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Reduction of Δ^2-Isoxazolines to β-Hydroxy Ketones with Iron and Ammonium Chloride as Reducing Agent

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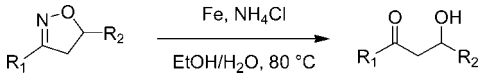
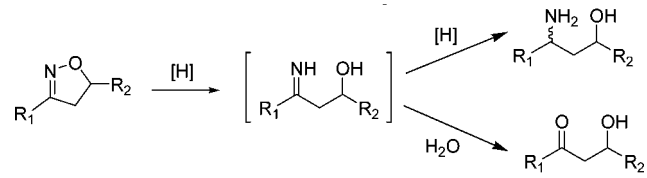


A detailed study of a procedure for the selective reduction of Δ^2-isoxazolines to the corresponding β-hydroxy ketones is reported. The use of iron and ammonium chloride as the reducing agent in the presence of water results in a facile and chemoselective protocol for the preparation of β-hydroxy ketones, including the conjugated β-hydroxy ketones.

β-Hydroxy ketones have been well demonstrated as important building blocks for the preparation of pharmaceuticals and natural products,[1] and their synthesis has attracted the interest of many organic chemists. During recent decades, the conversion of Δ^2-isoxazolines to β-hydroxy ketone derivatives has developed into a powerful alternative to traditional carbonyl condensation methods for the stereoselective synthesis of aldol adducts.[2] However, the sensitivity of other functionalities to the catalytic hydrogenolysis employed for the isoxazoline ring opening remains a challenge.[3,4] To avoid concomitant reduction of a conjugated olefin, E. Carreira and J. Bode described a selective method for the reduction of conjugated Δ^2-isoxazolines to the corresponding unsaturated β-hydroxy ketones.[5]

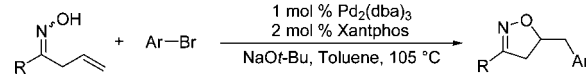
SCHEME 1. Reductive N−O Bond Cleavage of Δ^2-Isoxazolines



Notwithstanding these antecedents, it still seems highly desirable to develop a simple, economical, and general protocol as an extension of this method for the reduction of both 3-vinyl and saturated Δ^2-isoxazolines to the corresponding β-hydroxy ketones.

In general, reductive ring opening of Δ^2-isoxazolines can result in either complete reduction to an amino alcohol or N−O bond reduction/hydrolysis to β-hydroxy ketones (Scheme 1) through hydroxyimine intermediates.[2b] We envisioned that a judicious choice of reducing agent other than the reported catalytic hydrogenolysis[2b,c] and transition metal induced reduction[2f,g,5] might also effect these transformations.

We have recently established a new method for the preparation of Δ^2-isoxazolines via Pd-catalyzed carboetherification of β,γ-unsaturated oximes [eq. 1].[6] During the course of our investigation of their N−O bond cleavage, we found that Fe/NH_4Cl can easily reduce the Δ^2-isoxazolines to the corresponding β-hydroxy ketones in the presence of water. Herein, we would like to report the details of this facile and economical procedure that has resulted in a new general method for the chemoselective reduction of Δ^2-isoxazolines to β-hydroxy ketones.



(1)

Aiming to develop an easier and less expensive method for the cleavage of N−O bond in Δ^2-isoxazolines, we became interested in investigating whether the easily available reducing agents that are effective in the reductive ring openings of isoxazolidines[7] and Δ^4-isoxazolines[8] would be applied in this case. Our initial screening with these methods proved unsuccessful in providing the desired γ-amino alcohol **3** or β-hydroxy ketone **2a**, so we began to investigate Fe/NH_4Cl in the presence of water as an alternative (Table 1).

