conditions (Table 2, entries 2, 12, and 13). The effect of conjugation is clearly seen from the comparison of the reduction of two isomeric compounds – 5-butyl-3-phenyl-4,5-dihydroisoxazole (**1b**, Table 2, entry 2) and 3-butyl-5-phenyl-4,5-dihydroisoxazole (**1d**, Table 2, entry 4). In the case of 5-cyclohexyl-3-(4-nitrophenyl)-4,5-dihydroisoxazole (**1p**), complete reduction of the nitro group was observed while the heterocyclic ring remained unchanged (Table 2, entry 14). Therefore, we tried to reduce the nitro groups in simple aromatic compounds **3a**,**b** and obtained the corresponding anilines **4a**,**b** in satisfactory yields (Table 2, entries 15, 16).

Table 2 Data on the Synthesis of β-Hydroxy Ketones by the Presented Method[15]

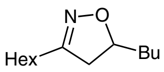
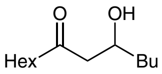
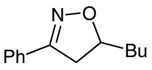
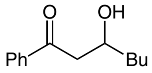
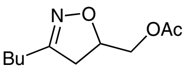
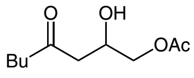
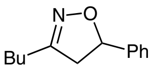
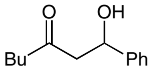
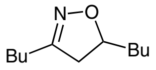
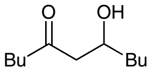
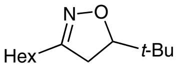
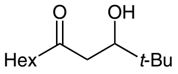
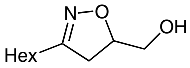
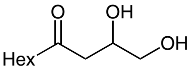
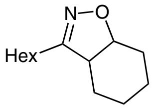
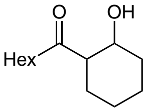
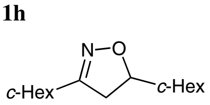
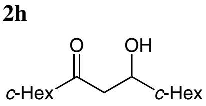
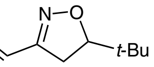
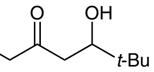
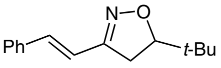
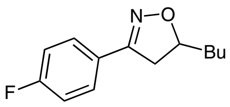
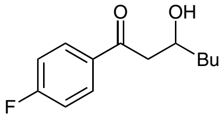
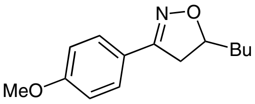
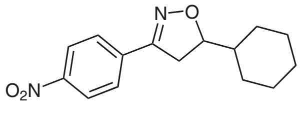
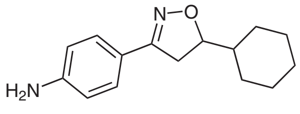
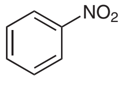
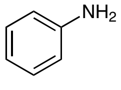
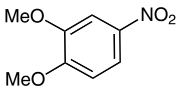
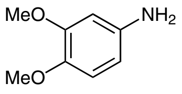
Entry	Starting material	Product	Yield (%)
1	 **1a**	 **2a**	84
2	 **1b**	 **2b**	14[a]
3	 **1c**	 **2c**	76

Table 2 Data on the Synthesis of β-Hydroxy Ketones by the Presented Method[15] (continued)

Entry	Starting material	Product	Yield (%)
4	 **1d**	 **2d**	72
5	 **1e**	 **2e**	52
6	 **1f**	 **2f**	74[b]
7	 **1g**	 **2g**	82[c]
8	 **1h**	 **2h**	76
9	 **1k**	 **2k**	89
10	 **1l**	 **2l**	71
11	 **1m**	no reaction	–
12	 **1n**	 **2n**	trace[a]
13	 **1o**	no reaction	–
14	 **1p**	 **1r**	80
15	 **3a**	 **4a**	79
16	 **3b**	 **4b**	75

[a] Incomplete conversion of the starting material.

[b] The product was unstable, and 20% of it converted into 2,2-dimethyl-3-undec-5-ene.

[c] The product was unstable, and 15% of it converted into 2-hexylfurane during workup.

In summary, the reduction using Al/$CuCl_2$ provides a facile, economical, and efficient protocol for the preparation of β-hydroxy ketones. The procedure is particularly useful for the transformation of nonconjugated Δ^2-isoxazolines to β-hydroxy ketones, as well as for reduction of aromatic nitro compounds. Moreover, this is the first example of using an in situ prepared aluminum/copper couple in organic synthesis. Advantages of the presented method include low cost, neutral media, and short reaction times (up to 10 min). This method should be of considerable interest for the construction of synthetically useful and complex biologically active molecules. The investigation of using the Al/Cu couple in organic synthesis is carrying out in our laboratory, and the results will be published in due course.

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(15) **Typical Procedure for the Reductive Cleavage of 3,5-Disubstituted 4,5-Dihydroisoxazoles 1**
To the mixture of the corresponding 3,5-disubstituted 4,5-dihydroisoxazole (**1**, 1 mmol) and Al dust (0.81 g, 30 mmol) in MeOH (5 mL) a solution of $CuCl_2 \times 2H_2O$ (1.75 g, 10 mmol) in H_2O (5 mL) was added dropwise under vigorous stirring. After the evolution of hydrogen and full consumption of the starting material (observed by TLC, approximately after 5–10 min), the mixture was diluted with H_2O (30 mL), and the product was extracted with $CHCl_3$ (2 ×30 mL). The organic layer was dried over Na_2SO_4, evaporated under the reduced pressure, and the residue purified by column chromatography to give **2**.
Analytical Data for 5-Hydroxy-7-tridecanone (2a)
Yield: 84%; colorless oil. IR (KBr): ν_{max} = 3410 (OH), 1706 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (3 H, t, J = 7.5 Hz, CH_3), 0.91 (3 H, t, J = 7.5 Hz, CH_3), 1.28–1.60 (14 H, m, 7 CH_2), 2.43 [2 H, t, J = 7.5 Hz, C(8)H_2], 2.48–2.54 [1 H, m, C(6)H], 2.57–2.64 [1 H, m, C(6)H], 3.03 (1 H, br s, OH), 3.99–4.07 [1 H, m, C(5)H] ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ = 13.8 (CH_3), 13.9 (CH_3), 22.4, 22.6, 23.5, 27.6, 28.7, 31.5, 36.1 (C-4), 43.6 (C-8), 48.9 (C-6), 67.5 (C-5), 212.6 (C-7) ppm. Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.84; H, 12.23. Found: C, 73.00; H, 12.19.
Compounds **1**–**4** were also fully characterized by IR, ^1H NMR, ^{13}C NMR spectroscopic and microanalytical data, and data for known compounds are in agreement with published data.