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REGIOSELECTIVE DEPROTONATION OF 3-METHYL-4,5-DIHYDROISOXAZOLES AND DIASTEREOSELECTIVE REACTION WITH ELECTROPHILES

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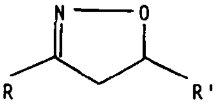
Abstract. Highly regioselective deprotonation of the title compounds is achieved by working with lithium-amide bases of different steric requirement. The effect of a 5-alkoxymethyl group in the Δ^2-isoxazoline ring on both the sense and the extent of the stereoselectivity observed in the reaction of C_4-anion with electrophiles is discussed.

Structural modifications of 4,5-dihydroisoxazole (Δ^2-isoxazoline) greatly enhanced the applicability of this versatile heterocycle to the stereoselective synthesis of a wide range of poly-functionalized molecules.[1] Among these modifications, the generation of an anion at the C_4 position and its stereocontrolled reaction with electrophiles is of relevant importance and can represent an alternative or a useful extension of the nitrile oxide-olefine cycloaddition route to isoxazolines.[2]



	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
R	Ph	Ph	Me	Et	Me	Et	Me	Me	Me	Me
R'	H	Me	Ph	Ph	H	CH_2OTHP	CH_2OCH_2Ph	C_5H_{11}-*n*	Bu-*n*	CH_2NEt_2

In his pioneering work on this topic Jäger[3] found that 3-phenyl isoxazolines such as (1) and (2) could be metallated (LDA, THF, -78°C) and reacted in good yields with various electrophiles.[1,3] However, when the problem of regioselectivity was addressed as in the case of (3) a 1.5-2:1 ratio of *endo* and *exo* products was observed.[3] As expected the formation of the *endo* product became more favourable on passing from 3-methyl (3) to 3-ethyl derivative (4). More recently Shatzmiller[4] evidenced a solvent dependence of regioselectivity in the metallation (BuLi, -65°C)/alkylation sequence of isoxazoline (5), the addition of HMPA shifting the reaction form the *exo* to the *endo* product. Finally Kozikowski showed that 3-ethyl-5-alkoxymethyl isoxazolines as (6) underwent exclusively *endo* deprotonation when metallated by LDA in THF/HMPA at -65°C. The same base/solvent system gave "preferential formation" of *endo* adduct with compounds (7) and (8).[5]

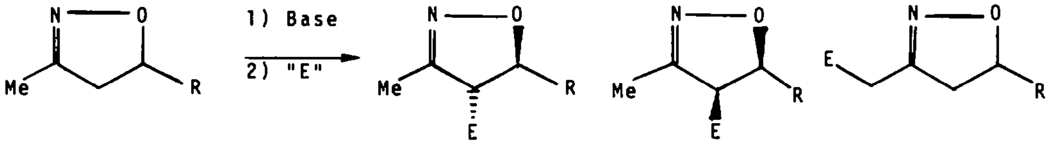
From the bulk of these data it could be inferred that predominance of C$_4$ deprotonation is achieved mainly by the use of HMPA. We here report a different approach to the solution of this problem which allows regioselective metallation even of a 3-methyl substituted isoxazoline.

As typical substrate we choose 5-[(benzyloxy)methyl]-3-methylisoxazoline (7), a substrate that can be considered a useful precursor for the synthesis of sugars[5] and amino-sugars[6].

As can be seen from the data reported in Table 1 LDA in THF is a poorly selective base, the formation of the *endo* product being slightly favoured by working at higher temperatures (entries 1 and 2), or by the addition of HMPA (entry 3).

A marked increase in regioselectivity (in both sense!) is achieved by changing the steric requirement of the lithium-amide base. Indeed, with lithium-diethylamide (LDEA) at -90°C[+] 5:1 ÷ 10:1 *endo*:*exo* ratios are observed (entries 4,6,7) the alkylation yields remaining reasonably good. *Endo* products still predominates in a non-polar solvent like toluene (entry 5).[4]

Scheme



(3),(7),(9),(10) (11a)-(19a) *anti* (11b)-(19b) *syn* (11c)-(19c)

(11) R = CH_2OCH_2Ph E = Me
(12) R = CH_2OCH_2Ph E = Bu-*n*
(13) R = CH_2OCH_2Ph E = CH_2COOBu-*t*
(14) R = CH_2OCH_2Ph E = COOEt
(15) R = CH_2OCH_2Ph E = OH
(16) R = CH_2OCH_2Ph E = CH(OH)Et
(17) R = Bu-*n* E = Me
(18) R = Ph E = Me
(19) R = CH_2NEt_2 E = Me

[+] This reaction temperature was choosen in order to minimize, even for long reaction time, retrocyclization process, shown to occur for C$_4$-anions.[3]

Table 1. Deprotonation and reaction with electrophiles of (3), (7), (9), and (10).