At first, substrate **1a** was subjected to a suspension of Fe powder (5 equiv) and NH_4Cl (5 equiv) in EtOH/H_2O (1:1) at 60 °C. It was found that only β-hydroxy ketones **2a** along with the unconsumed starting material were obtained after 5 h (entry 7, Table 1). No products from retroaldol reaction

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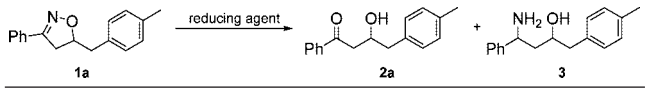
TABLE 1. Study into the Effects of Reducing Agent and Reaction Condition



	reducing agent	solv. (T[°C])	yield of **2a**	yield of **3**
1[a]	$ClSi(CH_3)_3$, KI	CH_3CN, H_2O (25)	0	0
2[a]	$LiAlH_4$	THF (60)	0	0
3[a]	$NaBH_3CN$, HCl	MeOH, H_2O (25)	0	0
4[a]	$NaBH_4$	AcOH (60)	0	0
5[a]	Zn	AcOH (60)	0	0
6[a]	Zn	AcOH, H_2O (60)	0	0
7	Fe, NH_4Cl	EtOH, H_2O (60)	46	0
8	Fe, NH_4Cl	EtOH, H_2O (80)	91	0

[a] Complete recovery of the starting material.

or β-hydroxy elimination were observed. When the reaction was carried out at 80 °C, the yield was increased dramatically due to the complete consumption of starting material (entry 8, Table 1). Optimal conditions that were general with respect to substrate scope were found to be the use of an excess (10 equiv) of Fe powder and NH_4Cl. Thus, the starting material was consumed completely within several hours. The use of other H^+ sources, such as acetic acid, led to decreased yield.

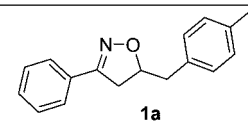
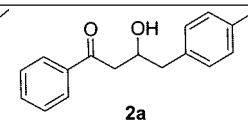
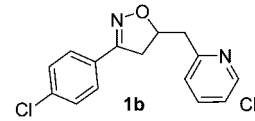
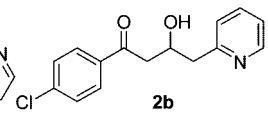
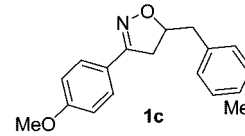
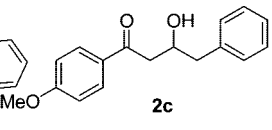
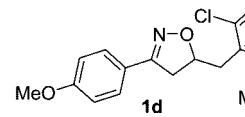
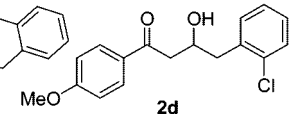
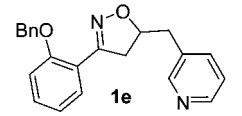
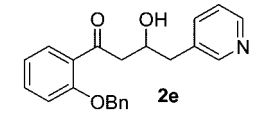
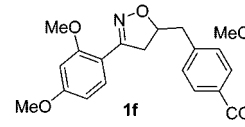
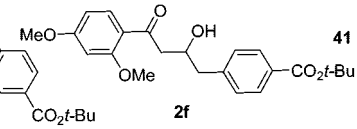
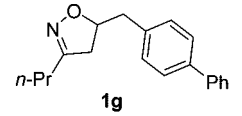
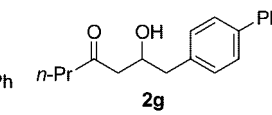
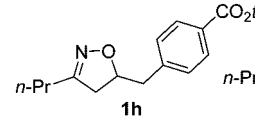
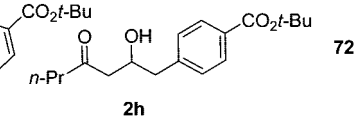
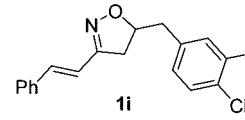
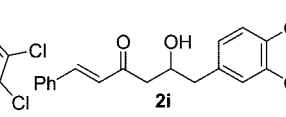
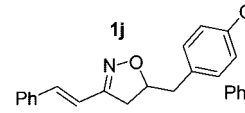
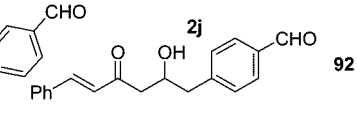
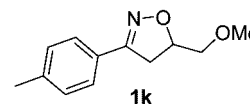
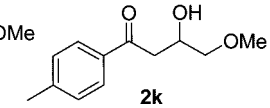
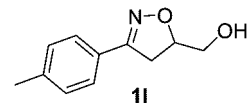
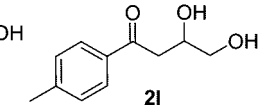
We next examined the substrate scope of the conversion. A range of substituted Δ^2-isoxazolines were synthesized according to our newly developed method[6] or using a [3 + 2] dipolar cycloaddition reaction of a nitrile oxide and alkene. The products were subjected to the optimized conditions for the reductive ring cleavage. As shown in Table 2, this method is effective for the reduction of a variety of substituted Δ^2-isoxazolines to the corresponding β-hydroxy ketones. Moderate to excellent yields were obtained in most cases. Δ^2-Isoxazolines, which bear electron-neutral (entries 1, 11, and 12) or electron-poor (entry 2) aryl substituents at the 3-position, provide high yields. With substrates bearing electron-rich (entries 3, 4, 5, and 6) and especially *o*-substituted (entries 5 and 6) aryl substituents at the 3-position, the reaction was sluggish, and the yields were relatively low due to the recovery of starting materials.

