Stereocontrolled Synthesis of 3-(Ethoxycarbonyl)-4-hydroxy-2-isoxazoline 2-Oxides. A New Approach to the Synthesis of 4-Hydroxylated 2-Isoxazolines

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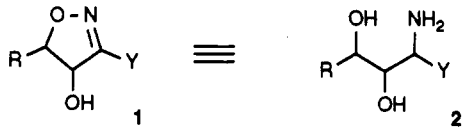
Summary: Treatment of 2-bromo aldehydes and ethyl nitroacetate with alumina without solvent, or in solution with a tertiary base, at room temperature gives the diastereoisomeric title compounds in fair yields by a tandem nitroaldol reaction–cyclization sequence opening a new route for the preparation of trans and cis 4-hydroxylated 2-isoxazolines in a predictable way.

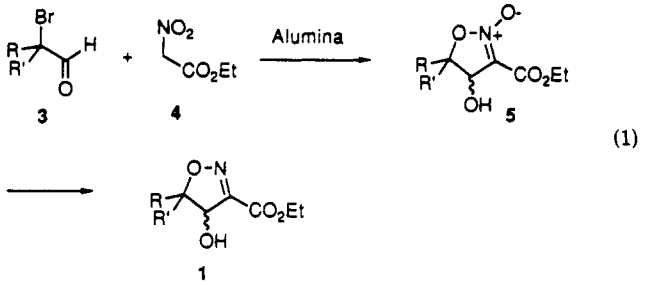
The stereoselective synthesis of 4-hydroxylated isoxazolines **1** is an important task in the context of synthetic strategies toward the preparation of biologically relevant target molecules such as polyhydroxylated amino acids, aminopolyols, and amino sugars. This assumption stems mainly from the synthetic equivalency of 2-isoxazolines **1** and the products **2**, which are obtained by hydride addition to C=N and reductive N–O bond cleavage of **1**. This conversion can be effected with preparatively useful diastereoselectivity.[2]



Y = COOH, CHO, CH_2OH

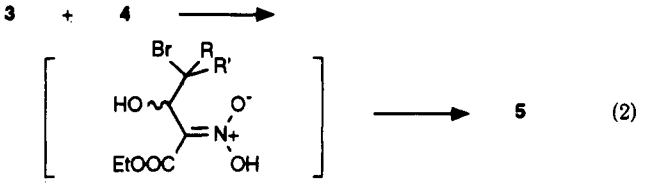
Nevertheless, 2-isoxazolin-4-ols **2** are not available directly by nitrile oxide cycloaddition to oxygenated alkenes.[3-5] In 1981, Jäger and Schwab[6,7] devised a route to prepare *trans*-2-isoxazolin-4-ols by reacting 2-isoxazoline 4-anions with borates, followed by oxidative workup. More recently, Ito and Sato[8] reported the preparation of *trans*-5-aryl- and -5-cyclopropyl-2-isoxazolin-4-ols via intramolecular ring opening of α,β-epoxy ketone oximes. However, both the methods consist in the elaboration of an already constructed carbon skeleton to prepare the trans isomer only and suffer from severe limitations. Thus, the stereoselective construction of 2-isoxazolin-4-ols is still considered a synthetic problem.

We wish to report here a new approach based on recent studies concerning the utilization of functionalized nitroalkanes in organic synthesis[9,10] (eq 1).



(1)

The key step of our route to trans and cis 5-substituted 3-(ethoxycarbonyl)-2-isoxazolin-4-ols **1** relies upon an efficient and stereoselective chain-lengthening reaction between 2-bromo aldehydes[11] **3** and ethyl nitroacetate[12] (**4**) that gives 2-isoxazolin-4-ol 2-oxides **5** in good yields. This reaction can be depicted as a tandem nitroaldol reaction–cyclization process in which the carbon–carbon bond forming step affords a 2-nitroalkanol and/or its *aci*-nitro form as a transient species. The successive step to compound **5** can occur by an ambidospecific cyclization on the electrophilic carbon bearing the bromine (eq 2).



(2)

Reactions were performed on alumina without solvent at room temperature and the general procedure reveals their simplicity.[13]

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(3) Nitrile oxide cycloadditions with enol ethers or esters afford the 5-oxygenated regioisomers.

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(5) Jäger, V.; Schohe, R. *Tetrahedron* **1984**, *40*, 2199.

(6) Jäger, V.; Schwab, W.; Buss, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 601.

(7) Schwab, W.; Jäger, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 603. See also: Jäger, V.; Schroter, D. *Synthesis* **1990**, 556.

