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SYNTHESES VIA ISOXAZOLINES II [1]. NOVEL 4-SUBSTITUTED 2-ISOXAZOLINES BY ENDO-DEPROTONATION/ALKYLATION [2]

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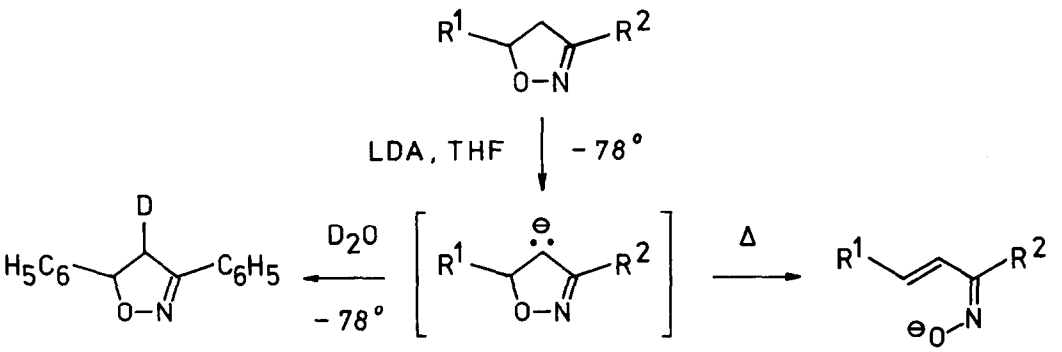
The concept of latent functionality and, more specifically, the utilization of heterocyclic systems as vehicles to construct functionalized carbon skeletons have seen many successful applications in organic synthesis [3]. The versatility of a heterocyclic system to serve this purpose depends on its accessibility, its readiness to undergo further elaboration and modification, and its ease to be "destroyed" in various ways.

2-Isoxazolines are familiar and readily available (from nitrile oxides and alkenes) compounds [4], however, examples of synthetically useful transformations are few: diastereoselective reduction to afford γ-aminoalcohols is outlined in the accompanying communication [5]; previously, 2-isoxazolines have been shown to be latent α,β-enoximes and enones [1,6].

In the latter sequence, ring-opening is initiated by base treatment. The intermediate 4-endo-anion 1 on warming isomerizes to an en-oximate, in the case of the 3.5-diphenyl derivative it has been intercepted by deuterium oxide [1]:



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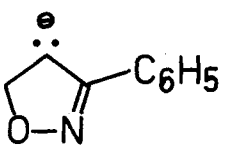
In this paper, elaboration of 2-isoxazolines via 4-endo-anions [7,8] is described, i.e. preparation of three new anions 2, 3, 4 and subsequent reactions with some electrophiles. 3-Phenyl derivatives were chosen for this study in order to exclude competing 3'-exo-anion formation shown to occur with 3-alkyl substituents present [1,8]. Deprotonation of 3-phenyl-2-isoxazoline to form anion 2 was effected at -78°C by lithium diisopropylamide

(LDA) in tetrahydrofuran with 1.5 to 3 equivalents of hexamethyl-phosphoramide (HMPA) added. Treatment of the dark-red solution with alkyl iodide ($\geq$ 2 equivalents) and usual work-up gave 4-substituted 2-isoxazolines 5 in good to excellent yield (see table 1)[9].

Remarkably, the tertiary proton of the 4-methyl derivative 5a may also be removed to form anion 3: deprotonation is nearly complete after 3 h at -78° as evidenced by isolation of the 4.4-dimethyl compound 6 in >70% yield! This successful gem-dialkylation to form a quaternary carbon in the product 6 is to be compared with recent reports on acyclic analogues (oximes and oxime ethers) where this has been stated to fail [7b, 7f].

