3,4-Disubstituted Isoxazolin-5-ones by Sodium Borohydride Reduction of 4-Arylmethylene- and 4-Alkylideneisoxazol-5(4*H*)-ones

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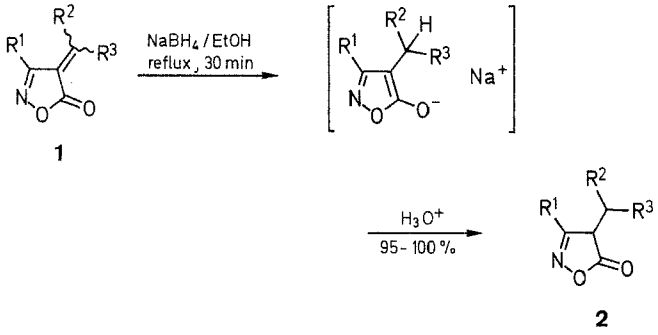
Reduction of 4-arylmethylene- and 4-alkylidenisoxazol-5(4*H*)-ones with sodium borohydride affords the corresponding 3,4-disubstituted isoxazol-5(4*H*)-ones.

The best general method to synthesize 3,4-disubstituted isoxazol-5(4*H*)-ones is the reaction between the appropriate β-ketoester (or β-ketoamide) and hydroxylamine.[1] The method is subjected to two restrictions, i.e. the availability of the 2-substituted β-ketoester, and the low yield of the reaction between the β-ketoester and hydroxylamine when the steric hindrance at the ketonic center is high.[2]

The catalytic hydrogenation of the exocyclic double bond of 4-arylmethylene- and 4-alkylideneisoxazol-5(4*H*)-ones is not a good method to obtain the corresponding 3,4-disubstituted derivatives, since the isoxazol-5(4*H*)-ones give, under these conditions, mostly open chain derivatives arising from the hydrogenolysis of the N–O bond.[3] In the case of 4-arylmethyleneisoxazol-5(4*H*)-ones a method for their reduction to the corresponding 4-arylmethylisoxazol-5-ones, which uses *o*-phenylenediamines and aldehydes, has been reported.[4]

We now wish to report that a selective reduction of the exocyclic double bond of the 4-arylmethylene-, 4-heteroarylmethylene- and 4-alkylideneisoxazol-5(4*H*)-ones **1** (Table 1) may be achieved simply and in quantitative yields using sodium borohydride in ethanol. The reduction is fast and a large excess of the reducing agent may be used without further reduction (Table 2).



1 **2**

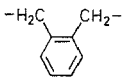
1, 2	R^1	R^2	R^3
a	Ph	H	CH=CHPh
b	Ph	H	Ph
c	Ph	$-(CH_2)_4-$	
d	Ph	CH_3	CH_3
e	Ph	H	3-thienyl
f	Ph	H	2-furyl
g	*n*-Pr	H	2-furyl
h	*n*-Pr	$-(CH_2)-$	
i	*n*-Pr	H	Ph
j	Ph	H	4-$NMe_2C_6H_4$
k	*t*-Bu	H	Ph
l	*t*-Bu	H	3-thienyl
m	CH_3		
n	Ph	H	$PhCH_2$

Table 2. 3,4-Disubstituted Isoxazol-5(4*H*)-ones **2** Prepared by $NaBH_4$ Reduction of Unsaturated Isoxazolones **1**

Product[a]	mp (°C) (solvent)[b]	Molecular Formula[c] or Lit. mp (°C)
2a	85 (ether/Hx)	$C_{18}H_{15}NO_2$ (277.3)
2b	109 (CH_2Cl_2/ether)	110[4]
2c	102–103 (ether/Hx)	$C_{14}H_{15}NO_2$ (229.3)
2d	101–102 (ether/Hx)	$C_{12}H_{13}NO_2$ (203.2)
2e	90–92 (ether/Hx)	$C_{14}H_{11}NSO_2$ (257.3)
2f	86–88 (ether/Hx)	$C_{14}H_{11}NO_3$ (241.2)
2g	oil	$C_{11}H_{13}NO_3$ (207.2)
2h	111–112 (ether/Hx)	$C_{11}H_{17}NO_2$ (195.2)
2i	48–50 (ether/Hx)	44–45[2]
2j	92–94 (ether/Hx)	$C_{18}H_{18}N_2O_2$ (294.3)
2k	111	111[2]
2l	81 (ether/Hx)	$C_{12}H_{15}NSO_2$ (237.3)

[a] The products are obtained in near quantitative yield.
[b] Hx = *n*-hexane.
[c] Satisfactory microanalyses obtained: C ±0.21, H ±0.08, N ±0.20.