It is worth noting that various functional groups and substitution patterns are tolerated in the process. Chloride (entries 2, 4, and 9), ester (entry 8), and free hydroxyl groups (entry 12) survive the isoxazoline reduction unscathed. Easily reduced benzyl (entry 5) and aldehyde groups (entry 10) were untouched in the reductive reaction. In contrast to many previously reported methods, these conditions can effect reduction of conjugated 3-vinyl Δ^2-isoxazolines without concomitant reduction of the α,β-unsaturated olefin (entries 9 and 10).

When 5-hydroxymethyl Δ^2-isoxazoline **1l** was subjected to the reductive conditions, the reaction occurred smoothly and cleanly, as judged by TLC (entry 12, table 2). However, the corresponding product **2l** is not stable, and about 10% of it undergoes hydroxyl elimination and subsequent condensation to form 2-*p*-tolylfuran during the workup and purification procedure.

In summary, we have successfully developed a facile, economical, and efficient protocol for the chemoselective reduction of Δ^2-isoxazolines to the corresponding β-hydroxy ketones using Fe/NH_4Cl as the reducing agent. The procedure revealed is general and is particularly useful for the transformation of both conjugated and nonconjugated Δ^2-isoxazolines to β-hydroxy ketones, a troublesome transformation with other known reagents. This finding should be of considerable interest for the construction of biologically active molecules.

TABLE 2. Reduction of Δ^2-Isoxazolines to β-Hydroxy Ketones with Fe and Ammonium Chloride as Reducing Agent[a]

	Substrate	Product	Yield (%)
1	 **1a**	 **2a**	91
2	 **1b**	 **2b**	88
3	 **1c**	 **2c**	58
4	 **1d**	 **2d**	55
5	 **1e**	 **2e**	35
6	 **1f**	 **2f**	41
7	 **1g**	 **2g**	93
8	 **1h**	 **2h**	72
9	 **1i**	 **2i**	86
10	 **1j**	 **2j**	92
11	 **1k**	 **2k**	76
12	 **1l**	 **2l**	78[b]

[a] Reaction conditions: 1.0 equiv of substrate **1**, 10 equiv of Fe powder, 10 equiv of NH_4Cl, EtOH/H_2O = 1:1, 80 °C. [b] The product was unstable, and 10% of it converted to *p*-(2-furanyl) toluene during the workup procedure.