Finally, the stereochemistry of isoxazoline carbanion reactions was examined with the 5-methyl derivative 4. Deprotonation was performed as above for 1 h at -85°. The product 7a (isolated in 90% yield), formed on addition of a precooled saturated solution of deuterium oxide in THF, showed 85% of deuterium incorporation and a cis/trans ratio of ~22:78 (see table 1). Alkylation by methyl and ethyl iodide to give 7b and 7c, respectively, proceeded with better stereoselectivity, the trans product now dominating by ~12:1. Synthetically, this is delightful, as it provides regio-controlled and stereoselective access to trans-4.5-substituted 2-isoxazolines not given otherwise [4,9]. The question whether these cyclic oxime ether anions have pyramidal (sp^3) or planar (sp^2) structure [7] cannot be answered as the approach of the electrophile may be controlled sterically by the 5-methyl group. However, the existence of configurationally stable carbanions (in the presence of HMPA!) can be excluded due to the differing cis/trans ratios observed on deuteration and alkylation, respectively, of 4 [10].

According to these results, various 4-mono-, 4.4-di-, and trans-4.5-disubstituted 2-isoxazolines may be prepared from simple and widely variable components: alkenes, (aryl) nitrile oxides and electrophiles. The synthetic possibilities in using 2-isoxazolines to assemble functionalized carbon skeletons are extended and now include a new quaternary centre [5,11,12].



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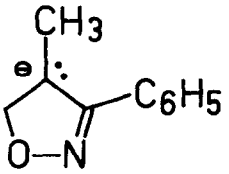

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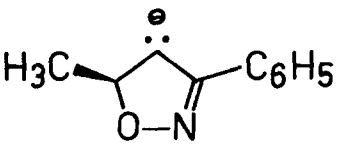

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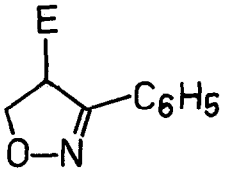

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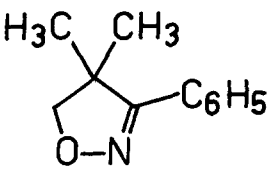

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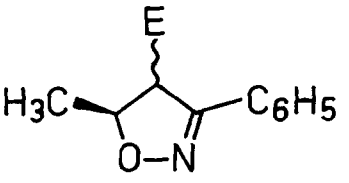

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Table 1, 4- and 4.5-substituted 3-phenyl-2-isoxazolines

Anion	electrophile E'	product	yield [a] / cis:trans ratio in crude product	m.p. [°C] or b.p. [°C/Torr] [b]
2	CH_3-I	5a	72%	42-43
2	C_2H_5-I	5b	91%	90-95/0.3-0.4
2	i-C_3H_7-I	5c	49% [c]	27-28
3	CH_3-I	6	76% [d]	~75/0.3-0.4
4	D_2O	7a	90% [e] / 22:78 (±5) [f]	49 [g]
4	CH_3-I	7b	73% (trans)/7:93 (± ~3) [f]	45-47
4	C_2H_5-I	7c	88% [h] / 8:92 (± 2) [f]	

a) 2-15 mmol runs; 1.2 equivalents each of diisopropylamine and butyllithium (in hexane), 1.5-3 equiv. of HMPA, 5-8 ml THF per mmol of isoxazoline; deprotonation 1-3 h at -78 to -85°; isolated yields; structures based on IR-, ^{1}H-NMR, ^{13}C-NMR spectral data and correct elemental analyses.

b) Kugelrohr distillation, bath temperature.

c) purified by column chromatography on silica; low yield due to incomplete reaction and difficult crystallization.

d) with 3-4% of educt 5a (^{1}H-, ^{13}C-NMR).

e) ~ 85% of (mono-)deuterated compound (^{13}C-NMR and high resolution mass spectroscopy).

f) analysis by ^{1}H-NMR integration (7a), ^{13}C-NMR (7b), GLC and ^{13}C-NMR (7c).

g) educt: m.p. 48-50°C [K. Bast, M. Christl, R. Huisgen, W. Mack, and R. Sustmann, Chem.Ber. 106, 3258 (1973)].

h) crude product with 7% of starting material, purification by column chromatography.