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(9) For reviews on the utilization of functionalized nitroalkanes in synthesis, see: (a) Rosini, G. The Henry (Nitroaldol) Reaction. In *Comprehensive Organic Synthesis*; Trost, B. M., Editor-in-Chief, Heathcock, C. H., Volume Ed.; Pergamon: Oxford, 1991; Vol. 2. (b) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423. (c) Rosini, G.; Ballini, R.; Petrini, M.; Marotta, E.; Righi, P. *Org. Prep. Proceed. Int.* **1990**, *22*, 707. (d) Ono, N. In *Nitro Compounds; Recent Advances in Synthesis and Chemistry*; Feuer, H., Nielsen, A. T., Eds.; VCH Publishers: New York, 1990; p 1. (e) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833. (f) Kabalka, G. W.; Varma, R. S. *Org. Prep. Proc. Int.* **1987**, *19*, 283. (g) Varma, R. S.; Kabalka, G. W. *Heterocycles* **1986**, *24*, 2645. (h) Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751. (i) Ono, N.; Kaji, A. *Synthesis* **1986**, 693. See also Nitroalkanes and Nitroalkenes in Synthesis; Tetrahedron Symposium in Print no. 41; Barrett, A. G. M., Guest Ed.; *Tetrahedron* **1990**, *46*, 7313.

(10) Rosini, G.; Galarini, R.; Marotta, E.; Righi, P. *J. Org. Chem.* **1990**, *55*.

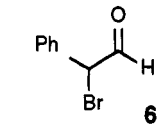
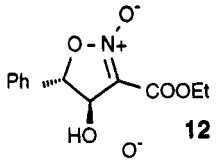
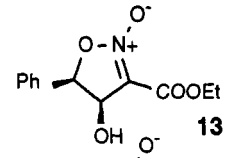
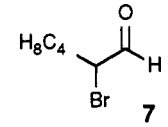
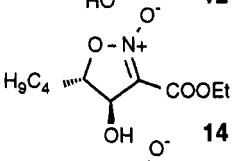
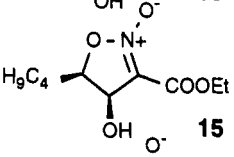
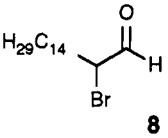
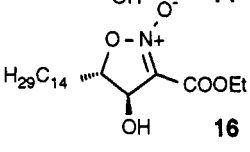
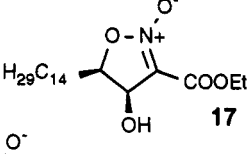
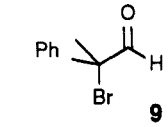
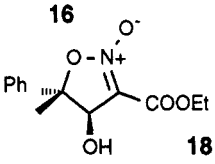
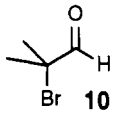
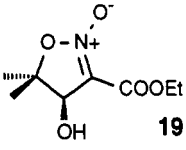
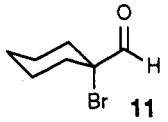
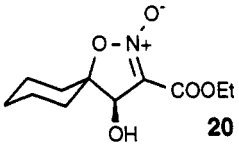
(11) 2-Bromo aldehydes **6-11** can be considered as representative of aldehydes having an additional electrophilic center adjacent to the carbonyl group and were prepared according to a well-established and efficient procedure: Bloch, R. *Synthesis* **1978**, 140.

(12) Shipchandler, M. T. *Synthesis* **1979**, 666.

(13) **General Procedure.** Reactions are performed simply by mixing equimolar amounts of the starting materials **3** and **4** and adding to this mixture, cooled at 0 °C and under vigorous stirring, a sufficient amount of commercial chromatographic alumina to absorb it completely. After standing for 5–70 h at room temperature with occasional stirring, products are isolated in fair to good yields by washing with dichloromethane, filtration of the organic extracts, and evaporation of the solvent under reduced pressure. The separation of diastereoisomers is accomplished by flash chromatography (Still, W. C.; Kahn, M.; Mitra, A. *J. org. Chem.* **1978**, *43*, 2923) on silica gel using diethyl ether–petroleum ether mixtures as eluent. For a more detailed procedure and for all characterization data, see the supplementary material.

0022-3263/91/1956-6258$02.50/0

Table I. Tandem Nitroaldol Reaction–Cyclization of 2-Bromo Aldehydes with Ethyl Nitroacetate on Alumina

entry	2-bromo aldehyde	yield[a] (%)	time (h)	products[b,c]	dr[d] trans/cis
1	 **6**	62	24	 **12**  **13**	9
2	 **7**	76	5	 **14**  **15**	9
3	 **8**	79	23	 **16**  **17**	19
4	 **9**	50	44	 **18**	>50
5	 **10**	46	70	 **19**	/
6	 **11**	44	36	 **20**	/

[a] The yield is based on the weight of a purified sample of the diastereoisomer mixture by a short column chromatography, before separation of each diastereoisomer. [b] The assignment of structure is based on IR, ^{13}C NMR, and ^{1}H NMR spectra. [c] Although only one enantiomer is depicted in each case, all structures represent racemates. [d] The ratio is based on integration of the ^{1}H NMR signals of the diastereoisomer mixture.