Entry	Product	Base	"E"	t^a (min)	Yield^b %	Isoxazoline^b recovered %	a+b : c^c ratio	a:b^c ratio
1	(11)	LDA[d]	MeI	30	100	-	1.4:1	≥25:1
2	(11)	LDA	MeI	30	95	5	1:1	≥25:1
3	(11)	LDA[e]	MeI	30	85	5	3:1	≥25:1
4	(11)	LDEA	MeI	30	58	26	5.5:1	
5	(11)	LDEA[f]	MeI	30	34	26	3.5:1	
6	(11)	LDEA	MeI	60	55	36	10:1	≥25:1
7	(11)	LDEA	MeI	120	76	5	5:1	≥25:1
8	(11)	LTMP	MeI	20	72	10	1:10	-
9	(17)	LDEA	MeI	120	33	10	2.4:1	10:1
10	(17)	LTMP	MeI	20	35	20	≤ 1:25	-
11	(18)	LDEA	MeI	120	36	13	9.5:1	15:1
12	(18)	LTMP	MeI	20	46	34	1:9	-
13	(19)	LDEA	MeI	120	26	70	3:1	≥25:1
14	(19)	LTMP	MeI	20	90	-	1:5.8	-
15	(12)	LDEA	*n*-BuI	120	55	32	≥25:1	14:1
16	(13)	LDEA	$\mathrm{BrCH_2COOBu}$-*t*	120	55	30	≥25:1	≥25:1
17	(14)	LDEA	ClCOOEt	120	41	30	≥25:1	12:1
18	(14)	LTMP	ClCOOEt	20	72	12	1:10	-
19	(15)	LDEA	$\mathrm{B(OMe)_3}$/tBuOOH	120	25	47	≥25:1	14:1
20	(16)	LDEA[g]	EtCHO	120	30[h]	50	≥25:1	≥25:1

[a] Deprotonation time; reaction temperature -90°C; condensation time with electrophiles 60 min. [b] Isolated yields. [c] As determined by ^{1}H NMR spectroscopy and/or isomer separation; a 25:1 ratio indicates that a single product was detected. [d] At -78°C. [e] In the presence of 4 mol. equiv. of HMPA. [f] In toluene as solvent. [g] Condensation time 3 min. [h] As mixtures of epimers at the OH-bearing carbon (see Text).

A complete reversal of regioselectivity is obtained by the use of lithium-2,2,6,6-tetramethylpiperidide (LTMP), a very bulky base that gives *exo*-alkylation in high yields (entry 8).

The base dependence of regioselectivity is at work also in the case of isoxazoline (9) (entries 9 and 10), and comparison between the behaviour of (7) and (9) (entries 6, 8 *vs* 9, 10) seems to suggest that intramolecular chelation with the ethereal oxygen is one of the factor directing the regiochemistry of the process.[§]

However a similar effect is also observed in the 5-phenyl substituted isoxazoline (3) for which a marked *endo* or *exo* selectivity (entries 11 and 12) is achieved. Control experiments carried out on compound (10), featuring a strongly chelating nitrogen atom, showed that in the conditions of *exo*-methylation the regio-selectivity is lower (entry 14 *vs* 8, 10, 12), and that with LDEA as base a very poor yield of the *endo*-product was obtained (entry 13). The latter result can be tentatively explained by the formation of a very stable and unreactive C_4-anion.

[§] Intramolecular chelation was proposed[5] to account for the stereochemical course of the alkylation.

A noticeable stereoselectivity is generally observed in the reaction at C_4 of 5-substituted isoxazolines with electrophiles,[1,3,5] the shielding of one of the diastereotopic faces of the ring by the C_5 substituent being invoked to rationalize the preferential or exclusive formation of C_4-C_5 *anti* products.

