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REGIOCHEMISTRY OF THE DIPOLAR CYCLOADDITIONS OF NITRILE OXIDES TO UNACTIVATED OLEFINS. APPLICATION TO THE STEREOSELECTIVE ELABORATION OF β-HYDROXYCARBONYL COMPOUNDS.

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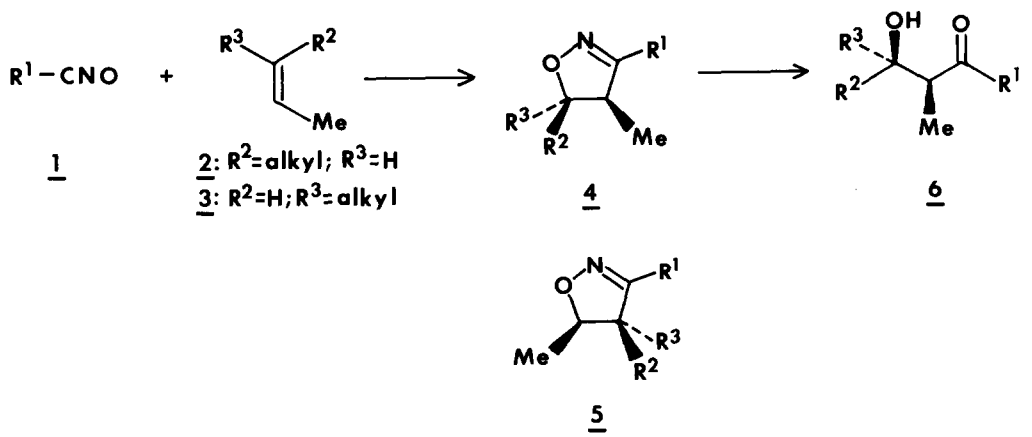
Abstract. The 1,3-dipolar cycloadditions of nitrile oxides 1 with Z-disubstituted olefins 2 proceeds with a high degree of regioselectivity to give the isoxazolines 4, whereas addition to E-disubstituted olefins 3 affords mixtures of the isomeric isoxazolines 4 and 5; the isoxazolines 4 may be converted into the corresponding β-hydroxyketones 6 by reduction/hydrolysis.

During the course of a synthetic project, we recently had occasion to elaborate stereoselectively a carbon-carbon double bond into a 2-alkyl-3-hydroxy carbonyl compound by effecting the net cis-vicinal addition of a hydroxyl and an acyl group. It occurred to us that an attractive approach to such a construction which merited scrutiny involved the hydrogenolysis and hydrolysis of substituted isoxazolines that were products of the 1,3-dipolar cycloadditions of nitrile oxides[2] with selected olefins according to Scheme 1. Although the sequence of either a

Scheme 1



bimolecular or an intramolecular cycloaddition of a nitrile oxide to an alkene followed by the manipulation of the isoxazolines thus produced to elaborate α,β-unsaturated carbonyl compounds,[3] 1,3-amino alcohols,[4] 3-hydroxycarbonyl compounds,[5] and 2-alkylated or 2-hydroxylated[6] derivatives thereof has been reported as have the applications of such processes to the total syntheses of natural products.[7] However, to our knowledge utilization of such a protocol for the stereoselective construction of 3-hydroxy-2-methyl carbonyl compounds from alkenes has not been exploited.

The crucial issue at the outset of our investigations was the extent to which the regiochemical course of the 1,3-dipolar cycloadditions of nitrile oxides with unactivated, unsymmetrical olefins was subject to steric effects alone.[8] To probe this question, the dipolar cycloadditions of a series of nitrile oxides with acyclic, disubstituted olefins were examined, and some representative results of these studies are summarized in Table 1. Only cis- and trans-1,2-dialkyl-substituted ethylenes 2 (R^2 = H; R^3 = i-Pr or t-Bu) and 3 (R^2 = i-Pr or t-Bu; R^3 = H) were chosen so that electronic factors would not play a significant role in directing the

Table 1. 1,3-Dipolar Cycloadditions of Nitrile Oxides to Unsymmetrical Olefins.