Table I displays the results of the reaction carried out using a series of 2-bromo aldehydes **6**–**11** which were chosen to demonstrate the generality of the procedure and to show the stereoselectivity of the process.[14]

The formation of the trans adducts is favored.[15] Diastereoisomer ratios (drs) exceeding or equal to 9:1 are found with monoalkyl- or -aryl-substituted 2-bromoethanals (entries 1–3). Still better selectivity has been observed in the case of 2-bromo-2-phenylpropanal (entry 4).[16] Further, almost the same results were observed by performing reactions always in the heterogeneous phase but in a solution of diethyl ether with alumina at room temperature.

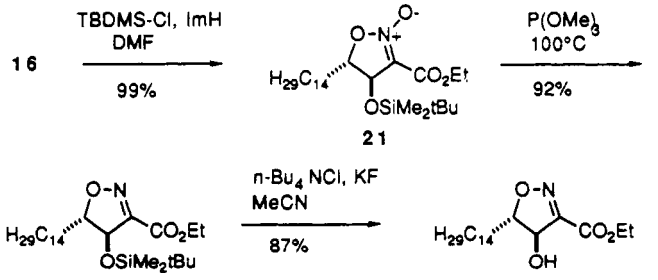
The high stereoselectivity of a reaction may become a stumbling block in organic synthesis when a procedure works well to prepare only one of the possible stereoisomers. Ideally, a reaction should be "tunable" so that, by altering reaction conditions, either stereoisomer may be produced.

Table II. Tandem Nitroaldol Reaction–Cyclization. Influence of Reaction Conditions on Stereoselectivity

base	solvent	dr 16/17
Al_2O_3[a]		19
Al_2O_3[a]	Et_2O	19
Al_2O_3[a]	EtOH	1.8
Et_3N[b]	Et_2O	8.1
Et_3N[b]	EtOH	0.43
Et_3N[b]	^{i}PrOH	0.47

[a] Reactions performed in heterogeneous conditions. [b] Reactions performed in homogeneous conditions.

Scheme I



Although reactions performed on alumina surface provide an efficient access to trans 5-substituted 2-isoxazolin-4-ol 2-oxides, a good control of diastereoselectivity to favor the formation of the cis isomer can be achieved by effecting the reactions of 2-bromo aldehydes and ethyl

(14) The compounds described are characterized by correct elemental analyses and IR; ^{1}H and ^{13}C NMR spectra are reported in the supplementary material.

(15) Trans and cis relationships between hydrogens on C4 and C5 of 2-isoxazolinic ring are apparent from ^{1}H NMR data ($J_{H4,H5trans}$ = 1.9–2.1 Hz; $J_{H4,H5cis}$ = 5.5–5.7 Hz).

(16) The assignment of the configuration of compound 18 was achieved by means of differential NOE (nuclear Overhauser enhancement) experiments: the saturation of the signal (δ = 7.45 ppm) of protons of the phenyl group on C5 produced and enhancement of the signal of C4H (δ = 5.10 ppm) eight times greater than the enhancement observed by saturation of the signal at δ = 1.65 ppm corresponding to the methyl group on C5. This indicates a configuration having the phenyl group on C5 and the C4H on the same side of the ring (trans configuration).

nitroacetate in homogeneous conditions. In fact, reactions performed in protic solvents with a base such as triethylamine afforded mixtures of diastereoisomers where the cis isomer is the main component. Table II summarizes some results concerning reactions of ethyl nitroacetate with, respectively, 2-bromohexadecanal (8) in heterogeneous and homogeneous conditions.

Our synthetic approach to 5-substituted 2-isoxazolin-4-ols needs now to be completed by effecting the deoxygenation of the parent 2-oxides. Scheme I shows this conversion for compound **16**. The 2-isoxazolin-4-ol **23** is a potential intermediate for the synthesis of phytosphingosine,[17] the backbone component of plant sphingolipids[18,19] as its D-(+)-erythro isomer. We carried out this reaction successfully on the *tert*-butyldimethylsilyl ether **21**[20] by heating at 100 °C in trimethyl phosphite[21] followed by easy removal of the protective group with fluoride anion.[22]

In summary, a new and general procedure for the stereoselective construction of 4-hydroxylated 2-isoxazolines from readily available starting materials has been developed. The sequence is amenable to prepare several 2-deoxy-2-amino-3,4-dihydroxyalkane derivatives **2** of current interest. Furthermore, the established connection of diastereoisomeric ratios of cis and trans isomers of compound **5** to the reaction conditions allows a good control of the stereochemistry in a predictable way and augurs well for its synthetic utility.