The results are reported in Table 2 and the structure of the new compounds follows from analytical and spectroscopic data (Table 3), as well as comparison with some representatives previously reported.

This reduction is a valuable synthetic method to prepare 3,4-disubstituted isoxazol-5(4*H*)-ones **2** because the starting isoxazolones **1** can be easily prepared in all cases by reaction of the 4-unsubstituted isoxazol-5(4*H*)-ones (accessible from commercial β-ketoesters and hydroxylamine) with aromatic aldehydes and also with ketones[1,5] or alternatively, by the action of the 4-unsubstituted isoxazol-5(4*H*)-ones on enamines[6] (Table 1).

This method failed in the case of 4-alkylideneisoxazolones such as **1m, n** that can give a highly delocalized benzylic anion with sodium borohydride.

Melting points are determined on a Büchi apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 298 instrument, in Nujol mull for solids and liquid films for oils. ^{1}H-NMR spectra were recorded on a Varian EM-390 spectrometer with TMS as an internal standard in $CDCl_3$ solution. Column chromatography is performed on Merck Kieselgel 60, 0.063–0.2 mm. Na_2SO_4 is used as drying agent. Evaporation is carried out under vacuum in a rotary evaporator.

Compounds **1a**;[7] **1b**;[8] **1c**;[5] **1f**;[9] **1j**;[10] **1k**;[11] and **1m**[5] were prepared according to literature. New compound **1n** was obtained by the method of Lawson[6] from 3-phenylisoxazol-5(4*H*)-one and 1-morpholino-2-phenylethylene.[14]

Table 1. New 4-Arylidene- and 4-Alkylideneisoxazol-5(4*H*)-ones **1**Prepared

Product	Reaction Conditions			Eluent[a] for Column Chromatography	Yield (%)	mp (°C) (solvent)[a]	Molecular Formula[b]
	Solvent	Catalyst	Time (h), Temp.				
1e	CH_2Cl_2	DBN	24, r.t.	Hx/CH_2Cl_2 (2:1)	68	176 (CH_2Cl_2/Hx)	$C_{14}H_9NSO_2$ (255.3)
1g	EtOH	–	1, reflux 16, r.t.	Hx/CH_2Cl_2 (2:1)	75	44–45 (ether/Hx)	$C_{11}H_{11}NO_3$ (205.2)
1h	EtOH	piperidine	6, reflux 14, r.t.	–[c]	55	117 (EtOH)	$C_{11}H_{15}NO_2$ (193.2)
1i	CH_2Cl_2	DBN	24, r.t.	Hx/ether (9:1)	58	87–89 (ether/Hx)	$C_{13}H_{13}NO_2$ (215.2)
1l	EtOH	–	1, reflux 16, r.t.	Hx/CH_2Cl_2 (2:1)	85	106 (ether/Hx)	$C_{12}H_{13}NSO_2$ (235.3)
1n	CH_2Cl_2	–	0.5, r.t.	–	80	135–136 (CH_2Cl_2)	$C_{17}H_{13}NO_2$ (263.3)

[a] Hx = *n*-hexane.
[b] Satisfactory microanalyses obtained: C ±0.20, H ±0.11, N ±0.16.
[c] Crystallized from the reaction mixture.