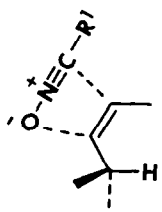
Entry	R^1	R^2	R^3	Method[a]	Yield(%)[b] (4+5)	Ratio 4/5
a	t-Bu	i-Pr	H	B	26	c
b		H	i-Pr	B	50	70:30
c		t-Bu	H	B	15	c
d		H	t-Bu	A	35	c
e	Ph_3C	i-Pr	H	C	96	c
f		H	i-Pr	C	99	68:32
g	Ph	i-Pr	H	A	28[d]	c
h		H	i-Pr	A	58	63:37
i		t-Bu	H	A	27	c
j		H	t-Bu	A	56	c
k	4-$MeOC_6H_4$	i-Pr	H	B	48[d]	c
l		H	i-Pr	B	53	64:36
m	PhCO	i-Pr	H	B	15	c
n		H	i-Pr	B	51	64:36
o	2,4,6-$Me_3C_6H_2$	i-Pr	H	C	92	c
p		H	i-Pr	C	94	62:38

[a]Method A: Et_3N (1.5 equiv) added with stirring to hydroxamoyl chloride (1.0 equiv) and excess alkene (either at RT or initially at 0°C and then warm to RT). Method B: Hydroxamoyl chloride (1.0 equiv) added To Et_3N (1.5 equiv) and excess alkene at reflux. Method C: Nitrile oxide and excess alkene heated at reflux. [b]Based upon hydroxamoyl chloride or nitrile oxide and not optimized. [c]Isoxazoline 4 was the only regioisomer isolated. [d]Product derived from the cycloaddition of the nitrile oxide to the initial cycloadduct was also isolated in 5 - 10% yield.

regioselectivity of the cycloadditions; the nitrile oxides 1 [R^1 = t-Bu, Ph_3C, Ph, 4-$MeOC_6H_4$, PhCO, and 2,4,6-$(CH_3)_3C_6H_2$] were selected as the reaction partners.

Several interesting facts emerge upon examination of these results. Whereas cis-4-methyl-2-pentene (2: R^2 = i-Pr; R^3 = H) underwent highly regioselective cycloaddition with each of the nitrile oxides to give the isoxazolines 4, trans-4-methyl-2-pentene (3: R^2 = H; R^3 = i-Pr) afforded mixtures of the isomeric isoxazolines 4 and 5 in ratios that varied from approximately 1.6:1 to 2.3:1. On the other hand, the cycloadditions of the nitrile oxides 1 (R^1 = t-Bu and Ph) with both cis- and trans-4,4-dimethyl-2-pentene (2: R^2 = t-Bu; R^3 = H and 3: R^2 = H; R^3 = t-Bu) occurred with a high (>95%) degree of selectivity affording only the respective isoxazolines 4. Based upon these data, it appears that if the size of the two alkyl groups attached to the two terminii of the double bond are not dramatically different, the cycloaddition with nitrile oxides ensues with an appreciable degree of regioselectivity only with the cis-alkenes 2. In additions of nitrile oxides to the trans-alkenes 3, the steric bulk of the substituent on the nitrile oxide appears to be of little consequence since the ratio varies only from 1.6 to 2.3:1. On the other hand, when one end of the double bond is significantly more congested than the other, the cycloaddition proceeds with a high regioselectivity such that the oxygen of the nitrile oxide becomes bonded to the more hindered terminus of the double bond. In view of these results it may appear that trans-4,5-dialkyl isoxazolines would not be readily accessible. However, since it is known that 5-alkyl-2-isoxazolines, which are the products of the cycloadditions of terminal alkenes with nitrile oxides, undergo highly stereoselective alkylation to give trans-dialkylated isoxazolines,[6a] the lack of regioselectivity in the cycloadditions of simple trans-alkenes with nitrile oxides does not impose a serious limitation upon this methodology.

The regioselectivity in the dipolar cycloadditions of nitrile oxides to cis- and trans-4-methyl-2-pentene may be rationalized by examining the possible transition states for the reaction. The preferred transition state for the addition of nitrile oxides to the cis-alkene should be that depicted in I in which the steric compression between the allylic methyl group and the isopropyl moiety as well as the nonbonded interactions between the R group of the nitrile oxide and the isopropyl group of the alkene are minimized. Since there is no clear bias for any one eclipsed conformation of trans-4-methyl-2-pentene in the ground state,[9] which seems in this instance to be a reasonable model for the transition state, the three transition states II- IV will be of approximately comparable energy, and the regioselectivity of the cycloaddition consequently decreases. On the other hand, for both cis- and trans-4,4-dimethyl-2-pentene, the



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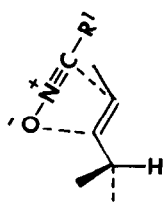

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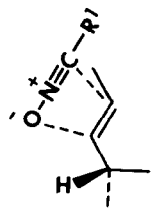

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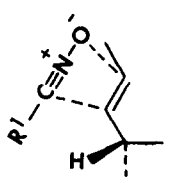

IV

transition state leading to the corresponding isoxazolines 4 should be greatly favored owing to the more severe nonbonded interactions in the alternatives.

