Tetrahedron Letters No. 43, pp 4167 - 4170.
©Pergamon Press Ltd. 1979. Printed in Great Britain.
0040-4039/79/1022-4167$02.00/0

NITRONE CYCLOADDITIONS. REGIOCHEMISTRY.

Sk. Asrof Ali, Pushpananda A. Senaratne, Carl R. Illig,
Harold Meckler, and Joseph J. Tufariello*

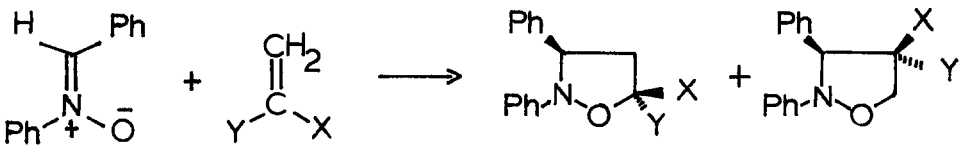
Department of Chemistry, State University of New York at Buffalo

Buffalo, New York 14214

Summary: The regiochemistry of nitrone cycloadditions has been reexamined. Certain nitrones afford regioisomeric mixtures of isoxazolidines, with a tendency toward increasing amounts of the 4-substituted regioisomer as the ionization potential of the dipolarophile is increased.

The development of the chemistry of 1,3-dipolar cycloaddition reactions,[1,2] which began in earnest in the late fifties,[3] has recently had a significant impact on the synthesis of natural products.[4] Such applications depend most heavily on an understanding of the factors which determine the regiochemistry of relevant cycloadditions.

That the additions of nitrones to a wide variety of dipolarophiles have been believed[1,5] to display high regiochemical control has been both pleasing and puzzling. Indeed, it is precisely this tendency toward regiospecificity which has provided the cornerstone for a biradical mechanism[6] for 1,3-dipolar cycloadditions as an alternative to the concerted view[7] of these transformations. The regiochemical control exhibited by nitrone-alkene cycloadditions has been accommodated by the development[8,9,10] of a frontier orbital MO treatment. Our interests in utilizing these cycloadditions in organic synthesis have refocused our attention on the degree of regioselectivity observed for the cycloadditions of nitrones with electron deficient dipolarophiles. Thus, in our hands, the reaction of C,N-diphenylnitrone (1) with a range of monosubstituted alkenes (2) leads to regioisomeric mixtures (Table 1).



1 2 3 4

a, X = Me, Y = H
b, X = H, Y = Me
c, X = Ph, Y = H
d, X = H, Y = Ph
e, X = CN, Y = H
f, X = H, Y = CN
g, X = CO_2Et, Y = H
h, X = H, Y = CO_2Et
i, X = COMe, Y = H
j, X = H, Y = COMe
k, X = CHO, Y = H
l, X = H, Y = CHO

All reactions were carried out under conditions which would reflect kinetic, rather than thermodynamic factors. Illustrative of our method is the cycloaddition of C,N-diphenylnitrone with ethyl acrylate. One of the diastereomeric 4-isoxazolidines (i.e. 4h), mp 50-51°C, could be chromatographically separated (TLC, silica gel). That this was one of the 4-substituted regioisomers was clear from its NMR spectrum which displays a characteristic doublet (J = 6 Hz) at δ 4.98 ppm assigned to H-3. The complete regiochemical analysis of the original mixture of isoxazolidine isomers was accomplished by conversion into the

Table 1

Reactions of C,N-diphenylnitrone with Dipolarophiles. Regiochemistry.

Dipolarophile	2a	2c	2e	2g	2i	2k
3 (5-isomer, %)	98.4	∿100	91	70	83	82
4 (4-isomer, %)	1.6	∿0	9	30	17	18

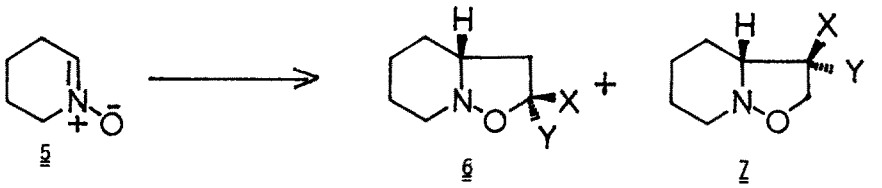
corresponding methyl derivatives (i.e., 3a, 3b, 4a and 4b) by reduction with lithium tetrahydroaluminate, mesylation, followed by Super-Hydride induced displacement of the mesylate function.[13] Four methyl doublets (J = 6 Hz) could be discerned in the δ 0.6-1.4 ppm region of the NMR spectrum. The two closely spaced downfield doublets at δ 1.31 and 1.29 ppm are assigned to the diastereomeric mixture of 5-substituted isoxazolidines (i.e. 3a and 3b) in an approximate ratio of 40:60, respectively. The two widely separated upfield doublets at δ 0.68 and 1.08 ppm are assigned to the 4-substituted isoxazolidines (i.e., 4a and 4b) in a 30:70 ratio, respectively. The latter pair of diastereomers were favorably compared with those obtained by the dimide reduction of 2,3-diphenyl-4-methyleneisoxazolidine, obtained from the reaction of 1 with allene[14]. The results of our regiochemical analysis are recorded in Table 1.[15] In a similar manner, the mixture of regioisomers derived from acrolein and 1 was converted by the same reduction, mesylation, displacement sequence into a mixture of 3ab and 4ab, (cf. Table 1.