Mechanistic studies to suggest a detailed picture of the function of alumina as solid support, the dependence of heteregeneous and homogeneous conditions on the diastereoisomeric ratio, and further applications of this route to natural product synthesis form the focus of our current endeavors and will be reported in due course.

Acknowledgment. This research was supported by research grants from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Italy, and the Consiglio Nazionale delle Ricerche, Italy, to whom we are grateful.

Supplementary Material Available: Detailed procedures and characterization data (correct elemental analyses, IR, ^{1}H NMR and ^{13}C NMR spectra) for compounds **6–23** (5 pages). Ordering information is given on any current masthead page.

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(18) Hakomori, S. *Handbook of Lipid Research: Sphingolipid Biochemistry*; Kanfer, J. N., Hakomori, S., Eds.; Plenum: New York, 1983; Vol. 3, pp 1–150.

(19) The presence of phytosphingosines in human brain and kidney lipids has also been reported: Karlsson, K. A. *Acta Chem. Scand.* **1964**, *18*, 2397.

(20) Deoxygenation reactions performed in the same conditions with *tert*-butyldimethylsilyl derivatives of compounds **18–20** gave good yields (85–95%) of the corresponding 2-isoxazolines.

(21) Melôt, J. M.; Texier-Boullet, F.; Foucaud, A. *Synthesis* **1988**, 558.

(22) Carpino, L. A.; Sau, A. C. *J. Chem. Soc., Chem. Commun.* **1979**, 514.

Homolytic and Heterolytic N–H Bond Strengths

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Summary: $E_{1/2}$ values for the reversible cyclic voltammetric (CV) oxidations of the nitranions derived from iminostilbene, phenoxazine, and phenothiazine, obtained at 1000 V/s scan rates, are in remarkable agreement with irreversible CV anodic peak potentials obtained at 0.1 V/s scan rates and therefore suggest that homolytic N–H bond dissociation energies based on the irreversible data do not suffer from large errors associated with electrochemical irreversibilities. Acidity and 10 000 V/s redox data for iminostilbene and its respective anion and radical, when compared to similar data for 9-phenylxanthene and its respective anion and radical, suggest that the N–H bond in iminostilbene is about 22 kcal/mol stronger, in a heterolytic cation/hydride forming sense, than the 9C–H bond in 9-phenylxanthene.

In efforts to gain new insight into the heterolytic and/or homolytic strengths of selected chemical bonds present in various organic and inorganic molecules, chemists have utilized thermochemical cycles comprised of solution-phase proton and electron transfer data.[1] An advantage of evaluating bond strengths in this way is that many of the data that result from the thermochemical cycles are often difficult to obtain using other techniques.

The dimethyl sulfoxide (DMSO) equilibrium acidity scale has proven to yield reliable data concerning the energetics of proton transfer to and from organic acids and anions.[2] Thermochemical cycles that incorporate DMSO acidity data have been shown to yield new facts concerning (a) heterolytic strengths of specific bonds in various neutral organic molecules[1a,3] and (b) homolytic strengths of various H–A bonds, where A is carbon,[1c,4] nitrogen,[5,6] oxygen, or sulfur.[7] For a given acid H–A, it has been demonstrated that the absolute DMSO acidity constant for H–A, combined with the irreversible oxidation potential for A^- (as shown in eq 1 where all parameters are in kcal/mol), yields

$$\Delta BDE(H\text{–}A) = \Delta pK_a(H\text{–}A) + \Delta E_{ox}(A^-) \quad (1)$$

(1) (a) Arnett, E. M.; Amarnath, K.; Harvey, N. G.; Cheng, J.-P. *Science* **1990**, *247*, 423–430. (b) Friedrich, L. E. *J. Org. Chem.* **1983**, *48*, 3851–3852. (c) Bordwell, F. G.; Bausch, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 1975–1979. (d) Bausch, M. J.; Guadalupe-Fasano, C.; Peterson, B. M. *J. Am. Chem. Soc.* In press.

(2) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463 and references contained therein.

(3) Arnett, E. M.; Amarnath, K.; Harvey, N. G.; Cheng, J.-P. *J. Am. Chem. Soc.* **1990**, *112*, 344–355.

(4) (a) Bausch, M. J.; Gostowski, R.; Jirka, G.; Selmarten, D.; Winter, G. *J. Org. Chem.* **1990**, *55*, 5805–5806. (b) Bausch, M. J.; Guadalupe-Fasano, C.; Gostowski, R.; Selmarten, D.; Vaughn, A. *J. Org. Chem.* In press.

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(6) Bausch, M. J.; David, B.; Prasad, V.; Vaughn, A.; Wang, L.-H. *J. Phys. Org. Chem.* In press.

(7) Bordwell, F. G.; Cheng, J.-P.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 1229–1231.

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