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SYNTHESES VIA ISOXAZOLINES III [1]. DIASTEREOSELECTIVE SYNTHESIS OF γ-AMINO-ALCOHOLS WITH 2 AND 3 CHIRAL CENTRES [2]

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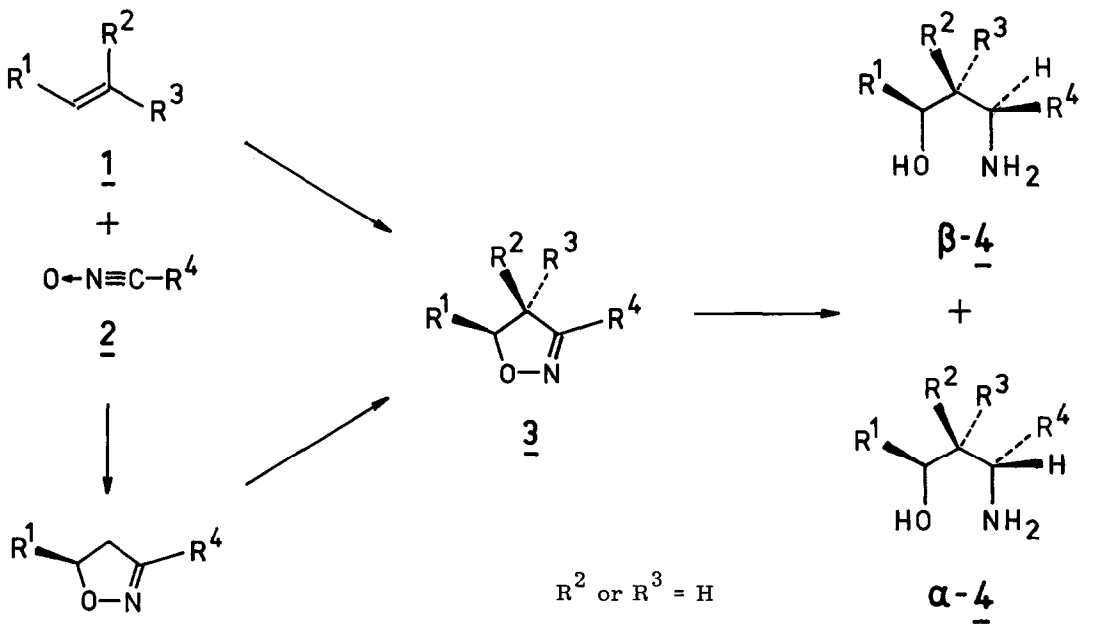
The stereoselective construction of acyclic compounds with multiple chiral centres is still considered a formidable synthetic problem [3]. We wish to report here our results on stereoselective hydroxy-α-aminoalkyl addition [4] to non-activated olefinic double bonds by the sequence 1 → 3 → 4, generating γ-amino-alcohols 4.

The first step, 1.3-dipolar cycloaddition of nitrile oxides to alkenes, produces 2-isoxazolines in high yield [5, 6]. It may be viewed as a C—C bond-forming process where N and O functionalities are arranged simultaneously in 1.3-position of the future acyclic system. The second step, 2-isoxazoline reduction, uncovers the γ-aminoalcohol unit [7] while creating an additional asymmetric centre. Moreover, ß-substituents may be added at the isoxazoline stage (see preceding paper) to provide 4-substituted isoxazolines such as 3e, 3f, 3g and the corresponding 4 on reduction:



Reductions of 3 have been described by several groups [5c, 8], however, the stereochemical result [9] has not attracted any attention or has been non-promising [5c, 8a, 8b]. We felt that the sequence 1 → 4 might bear considerable potential for the stereoselective synthesis of simple γ-amino-alcohols as well as of more complex natural products, such as amino-sugars [11] or α-amino γ-hydroxy acids [8b, 12]. Three aspects of this reduction therefore have been examined in detail:

1) the stereoselectivity of various reducing agents,
2) the degree of asymmetric induction caused by substituents in the 4- and/or 5-position of the isoxazoline ring,
3) configurational assignment to ß- and α-4 diastereomers [2c].