References and Notes

1. V. Jäger and H. Grund, Angew.Chem. 88, 27 (1976); Angew. Chem. Int.Ed.Eng. 15, 242 (1976)(part 1).

2. Part of the diploma thesis of W.S., 1978.

3. a) D. Lednicer, Adv.Org.Chem. 8, 179 (1972);
b) A.I. Meyers, Heterocycles in Organic Synthesis, J.Wiley a.Sons, New York·London·Sydney·Toronto 1974.
c) cf. recent examples of isoxazole-mediated syntheses of corphin and corrin systems: R.V. Stevens et al., J.Amer.Chem.Soc. 98, 6313, 6317 (1976) and references cited.

4. For reviews and leading references see A. Quilico in A. Weissberger (ed.), The Che-

mistry of Heterocyclic Compounds, Vol. XVII, p.95, Interscience Publ., New York· London 1962; C. Grundmann and P. Grünanger, The Nitrile Oxides, p. 96, Springer-Verlag, Berlin·Heidelberg·New York 1971; R. Huisgen, J.Org.Chem. 41, 403 (1976).

5. V. Jäger, V. Buß and W. Schwab, following paper; cp. also literature cited therein.
6. Some other useful conversions in this context are: aziridine formation from 3.4-diphenyl-2-isoxazolines [K. Kotera, Y. Takano, A. Matsuura and K. Kitahonoki, Tetrahedron 26, 539 (1970)]; conversion to isoxazoles which, in turn, are widely-used "vehicles" [3].
7. Cp. related dianions of oximes: a) F.E. Henoch, K.G. Hampton, and C.R. Hauser, J.Amer.Chem.Soc. 91, 676 (1969); C.F. Beam, M.C.D. Dyer, R.A. Schwarz, and C.R. Hauser, J.Org.Chem. 35, 1806 (1970); C.F. Beam et al., J.Pharm.Sci. 65, 1408 (1976); b) W.G. Kofron and M.-K. Yeh, J.Org.Chem. 41, 439 (1976); c) M.E. Jung, P.A. Blair, and J.A. Lowe, Tetrahedron Letters 1976, 1439; d) R.E. Lyle et al., Tetrahedron Letters 1976, 4431; anions of acyclic oxime ethers: e) T.A. Spencer and C. W.Leong, Tetrahedron Letters 1975, 3889; f) R.R. Fraser and K.L. Dhawan, J.C.S. Chem.Commun. 1976, 674.
8. 4-Endo-anions here correspond to syn; 3'-exo-anions of 2-isoxazolines to anti-anions of acyclic analogues such as oximes or oxime ethers.
9. Nitrile oxide addition to mono-substituted alkenes exclusively furnishes 5-alkyl derivatives. We are aware of only two mono-cyclic 4-substituted 2-isoxazolines that have been obtained in low yield from enone precursors: R.J. MacConaill and F.L. Scott, Tetrahedron Letters 1970, 2993; K. Kotera et al., see ref. [6]. Annulated 3.4-disubstituted isoxazolines have been obtained by intramolecular 1.3-dipolar cycloaddition: R. Fusco, L. Garanti, and G. Zecchi, Chim.Ind. (Milano) 57, 16 (1975); L. Garanti, A. Sala, and G. Zecchi, J.Org.Chem., 40, 2403 (1975); V. Jäger and H.J. Günther, Angew.Chem. 89, 253 (1977); Angew.Chem. Int.Ed.Engl. 16, 246 (1977).
10. Equilibration of cis/trans isomers by proton or deuterium transfer during work-up is unlikely: 7a in this case should consist of a ~1:1 cis/trans-mixture; further, in a preliminary experiment to deprotonate/deuterate cis-4.5-dimethyl-3-phenyl-2-isoxazoline, the non-deuterated part of the product contained only educt and none of the trans isomer.
11. This work was supported by the Deutsche Forschungsgemeinschaft.
12. This and the following paper are dedicated to Prof. F. Kröhnke on the occasion of his 75th birthday.

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