Table 3. Spectral Data of New Compounds **1**, **2** Prepared

Compound	IR (film or Nujol) ν (cm^{-1})	^{1}H-NMR (solvent/TMS) δ, J(Hz)
1e	1738, 1610	$CDCl_3$: 7.4 (dd, 1H, J = 3.5); 7.6 (m, 6H); 7.92 (d, 1H, J = 5); 9.02 (d, 1H, J = 3)
1g	1740, 1610	$CDCl_3$: 1.08 (t, 3H, J = 7.5); 1.8 (m, 2H); 2.66 (t, 2H, J = 7.5); 6.73 (m, 1H); 7.29 (s, 1H); 7.82 (d, 1H, J = 2); 8.57 (d, 1H, J = 4)
1h	1750, 1640	$CDCl_3$: 1.08 (t, 3H, J = 7.5); 1.9 (m, 6H); 2.67 (t, 2H, J = 7.5); 2.9 (m, 2H); 3.14 (m, 2H)
1i	1730, 1615	$CDCl_3$: 1.1 (t, 3H, J = 7.5); 1.83 (m, 2H); 2.7 (t, 2H, J = 7.5); 7.5 (m, 4H); 8.35 (m, 2H)
1l	1745, 1590	$CDCl_3$: 1.48 (s, 9H); 7.4 (dd, 1H, J = 3, 4.5); 7.87 (m, 2H); 9.04 (d, 1H, J = 3)
1n	1690	DMSO-d_6: 6.8 (d, 1H, J = 17); 7–7.8 (m, 11H); 8.4 (br s, 1H)
2a	1780, 1670	$CDCl_3$: 2.9 (m, 2H); 4 (t, 1H, J = 5); 5.87 (dt, 1H, J = 7, 15); 6.3 (d, 1H, J = 15); 7.22 (s, 5H); 7.6 (m, 5H)
2c	1690, 1677	$CDCl_3$: 1.3–2.5 (m, 9H); 3.9 (d, 1H, J = 4); 7.5 (m, 5H)
2d	1790	$CDCl_3$: 0.9 (d, 3H, J = 7); 1.32 (d, 3H, J = 7); 2.43 (m, 1H); 3.75 (d, 1H, J = 3.5); 7.53 (m, 5H)
2e	1695sh, 1670	DMSO-d_6: 3.7 (s, 2H); 6.96 (m, 1H); 7.1 (m, 1H); 7.4 (m, 1H); 7.58 (s, 5H)
2f	1690sh, 1670	DMSO-d_6: 3.76 (s, 2H); 6.07 (s, 1H); 6.33 (m, 1H); 7.6 (m, 7H)
2g	1790, 1685, 1590	DMSO-d_6: 0.9 (t, 3H, J = 7); 1.52 (m, 2H); 2.47 (t, 2H, J = 7); 3.54 (s, 2H); 6.05 (m, 1H); 6.33 (m, 1H); 7.5 (m, 1H)
2h	1660, 1580	$CDCl_3$: 1.03 (t, 3H, J = 7); 1.7 (m, 10H); 2.4 (m, 3H); 3.4 (d, 1H, J = 5)
2j	1685sh, 1668	$CDCl_3$: 2.9 (s, 6H); 3.3 (d, 2H, J = 5); 4.06 (t, 1H, J = 5); 6.5 (d, 2H, J = 9); 6.68 (d, 2H, J = 9); 7.52 (m, 5H)
2l	1678, 1655	DMSO-d_6: 1.25 (s, 9H); 3.65 (s, 2H); 7 (m, 2H); 7.4 (m, 1H); 12 (br s, 1H)

4-Arylmethylene- and 4-Alkylideneisoxazol-5(4*H*)-ones 1e, 1g–i, and 1l; General Procedure:

The 4-unsubstituted isoxazolin-5-one (5 mmol; 3-phenylisoxazolin-5-one for **1e**; 3-propylisoxazolin-5(4*H*)-one[12] for **1g–i**, and 3-*tert*-butylisoxazol-5(4*H*)-one[13] for **1l**) is dissolved in the appropriate solvent (40 mL) and then the appropriate carbonyl compound (7.5 mmol; 3-thiophenecarboxyaldehyde for **1e, l**; 2-furaldehyde for **1g**; cyclopentanone for **1h** and benzaldehyde for **1i**) is added. In some cases a catalytic amount of a base is added. The mixture is reacted for the time indicated in Table 1. After evaporation of the solvent, the residue is purified by coloumn chromatography on silica gel or direct crystallization. Reaction conditions and analytical data for new compounds are listed in Table 1.

3,4-Disubstituted Isoxazol-5(4*H*)-ones 2 from Isoxazol-5-(4*H*)-ones 1; General Procedure:

The isoxazol-5(4*H*)-one **1** (5 mmol) is dissolved in EtOH (50 mL) and then $NaBH_4$ (570 mg, 15 mmol) is added. After 10 min at room temperature, the mixture is heated under reflux for 30 min. The residue obtained by evaporating the solvent is taken up in water (30 mL) and the solution acidified with 9% HCl. In the case of **1j**, 4.5% acid is added until pH 7. The mixture is extracted with CH_2Cl_2 (2 × 30 mL), the organic layer is dried, filtered, and evaporated. The residue is crystallized from the reported solvent (see Table 2).

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