Selective Reduction of the Exocyclic Double Bond of Isoxazolones and Pyrazolones by Hantzsch 1,4-Dihydropyridine

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Abstract: Hantzsch 1,4-dihydropyridine (HEH) was used to realize the selective reduction of the exocyclic double bond of 4-arylmethylene- and 4-alkylidene-4*H*-isoxazol-5-ones and 4-arylmethylene-4*H*-pyrazol-5-ones.

Key words: Hantzsch 1,4-dihydropyridine, reduction, isoxazol-5-one, pyrazol-5-one

Hantzsch 1,4-dihydropyridine (HEH), a well-known model compound of co-enzyme nicotinamide adenine dinucleotide (NADH), has been extensively studied from both mechanistic and synthetic points of view.[1] Recent attention has been focused on using this compound as an attractive biomimetic reducing agent for synthetically useful organic transformations,[2–6] such as organocatalytic and enantioselective conjugated reduction of α,β-unsaturated aldehydes,[2] reduction of conjugated olefins,[3] reductive amination of carbonyl compounds[4] and reductive cyclization of electron deficient double bonds.[5] We found previously that photoexcited HEH could reduce carbon tetrachloride,[7] and selectively break the C_α–O bond of α,β-epoxy ketones to give the corresponding β-hydroxy ketones.[8] Herein we wish to report that HEH could selectively reduce the exocyclic double bond of 4-arylmethylene- and 4-alkylidene-4*H*-isoxazol-5-ones (**1**) to the corresponding 3,4-disubstituted 2*H*-isoxazol-5-ones (**2**) with high efficiency (Scheme 1 and Table 1).

An ethanolic solution (3 mL) of the 4*H*-isoxazol-5-one (**1**, 1 mmol) and HEH (1 mmol) was refluxed under argon atmosphere. The reaction was completed within 20–30 minutes as monitored by thin layer chromatography. After removal of the solvent under reduced pressure, the products were isolated by flash chromatography on silica gel, purified by recrystallization from chloroform–hexane, and identified by ^{1}H NMR and mass spectroscopy as the 3,4-disubstituted 2*H*-isoxazol-5-one (**2**) and the pyridine derivative **3**. The results are listed in Table 1.

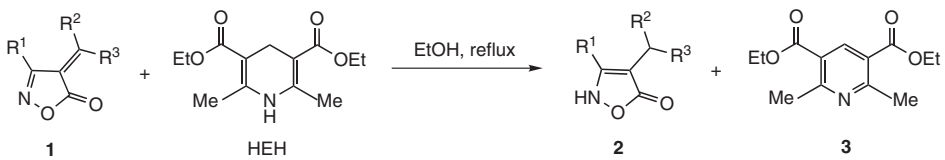
Table 1 Reduction of the 4*H*-Isoxazol-5-ones (**1**) by HEH

Substrate	R^1	R^2	R^3	Product	Yield (%)[a]
1a	CH_3	H	Ph	**2a**	94
1b	CH_3	H	4-CH_3-C_6H_4	**2b**	93
1c	CH_3	H	4-CH_3O-C_6H_4	**2c**	95
1d	CH_3	H	4-Cl-C_6H_4	**2d**	93
1e	CH_3	H	4-HO-C_6H_4	**2e**	94
1f	CH_3	H	Ph-CH=CH	**2f**	93
1g	Ph	H	Ph	**2g**	96
1h	Ph	H	4-NO_2-C_6H_4	**2h**[b]	98
1i	Ph	H	4-NMe_2-C_6H_4	**2i**	92
1j	Ph	H	2-Furyl	**2j**	95
1k	Ph	H	Ph-CH=CH	**2k**	90
1l	Ph	-$(CH_2)_4$-		**2l**	94

[a] Isolated yields. All the products, except **2h**, were identified by comparing their mp, ^{1}H NMR and MS spectral data with those reported in the literature.[9c,d]

[b] A new compound characterized by ^{1}H- and ^{13}C NMR, EI- and HR-MS.[10]

The 2*H*- and 4*H*-isoxazol-5-ones are versatile organic intermediates because the existence of three different tautomers that leads to a variety of interesting chemistry.[11] A practical way for the preparation of 4-arylmethyl isoxazol-5-ones is the reduction of the exocyclic double bond of the readily available 4-arylmethylene isoxazol-5-ones.[9]



Scheme 1

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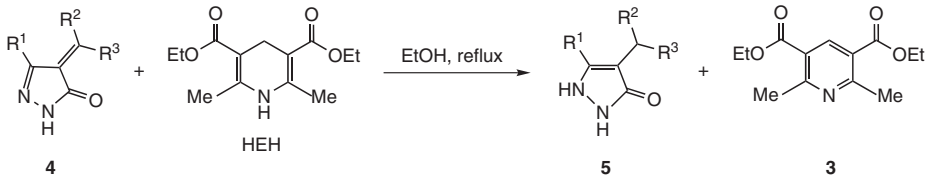

4 5 3

Scheme 2

Palladium-catalyzed hydrogenation,[9a] in situ generated benzimidazolines,[9b,c] and sodium borohydride[9d] have been used for such reduction. However, the yield was generally not satisfactory due to the cleavage of the isoxazolone ring[9a] and/or the formation of dimers[9c] and other by-products.[9b]

It is seen from Table 1 that the present procedure affords a very clean, mild and efficient approach for the selective reduction of the exocyclic double bond of 4-arylmethylene- and 4-alkylidene-4*H*-isoxazol-5-ones. The corresponding 2*H*-isoxazol-5-ones were obtained as a single reduction product with excellent yield. HEH was transformed in a quantitative way to its pyridine derivative, which could easily be removed by chromatography. The approach is applicable to substrates with either electron-donating or electron-withdrawing substituents, and is tolerant to carbonyl and nitro functionalities.