The reaction of propylene with nitrone 1 gave four adducts. After the removal of most of the major regioisomeric adduct (3a) by fractional crystallization from pentane, an NMR analysis of the mixture remaining in the mother liquors, plus a knowledge of the amount of 3a formed, permitted a determination of the amounts of various regioisomers, 3a (90.4%), 3b (7.9%), 4a (0.4%) and 4b (1.3%), present in the original reaction mixture.

The reaction mixture from 1 and methyl vinyl ketone displays three methyl singlets at δ 2.00, 2.22 and 2.28 ppm. Moreover, a doublet (J = 6 Hz) characteristic of H-3 of the 4-substituted regioisomers is clearly indicated at δ 4.84 ppm. An NMR analysis of the δ 2.0-2.3 ppm region reveals the presence of 3ij and 4i(or j) in an 83:17 ratio.

Acrylonitrile and 1 produce a mixture of regioisomeric isoxazolidines, 3ef and 4ef. The minor 4-cyano isomer (3%), 4e (mp 96-7°C), was separated chromatographically (NMR ($CDCl_3$) δ 3.75 (q, 1, J = 7 Hz), 4.28 (m, 2), 4.68 (d, 1, J = 8 Hz), and 6.8-7.6 ppm (m, 10)). An NMR spectrum of the reaction mixture revealed the presence of 4f by displaying a signal (i.e. due to H-4) at δ 3.34 ppm (q, J = 6 Hz) of approximately twice the area of the signal (δ 3.75 ppm) noted for 4e.[16] Thus, the ratio of regioisomers, 3ef and 4ef, is approximately 91:9, respectively.

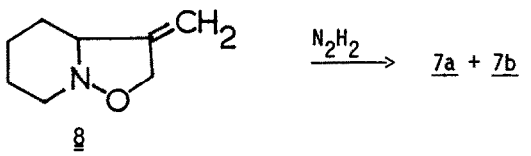
We have also studied the regiochemical aspects of the reaction of 3,4,5,6-tetrahydropyridine 1-oxide (5) with several dipolarophiles. While propylene and methyl vinyl ketone appear to undergo very highly regioselective additions to 5 (i.e. to give 6a[13] and 6ef, respectively), methyl acrylate and 5 afford 6cd and 7cd in a 84:16 ratio, respectively. This was determined by conversion of the crude mixture of isoxazolidines into the corresponding methyl derivatives, 6a, 6b, 7a and 7b, and analyzing the δ 0.9-1.3 ppm region of the NMR spectrum (vide supra). That the two overlapping doublets at δ 0.9 ppm (60:40 ratio and 7a and 7b) can be attributed to the 4-substituted regioisomers was confirmed by reduc-



5 6 7

a, X = Me, Y = H c, X = CO_2Me, Y = H e, X = COMe, Y = H
b, X = H, Y = Me d, Y = H, Y = CO_2Me f, X = H, Y = COMe

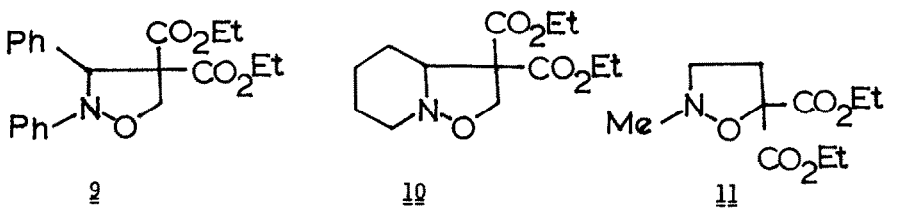
tion of adduct 8, derived from allene and 5, with diimide.[14] This led to a mixture of 7a and



8

7b exhibiting methyl doublets at precisely the same chemical shifts noted for the minor isomers derived from methyl acrylate and 5 by the chemical transformations noted earlier.