With respect to stereoselectivity and yield, lithium aluminium hydride proved superior to other reducing systems applied [2c] [H_2/Pd [8a, b], Na-Hg/H_2O [8a, b], Na/ethanol, Na/tert.-butanol, $Me_2S \cdot BH_3$, $NaAlH_2(OCH_2CH_2OCH_3)_2$]. Diastereomer [2c] ratios and yields of isolated products 4 are given in table 1. The following conclusions may be drawn from these data:

a) major components correspond to the diastereomer expected from steric approach control of the hydride-transferring step;
b) 5-substituents exhibit greater steric hindrance than do 4-substituents, i.e. 1.3-exceeds 1.2-asymmetric induction [3]!;
c) for the reduction of cis- and trans-4.5-dimethyl compounds 3h and 3i we state additivity of substituents effects ($\Delta\Delta G^{\ddagger}_{5\text{-}CH_3} \pm \Delta\Delta G^{\ddagger}_{4\text{-}CH_3} = 1.11 \pm 0.49$ kcal·mol^{-1}; 35°C) within experimental error of ß/α determination:

3h → 4h: estimated 1.6 (ß:α 93:7), found 1.35 (90:10)

3i → 4i: estimated 0.62 (73:27), found 0.58 (72:28)

To our opinion, the sequence 1 → 4 constitutes the most convenient and versatile way to assemble N-unsubstituted γ-amino-alcohols. The present results should further enable to predict the stereochemical outcome of this route for a variety of other γ-amino-alcohols with non-complexing substituents.

Experimental procedure, γ-aminoalcohols 4 from isoxazolines 3:

10 mmol of 3 in abs. ether are added with stirring to an ice-cold mixture of 10-14 mmol of $LiAlH_4$ in ether (30-100 ml total depending on the solubility of 3). Complete reaction (f.e. 3.5 h of reflux with 3a, 8 h at 0°C with 3b) is assured by TLC control. Per g of $LiAlH_4$ used, 1 ml of water, 0.75 ml of a 20% NaOH solution and 3.5 ml of water are then added slowly. The solids are filtered off and washed carefully with ether, then $CHCl_3$ or extraxted with $CHCl_3$ in a soxhlet apparatus. The organic solutes are combined, dried (Na_2SO_4) and evaporated. The residue is distilled or crystallized (from benzene/pentane or cyclohexane/pentane) and dried (P_2O_5). - Aminoalcohols 4 readily absorb CO_2; they should further be stored and handled with exclusion of water and oxygen.

Table 1, γ-Aminoalcohols 4 from $LiAlH_4$ reduction of 2-isoxazolines 3 [a]

Compound	R^1	R^2	R^3	R^4	ß/α-4 [b]	Yield [c]	m.p. [°C] or b.p. [°C/Torr]
4a	CH_3	H	H	CH_3	85:15	74	95/19 [d]
4b	CH_3	H	H	C_6H_5	87:13	79	65-68
						ß:47 [e]	75
4c	C_6H_5	H	H	CH_3	≳95:5	78	58-59
4d	C_6H_5	H	H	C_6H_5	95:5	98	111-115
						ß:62 [e]	118-119
4e	H	CH_3	H	C_6H_5	69:31	82	84-96/ ≈ 10^{-4} d
						ß:9 [e]	57.5-59
4f	H	C_2H_5	H	C_6H_5	72:28	89	75/ ≈10^{-4} d
4g	H	i-C_3H_7	H	C_6H_5	85:15 [f]	82	80/ ≈10^{-4}d
4h	CH_3	CH_3	H	C_6H_5	90:10	ß:65 [e]	56
4i	CH_3	H	CH_3	C_6H_5	72:28	89	66-78
						ß: 24 [e]	84-85
4j	-$(CH_2)_3$-		H	CH_3	97:3	87	55/0.35
4k	-$(CH_2)_3$-		H	C_2H_5	96:4	73	83/1
4l	-$(CH_2)_3$-		H	C_6H_5	>95:5	97	96-106/ ≈ 10^{-4} d

a) prepared according to Mukaiyama's or Huisgen's method [5] or as indicated in note [6].

b) from crude products; determined by ^{1}H- or ^{13}C-NMR integration, estimated error ≲ ± 3.

c) structures of 4 are secured by IR-, ^{1}H-NMR-, ^{13}C-NMR spectral data as well as correct elemental analysis for 4 and ß-4, respectively, except for 4b (not analyzed)[2c].

d) Kugelrohr distillation, bath temperature.

e) ß-4b with ≲2, ß-4d with 4, ß-4h with 5, ß-4i with <5% α (NMR).

f) α assignment to the minor component and ß/α ratio tentative due to several overlapping peaks in the ^{13}C-NMR spectrum.