Similarly, the exocyclic double bond of 4-arylmethylene-4*H*-pyrazol-5-ones (**4**) could also be selectively reduced by HEH under the same conditions to give the corresponding 2*H*-pyrazol-5-ones (**5**) in excellent yield (Scheme 2, Table 2).

Table 2 Reduction of Pyrazol-5-ones (**4**) by HEH

Substrate	R^1	R^2	R^3	Product	Yield (%)[a]
4a	CH_3	H	Ph	**5a**	94
4b	Ph	H	Ph	**5b**	96
4c	Ph	H	4-CH_3O-C_6H_4	**5c**	95
4d	Ph	H	4-CH_3-C_6H_4	**5d**	98

[a] Isolated yields. All the products were identified by comparing their mp, ^{1}H NMR and MS spectral data with those reported in the literature.[9c]

In conclusion, the selective reduction of the exocyclic double bond of the 4-arylmethylene- and 4-alkylidene-4*H*-isoxazol-5-ones and 4-arylmethylene-4*H*-pyrazol-5-ones can be effectively achieved by using Hantzsch 1,4-dihydropyridine as the reducing agent. This method is clean, mild and efficient, and is expecting to be useful for other selective conjugate reductions.

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References

(1) (a) Marukami, Y.; Kikuchi, J.; Hisaida, Y.; Hayashida, O. *Chem. Rev.* **1996**, *96*, 721. (b) Yasui, S.; Ohno, A. *Bioorg. Chem.* **1986**, *14*, 70. (c) Fukuzumi, S.; Tanaka, T. In *Photoinduced Electron Transfer*, Part C; Fox, M. A.; Chanon, M., Eds.; Elsevier: Amsterdam, **1988**, 578. (d) Fukuzumi, S.; Suenobu, T.; Kawamura, S.; Ishida, A.; Mikami, K. *Chem. Commun.* **1997**, 291. (e) Fujii, M.; Yasui, S.; Nakamura, K. In *Reviews on Heteroatom Chemistry, Oae S.*, Vol. 20; MYU: Tokyo, **1999**, 167.

(2) (a) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *Angew. Chem. Int. Ed.* **2004**, *43*, 2. (b) Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 108. (c) Ouellet, S. G.; Tuttle, J. B.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32.

(3) Garden, S. J.; Guimarães, C. R. W.; Corréa, B.; Oliveira, C. A. F.; Pinto, A. C.; Alencastro, R. B. *J. Org. Chem.* **2003**, *68*, 8815.

(4) (a) Itoh, T.; Nagata, A.; Kurihara, A.; Miyazaki, M.; Ohsawa, A. *Tetrahedron Lett.* **2002**, *43*, 3105. (b) Takashi, I.; Kazuhiro, N.; Michiko, M.; Hiroyuki, I.; Ayako, K.; Akio, O. *Tetrahedron* **2004**, *60*, 6785.

(5) Zhu, X.-Q.; Wang, H.-Y.; Wang, J.-S.; Liu, Y.-C. *J. Org. Chem.* **2001**, *66*, 344.

(6) (a) Lee, H. W.; Kim, B. Y.; Ahn, J. B.; Son, H. J.; Lee, J. W.; Ahn, S. K.; Hong, C. I. *Heterocycles* **2002**, *57*, 2163. (b) Torchy, S.; Cordonnier, G.; Barbry, D.; Eynde, J. J. V. *Molecules* **2002**, *7*, 528.

(7) Jin, M.-Z.; Yang, L.; Wu, L.-M.; Liu, Y.-C.; Liu, Z.-L. *Chem. Commun.* **1998**, 2415.

(8) Zhang, J.; Jin, M.-Z.; Zhang, W.; Yang, L.; Liu, Z.-L. *Tetrahedron Lett.* **2002**, *43*, 9687.

(9) (a) Shaw, G. *J. Chem. Soc.* **1950**, 720. (b) Risitano, F.; Grassi, G.; Foti, F. *Tetrahedron Lett.* **1983**, *24*, 5893. (c) Risitano, F.; Grassi, G.; Caruso, F.; Foti, F. *Tetrahedron* **1996**, *52*, 1443. (d) Beccalli, E. M.; Benincori, T.; Marchesini, A. *Synthesis* **1988**, 886.

(10) 3-Phenyl-4-(4-nitrophenylmethyl)-2*H*-isoxazol-5-one (**2h**): colorless needles; mp 169–171 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.42 (1 H, br), 3.82 (2 H, s), 7.43 (2 H, d, *J* = 8.2 Hz), 7.53 (5 H, s), 8.12 (2 H, d, *J* = 8.2 Hz). ^{13}C NMR (75.43 MHz, DMSO-d_6): δ = 27.4, 94.7, 123.7 × 2 C, 127.5 × 2 C, 127.4, 129.1 × 2 C, 129.3 × 2 C, 131.2, 146.1, 147.8, 162.0, 172.4. MS (EI): *m/z* (%) = 296 (2) [M$^+$], 136 (100), 77 (5). ESI-HRMS: *m/z* calcd for $C_{16}H_{12}N_2O_4$ + H$^+$: 297.0870; found: 297.0870.

(11) (a) Batra, S.; Akhatar, M. S.; Seth, M.; Bhaduri, A. P. *J. Heterocycl. Chem.* **1990**, *27*, 337. (b) Beccalli, E. M.; Gelmi, M. L.; Marchesini, A. *Tetrahedron* **1998**, *54*, 14401. (c) Beccalli, E. M.; Marchesini, A.; Pilati, T. *Synthesis* **1991**, 127. (d) Beccalli, E. M.; Marchesini, A.; Pilati, T. *Synth. Commun.* **1993**, *23*, 685.