The conversion of isoxazolines into 3-hydroxy carbonyl compounds is now well known and may be achieved in a variety of ways.[5] In a slight modification of established procedures, we discovered that isoxazolines such as 4k and 4l could be readily transformed with a high degree (>95%) of stereoselectivity into the respective aldols 6k and 6l in excellent yields by catalytic hydrogenation and hydrolysis using Raney nickel in EtOH/H_2O (10:1) in the presence of $BF_3 \cdot Et_2O$ (5 equiv). When this reduction/hydrolysis was attempted in aqueous ethanol in the presence of other acid catalysts, the results were sometimes less satisfactory.

Thus, it appears that the sequence of regioselective nitrile oxide addition to unsymmetrical acyclic olefins and subsequent cleavage of the intermediate isoxazolines thereby produced provides a useful entry to some β-hydroxy carbonyl compounds. The application of this protocol to the synthesis of natural products is the subject of present investigations, the results of which will be reported in due course.

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REFERENCES

1. Recipient of a National Institutes of Health (National Cancer Institute) Research Career Development Award 1980-1985.

2. (a) For a review see Grundman C.; Grunanger, P. "The Nitrile Oxides," Springer-Verlag, Berlin, 1971. See also (b) Bast, K.; Christl, M.; Huisgen, R.; Mack, W. Chem. Ber. 1973, 106, 3312. (c) Christl, M.; Huisgen, R. Ibid. 1973, 103, 3345.

3. Grund, H.; Jager, V. Liebigs Ann. Chem. 1980, 80.

4. (a) Drefahl, G.; Horhold, H.-H. Chem. Ber. 1964, 97, 159. (b) Jager, V.; Buss, V. Liebigs Ann. Chem. 1980, 101. (c) Jager, V.; Buss, V.; Schwab, W. Ibid. 1980, 122. (d) Lathbury, D. C.; Parsons, P. J. J. Chem. Soc., Chem. Commun. 1982, 291.

5. (a) Wollenberg, R. H.; Goldstein, J. E. Synthesis, 1980, 757. (b) Asaoka, M.; Mukuta, T.; Takei, H. Tetrahedron Lett. 1981, 22, 735. (c) Kametani, T.; Furuyama, H.; Honda, T. Heterocycles, 1982, 19, 357. (d) Andersen, S. H.; Das, N. B.; Jorgensen, R. D.; Kjeldsen, G.; Knudsen, J. S.; Sharma, S. C.; Torssell, K. B. G. Acta Chem. Scand. 1982, 36(B), 1. (e) Curran, D. P. J. Am. Chem. Soc. 1982, 104, 4024. (f) Kozikowski, A. P.; Adamczyk, M. Tetrahedron Lett. 1982, 23, 3123.

6. (a) Jager, V.; Schwab, W. Tetrahedron Lett. 1978, 3129. (b) Schwab, W.; Jager, V. Angew. Chem. Internat. Ed. Eng. 1981, 20, 603.

7. (a) Confalone, P. N.; Lollar, E. D.; Pizzolato, G.; Uskokovic. J. Am. Chem. Soc. 1978, 100, 6291. (b) Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. Ibid. 1978, 100, 7069. (c) Kozikowski, A. P.; Ishida, H. Ibid. 1980, 102, 4265. (d) Kozikowski, A. P.; Chen, Y. -Y. J. Org. Chem. 1981, 46, 5248. (e) Kametani, T.; Huang, S.-P.; Nagahara, T.; Ihara, M. J. Chem. Soc. Perkin Trans I 1981, 2282. (f) Asaoka, M.; Abe, M; Mukuta, T.; Takei, H. Chem. Lett. 1982, 215. (g) Kozikowski, A. P.; Stein, P. D. J. Am. Chem. Soc. 1982, 104, 4023.

8. For some examples of the role of steric effects in nitrile oxide cycloadditions, see (a) Bianchi, G.; De Micheli, C.; Gandolfi, R.; Grunanger, P.; Finzi, P.V.; de Pava, O. V. J. Chem. Soc. Perkin Trans I 1973, 1148. (b) Caramella, P.; Cellerino, G. Tetrahedron Lett. 1974, 229. (c) Bianchi, G.; De Micheli, C.; Gandolfi, R. J. Chem. Soc. Perkin Trans I, 1976, 1518.(d) McAlduff, E. J.; Caramella, P.; Houk, K. N. J. Am. Chem. Soc. 1978, 100, 105.

9. Bothner-By, A. A.; Naar-Colin, C.; Gunther, H. J. Am. Chem. Soc. 1962, 84, 2748.

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