We investigated the stereochemical outcome of the reaction of isoxazolines (3), (7), (9), and (10) with a series of electrophiles (Scheme and Table 1). The reported data deserve a few comments. Good *anti* diastereoselectivities are generally obtained independently on the nature and/or the steric requirement of the electrophile. A coordinating or a bulky substituent at C_5 secures at least 12:1 *anti*-*syn* selectivity. A slight increase in stereocontrol is obtained by avoiding the use of HMPA in the methylation of (7); indeed in our conditions (11a) is the only detectable *endo* product, instead of the 15.7:1 (11a)::(11b) mixture obtained previously.[5] A satisfactory regio- and stereo-selectivity is achieved, unfortunately in poor chemical yields, in the synthesis of the 4-hydroxy derivatives (15a), an amino-sugars precursor[6] obtained *via* Jäger method.[7] Different electrophilic hydroxylating reagents such as MoO_5-Py-HMPA[8] or 2-(phenylsulphonyl)-3-phenyloxaziridine[9] gave even lower yields of (15a). Finally the aldol-type condensation between metallated (7) and propionaldehyde was studied. The reaction proceeds in low yield to give exclusively the *endo* products. These are isolated as a 2:1 mixture of 2 diastereoisomers, likely epimers at the OH-bearing carbon, as suggested by inspection of ^1H NMR spectra and in line with the definite preference for the formation of C_4-C_5 *anti*-products.

EXPERIMENTAL

^1H NMR spectra were recorded on a Varian EM-390 or a XL 200 instrument, using tetramethylsilane as internal standard and $CDCl_3$ as solvent. Infrared spectra were recorded on a Perkin-Elmer 457 spectrometer. Elemental analyses were performed with a Perkin Elmer 240 instrument. Silica gel was used for analytical and flash chromatography; organic extracts were dried over sodium sulphate and filtered before removal of the solvent under reduced pressure. THF was distilled from $LiAlH_4$, toluene from sodium, HMPA and amines from CaH_2. All reactions employing anhydrous solvents were run under Argon. Isoxazolines (3),[3] (7),[5] and (9)[10] were known compounds. (10) was prepared in 59% yield by the "Mukaiyama method", starting from allyl-N,N-diethylamine;[12] it was purified by flash chromatography with a diethylether-methanol 10:1 mixture as eluant. Found: C% 63.17; H% 10.51; N% 16.61. $C_9H_{18}N_2O$ requires: C% 63.49; H% 10.65; N% 16.45. ^1H NMR: δ 1.00 (t, 6H, J = 7Hz, $\underline{CH_3}$-CH_2); 1.95 (s, 3H, CH_3-CN); 2.30-2.80 (m, 8H, $4CH_2$); 4.30-4.65 (m, 1H, CH).

General procedure for the synthesis of endo-adducts. To a stirred solution of diethylamine (1.1 mmol; 0.115 ml) in THF (5 ml), *n*-BuLi (1.1 mmol; approximately 1.3 M in hexane) was added dropwise. After 10 min stirring at 0°C the solution was cooled at -90°C and a solution of isoxazoline (1.0 mmol) in THF (2 ml) was added dropwise. After the metallation time indicated in Table 1, 3.3 mmol of electrophile were added in one portion and the reaction mixture stirred at -90°C for 60 min. The reaction was quenched by the addition of 5 ml of a saturated aqueous solution of ammonium chloride and worked-up in the usual way. The products were purified by flash chromatography with diethylether-hexanes mixtures as eluants. Adduct (15a,b) was prepared following Jäger's procedure.[7] Compounds (11a,b)[5] and (18a,b)[3] were known products.

Compound (12a,b): eluant diethylether: hexanes 1:1. Found: C% 73.38; H% 8.88; N% 5.48; $C_{16}H_{23}NO_2$: C% 73.53; H% 8.87; N% 5.36. ^1H NMR: δ 0.78-0.90 (m, 3H, $\underline{CH_3}$-CH_2);

1.10-1.70 (m, 6H, 3CH$_2$); 1.88 and 1.91 (two s in 14:1 ratio, 3H, CH$_3$CN of (12a) and (12b), respectively); 2.85-2.96 (m, 1H, $\underline{CH}$-Bu-*n*); 3.41-3.55 (m, 2H, CH-$\underline{CH}_2$O); 4.26-4.38 (m, 1H, J$_{CH-CH}$= 6.5 Hz, for (12a), CH-O); 4.52 (s, 2H, CH$_2$-Ph); 7.16-7.30 (m, 5H, C$_6$H$_5$).

Compound (13a,b): eluant diethyl ether:hexanes 1:1. Found: C% 67.49; H% 7.76; N% 4.51. C$_{18}$H$_{25}$NO$_4$ requires: C% 67.69; H% 7.89; N% 4.39. ^{1}H NMR: δ 1.09 (t, 3H, J = 7 Hz, $\underline{CH}_3$-CH$_2$); 2.03 (s, 3H, CH$_3$CN), 3.63 and 3.70 (two d in 12:1 ratio, 2H, J = 4.7 and J = 6.1 Hz, CH$\underline{CH}_2$O of (13a) and (13b), respectively); 4.15-4.29 (m, 2H, $\underline{CH}_2$-CH$_3$); 4.58 (s, 2H, CH$_2$Ph); 4.95-5.04 (m, 1H, J$_{CH-CH}$= 7.8 Hz for (13a), CHO); 7.25-7.41 (m, 5H, C$_6$H$_5$).