Experimental Section

General Procedure for the Reduction of Δ^2-Isoxazolines to β-Hydroxy Ketones with Fe/NH_4Cl as Reducing Agent. To a stirred solution of Δ^2-isoxazoline **1a** (**1b**−**l**, 0.3 mmol) and NH_4Cl (161 mg, 3 mmol) in ethanol and water (1:1, 15 mL) was added Fe powder (168 mg, 3 mmol). The mixture was heated to 80 °C and was allowed to stir at this temperature for 6 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a silica pad. The filtrate was washed with brine, and the organic layer was separated, dried over $MgSO_4$, and evaporated in vacuo. The residue was then purified by flash chromatography on silica gel to give the desired product **2a** (**2b**−**l**).

3-Hydroxy-1-phenyl-4-p-tolylbutan-1-one (2a). White solid, mp 56−59 °C. ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 7.90−7.93 (2H, m), 7.56−7.58 (1H, m), 7.43–7.48 (2H, m), 7.15−7.18 (4H, m), 4.45−4.49 (1H, m), 3.25 (1H, s), 3.09−3.15 (2H, m), 2.94 (1H, dd, J = 7.0, 13.6 Hz), 2.82 (1H, dd, J = 6.5, 13.6 Hz), 2.34 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 200.5, 136.7, 136.0, 134.8, 133.5, 129.3, 129.2, 128.6, 128.0, 68.9, 44.1, 42.4, 21.0; IR (KBr, cm^{-1}) 3399, 3354, 3023, 2928, 1683, 1594, 1578, 1512, 1444, 1372, 1267, 1094; MS (GC-MS) calculated for $C_{17}H_{18}NaO_2$ [M+Na^+]: 277.12; found: 277.12.

1-(4-Chlorophenyl)-3-hydroxy-4-(pyridin-2-yl)butan-1-one (2b). Brown solid, mp 79−81 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48−8.49 (1H, m), 7.89 (2H, d, J = 8.5 Hz), 7.59−7.64 (1H, m), 7.41 (2H, d, J = 8.5 Hz), 7.14−7.19 (2H, m), 5.10 (1H, br), 4.64−4.69 (1H, m), 3.28 (1H, dd, J = 16.7, 7.1 Hz), 2.95−3.14 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 159.3, 148.6, 139.7, 136.7, 135.3, 129.6, 128.9, 123.9, 121.7, 67.7, 45.1, 43.0; IR (KBr, cm^{-1}) 3344, 3259, 3088, 3014, 2910, 1679, 1586, 1568, 1482, 1436, 1397, 1088, 1077, 818; HRMS-ESI (m/z): [M+$Na]^+$ calcd for $C_{15}H_{14}ClNNaO_2$: 298.0605; found: 298.0612.

3-Hydroxy-1-(4-methoxyphenyl)-4-phenylbutan-1-one (2c). White solid, mp 67−68 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87−7.91 (2H, m), 7.24−7.35 (5H, m), 6.90−6.94 (2H, m), 4.45−4.49 (1H, m), 3.86 (3H, s), 3.40 (1H, br), 3.12 (1H, dd, J = 17.4, 3.3 Hz), 2.94−3.05 (2H, m), 2.84 (1H, dd, J = 13.5, 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 163.8, 138.1, 130.4, 129.8, 129.4, 128.5, 126.5, 113.7, 69.0, 55.4, 43.5, 42.9; IR (KBr, cm^{-1}) 3423, 3058, 3027, 2934, 2893, 2838, 1672, 1599, 1575, 1509, 1452, 1416, 1376, 1257, 1091, 814; HRMS-ESI (m/z): [M+$Na]^+$ calcd for $C_{17}H_{18}NaO_3$: 293.1148; found: 293.1153.

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Supporting Information Available: NMR spectra of **1d, 1j**−**l,** and **2a**−**l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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