References and Notes

1. Part 2: V. Jäger and W. Schwab, preceding.
2. Results of a) the dissertation of V.B., to be completed in 1978, and b) the diploma thesis of W.S., 1978; presented in part during lectures at Brussels (Soc.Chim.Belg., Jan. 1977) and Marburg (July 1977); c) detailed accounts on results with other reducing agents and NMR work on configurations and conformations of 4 will appear elsewhere.
3. For reviews and recent successful examples (also leading references) see a) J.W. Scott and D. Valentine, Jr., Science 184, 943 (1974); J.D. Morrison and H.S. Mosher, Asymmetric Organic Reactions, ACS, Washington, D.C. 1976; b) P.A. Bartlett and K.K. Jernstedt, J.Amer.Chem.Soc. 99, 4829 (1977); c) C.T. Buse and C.H. Heathcock, J.Amer.Chem.Soc. 99, 8109 (1977); d) Y. Okude et al., J.Amer.Chem.Soc. 99, 3179 (1977); e) J. Mulzer, J. Segner, and G. Brüntrup, Tetrahedron Letters 1977, 4651.
4. Related sequences are known or possible with nitrone or amidomethylium cycloadditions to alkenes: see, f.e. D.St.C. Black, R.F. Crozier, and V.D. Davies, Synthesis 1975, 205; R.R. Schmidt and A.R. Hoffmann, Chem.Ber. 107, 78 (1974); C. Giordano and L. Abis, Gazz.Chim.Ital. 104, 1181 (1974); cp. also U. Schöllkopf, R. Jentsch, K. Madawinata, and R. Harms, Liebigs Ann.Chem. 1976, 2105.
5. a) T. Mukaiyama and T. Hoshino, J.Amer.Chem.Soc. 82, 5339 (1960); b) M. Christl and R. Huisgen, Chem.Ber. 106, 3345 (1973); R. Huisgen, J.Org.Chem. 41, 403 (1976) and previous work cited; c) for an extensive review see C. Grundmann and P. Grünanger, The Nitrile Oxides, p. 96, Springer, Berlin 1971.
6) Although quite general, this route does not offer direct access to 4-substituted isoxazolines such as 3e, 3f, 3g. These compounds have been obtained by deprotonation / alkylation of 3-phenyl-2-isoxazolines [1].
7) For excellent reviews on "Latent Functionality" see D. Lednicer, Adv.Org.Chem. 8, 179 (1972); A.I. Meyers, Heterocycles in Organic Synthesis, Wiley, New York 1974.
8) a) W. Stühmer and W. Heinrich, Chem.Ber. 84, 224 (1951); b) G. Drehfahl and H.H. Hörhold, Chem.Ber. 97, 159 (1964); c) G.W. Perold and F.V.K. von Reiche, J.Amer. Chem.Soc. 79, 465 (1957).
9) ß-4d has been obtained by $LiAlH_4$ reduction of 3d in 62% crude yield [8c], after some controversy, the erythro configuration of ß-4d now is generally accepted [10].
10) J. English, Jr., and A.D. Bliss, J.Amer.Chem.Soc. 78, 4057 (1956), cf. also for previous discussions regarding the configurational assignment of 4d diastereomers; R. Lukeš, J. Kovář and K. Bláha, Collect.Czech.Chem.Commun. 25, 2179 (1960), and references given.
11) Cf. J.S. Glasby, Encyclopaedia of Antibiotics, J.Wiley a. Sons, London·New York· Sydney·Toronto 1976.
12) Amino-acid analogues of 4 (R^4 = COOH) have been found in toxic mushroom peptides (amanita species): Th. Wieland, Naturwissenschaften 59, 225 (1972); A. Gieren, P. Narayan, W. Hoppe, M. Hasan, K. Michl, Th. Wieland, H.O. Smith, G. Jung, and E. Breitmaier, Liebigs Ann.Chem. 1974, 1561 and previous work in this area.

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