Compound (14a): eluant diethylether:hexanes 5:4. Found: C% 65.05; H% 6.82; N% 5.06; C$_{15}$H$_{19}$NO$_4$ requires: C% 64.96; H% 6.91; N% 5.05. ^{1}H NMR: δ 1.41 (s, 9H, (CH$_3$)$_3$-C); 1.92 (s, 3H, CH$_3$CN); 3.36-3.42 (m, 1H, CHCN); 3.59 (d, 2H, J = 4.8 Hz, CH-$\underline{CH}_2$-O); 4.37-4.48 (m, 1H, J$_{CH-CH}$= 6.4 Hz, CHO); 4.58 (s, 2H, CH$_2$Ph); 7.21-7.39 (m, 5H, C$_6$H$_5$).

Compound (15a,b): eluant diethylether:hexanes 7:3. Found: C% 65.00; H, 6.91; N% 6.31. C$_{12}$H$_{15}$NO$_3$ requires: C% 65.14; H% 6.83; N% 6.33. ^{1}H NMR: δ 2.03 and 2.05 (two s in 14:1 ratio, 3H, CH$_3$CN of (15a) and (15b) respectively); 2.63 (bs, 1H, OH); 3.45-3.68 (m, 2H, CH-$\underline{CH}_2$O); 4.38-4.41 (m, 1H, CHON); 4.55 (s, 2H, CH$_2$Ph); 4.85 (d, 1H, J$_{CH-CH}$= 5.0 Hz for (15a), CH-O); 7.15-7.30 (m, 5H, C$_6$H$_5$).

Compound (16a): eluant diethylether:hexanes 10:4. Found: C% 68.58; H% 7.98; N% 5.24. C$_{15}$H$_{21}$NO$_3$ requires: C% 68.42; H% 8.04; N% 5.32. Two epimers of (16a) were isolated. The first eluted one had ^{1}H NMR: δ 0.97 (t, 3H, J = 7 Hz, $\underline{CH}_3$-CH$_2$); 1.36-1.52 (m, 2H, $\underline{CH}_2$-CH$_3$); 1.96 (s, 3H, CH$_3$-CN); 3.20 (m, 1H, J$_{CH-CHOH}$ 6.2 Hz, J$_{CH-CHON}$ 6.7 Hz, CH-CN); 3.42-3.65 (m, 2H, CH-$\underline{CH}_2$O); 3.69-3.78 (m, 1H, $\underline{CH}$-OH); 4.55 (s, 2H, CH$_2$Ph); 4.51-4.60 (m, 1H, CH-ON); 7.26-7.34 (m, 5H, C$_6$H$_5$). The second eluted one had ^{1}H NMR: δ 0.95 (t, 3H, J 7 Hz, $\underline{CH}_3$-CH$_2$); 1.36-1.54 (m, 2H, $\underline{CH}_2$-CH$_3$); 1.98 (s, 3H, CH$_3$CN); 3.14 (dd, 1H, J$_{CH-CHOH}$ 2.6 Hz), J$_{CH-CHON}$ 6.5 Hz, CH-CN); 3.45-3.65 (m, 2H, CH-$\underline{CH}_2$O); 3.76-3.83 (m, 1H, $\underline{CH}$-OH); 4.57 (s, 2H, CH$_2$Ph); 4.60-4.68 (m, 1H, CH-ON); 7.26-7.34 (m, 5H, C$_6$H$_5$).

Compound (17a,b): eluant diethylether:hexanes 1:4. Found: C% 69.50; H% 11.10; N% 8.90. C$_9$H$_{17}$NO requires: C% 69.63; H% 11.04; N% 9.02. ^{1}H NMR: δ 0.82-0.94 (m, 3H, CH$_2$-$\underline{CH}_3$); 1.00 and 1.14 (two d in 1:10, ratio, 3H, J = 7Hz, $\underline{CH}_3$-CH of (17b) and (17a), respectively); 1.25-1.80 (m, 6H, 3CH$_2$); 1.87 and 1.91 (two s in 10:1 ratio, 3H, CH$_3$-CN of (18a) and (18b), respectively); 2.65-2.80 (m, 1H, $\underline{CH}$-CH$_3$); 3.94-4.06 (m, 1H, J$_{CH-CH}$= 7 Hz for (17a), CH-O).

Compound (19a): eluant diethylether:triethylamine 96.5:3.5. Found: C% 65.40; H% 10.98; N% 15.35. C$_{10}$H$_{20}$N$_2$O requires: C% 65.18; H% 10.94; N% 15.20. ^{1}H NMR: δ 1.00 (t, 6H, J = 7 Hz, 2 $\underline{CH}_3$-CH$_2$N); 1.17 (d, 3H, J = 7 Hz, $\underline{CH}_3$-CH); 1.90 (s, 3H, CH$_3$CN); 2.41-2.76 (m, 6H, 3 CH$_2$N); 2.83-2.97 (m, 1H, $\underline{CH}$-CH$_3$); 4.12-4.22 (m, 1H, J$_{CH-CH}$= 8 Hz, CHO).

General procedure for the synthesis of exo-adducts. To a stirred solution of 2,2,6,6-tetramethylpiperidine (1.1 mmol, 0.185 ml), in THF (5 ml), *n*-BuLi (1.1 mmol, approximately 1.3 M in hexane) was added dropwise. After 15 mm stirring at 0°C the solution was cooled at -90°C and a solution of isoxazoline (1.0 mmol) in THF (2 ml) added dropwise. After 20 min, 3.3 mmol of the electrophile were added in one portion and the reaction mixture stirred at -90°C for 60 min. The work-up described above afforded the products. Compound (18c)[3] was a known product.

Compound (11c): eluant diethyl ether:hexanes 3:2. Found: C% 71.05; H% 7.75; N% 6.51. C$_{13}$H$_{17}$NO$_2$ requires: C% 71.20; H% 7.81; N% 6.39. ^{1}H NMR: δ 1.15 (t, 3H, J = 7 Hz, $\underline{CH}_3$-CH$_2$); 2.29 (q, 2H, CH$_3$-$\underline{CH}_2$); 2.55-3.05 (m, 2H, CH$_2$CN); 3.35-3.55 (m, 2H, CH-$\underline{CH}_2$O); 4.52 (s, 2H, CH$_2$Ph); 4.45-4.70 (m, 1H, CHO); 7.15-7.30 (m, 5H, C$_6$H$_5$).

Compound (14c): eluant diethyl ether:hexanes 5:4. Found: C% 65.05; H% 7.00; N% 4.98. C$_{15}$H$_{19}$NO$_4$ requires C% 64.96; H% 6.91; N% 5.05. ^{1}H NMR: δ 1.25 (t, 3H, J = 7 Hz, $\underline{CH}_3$-CH$_2$); 2.79-3.32 (m, 2H, CH$_2$CN); 3.46 (s, 2H, CH$_2$-COO); 3.59 (d, 2H, J = 6 Hz, $\underline{CH}_2$-CHO); 4.18 (q, 2H, $\underline{CH}_2$-CH$_3$); 4.61 (s, 2H, CH$_2$Ph); 4.66-4.95 (m, 1H, CHO); 7.19-7.32 (m, 5H, C$_6$H$_5$).

Compound (17c): eluant diethylether:hexanes 1:4. Found: C% 69.93; H% 11.17; N% 8.96. C$_9$H$_{17}$NO requires: C% 69.63; H% 11.04; N% 9.02. ^{1}H NMR: δ 0.80-1.75 (m, 12H, 2 CH$_3$ and 3 CH$_2$); 2.27 (q, 2H, J = 8 Hz, CH$_3$-$\underline{CH}_2$-CN); 2.24-3.04 (m, 2H, CH-$\underline{CH}_2$-CN); 4.17-4.53 (m, 1H, CHO).

Compound (19c): eluant diethylether:triethylamine 96.5:3.5. Found C% 65.00; H% 10.79; N% 15.40. C$_{10}$H$_{20}$NO requires: C% 65.18; H% 10.94; N% 15.20. ^{1}H NMR: δ 0.97 (t, 6H, J = 7 Hz, 2 $\underline{CH}_3$-CH$_2$N); 1.12 (t, 3H, J = 8 Hz, $\underline{CH}_3$-CH$_2$CN); 2.31 (q, 2H, J = 8 Hz, CH$_3$-$\underline{CH}_2$CN); 2.39-3.04 (m, 8H, 3 CH$_2$N and CH-$\underline{CH}_2$CN); 4.55-4.75 (m, 1H, CHO).

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