The results described above are in general accord with the frontier orbital treatment of nitrone 1,3-dipolar cycloadditions.[8-11] This view suggests that most dipolarophiles should undergo cycloaddition to afford 5-substituted isoxazolidines with high regioselectivity As the ionization potential of the dipolarophile increases (i.e., as the HO level decreases in energy), an increasing tendency is expected towards production of 4-substituted isoxazolidines.[11] It appears that these cycloadditions are generally nonsynchronous,[8-10] with carbon-carbon bond formation leading carbon-oxygen bond formation for most dipolarophiles; however, it would seem likely that the presence of strongly electron attracting groups on the dipolarophile tends to favor a transition state where carbon-oxygen bond formation leads (Michael-like character). Indeed, we find that diethyl methylenemalonate (like nitroethylene[11c]) undergoes a complete reversal of regiochemistry with both C,N-diphenylnitrone



9 10 11

(1) and 3,4,5,6-tetrahydropyridine 1-oxide (5) to give 9, which exhibits the expected one-proton singlet attributable to H-3 at δ 5.52 ppm and 10, which displays its C-5 protons as an AB pattern (δ 4.44 (J = 8 Hz) and 4.12 ppm (J = 8 Hz)) partially obscured by the ester methylene signal; however, N-methylnitrone[17] adds to the same dipolarophile to give only the 5,5-disubstituted regioisomer 11, which displays the complex pattern between δ 2.6 and 3.4

ppm (protons at C-3 and C-4) characteristic of other 5-substituted isoxazolidines derived from this nitrone.[17] Thus it is clear that substitution of the carbon of the nitrone functionality increases the tendency toward formation of the 4-regioisomer. It can be presumed that both steric and electronic factors[11c] are involved.

We find it difficult to accommodate our results with a two-step (i.e. diradical) view[6] of these cycloadditions since this perception can not easily accommodate the changes in regiochemistry that we observe.

We gratefully acknowledge the support obtained from the National Institutes of Health (GM 25303).

References and Notes:

1. R. Huisgen, Angew. Chem. Int. Ed., Engl., 2, 565, 633 (1963).

2. (a) J. Hamer and A. Macaluso, ibid., 64, 473 (1964); (b) D. St. C. Black, R. F. Crozier and V. C. Davis, Synthesis, 7, 205 (1975); (c) A. Padwa, Angew. Chem. Int. Ed., Engl., 15, 123 (1976); (d) W. Oppolzer, ibid., 16, 10 (1977).

3. (a) N. A. LeBel and J. J. Wang, J. Am. Chem. Soc., 81, 6334 (1959); (b) C. W. Brown, K. Marsden, M. A. T. Rogers, C. M. B. Tylor, R. Wright Proc. Chem. Soc. (London) 254 (1960); (c) R. Grashey, R. Huisgen and H. Leitermann, Tetrahedron Lett., 9 (1960).

4. For example, see (a) J. J. Tufariello and J. P. Tette, J. Chem. Soc. Chem. Commun., 469 (1971); (b) J. J. Tufariello and J. J. Tegeler, Tetrahedron Lett., 4037 (1976); (c) W. Oppolzer and M. Petrzila, J. Am. Chem. Soc. 98, 6722 (1976); (d) P. N. Confalone, E. D. Lollar, G. Pizzolato, and M. Uskokovic, ibid., 100, 6291 (1978); (e) J. J. Tufariello, G. B. Mullen, J. J. Tegeler, E. J. Trybulski, S. C. Wong, and Sk. Asrof Ali, ibid, 101, 2435 (1979).

5. R. Huisgen, H. Seidl, and I. Bruning, Chem. Ber., 102, 1102 (1969), and references cited therein.

6. R. A. Firestone, Tetrahedron, 39, 3009 (1977).

7. R. Huisgen, J. Org. Chem., 41, 403 (1976).

8. K. Fukui, Accts. Chem. Res., 4, 57 (1971).

9. R. Sustmann, Tetrahedron Lett., 2717 (1971); R. Sustman and H. Trill, Angew Chem. Int. Ed. Engl., 11, 838 (1972).

10. J. Batide, N. El Gandour, and O. Henri-Rousseau, Tetrahedron Lett., 4225 (1973); Bull. Soc. Chem. Fr., 2290 (1973); J. Bastide and O. Henri-Rousseau, ibid., 2294 (1973).

11. (a) K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, J. Am. Chem. Soc., 95, 7287 (1973); (b) K. N. Houk, J. Sims, C. R. Watts and L. J. Luskus, ibid., 95, 7301 (1973); (c) J. Sims and K. N. Houk, ibid., 95 5798 (1973); (d) K. N. Houk, Acc. Chem. Res., 8, 361 (1975).

12. (a) G. Leroy and M. Sana, Tetrahedron, 31 2091 (1975); (b) ibid, 32, 709 (1976); (c) G. Leroy, M. T. Nguyen, and M. Sana, Tetrahedron, 34, 2459 (1978).

13. J. J. Tufariello and Sk. Asrof Ali, Tetrahedron Lett., 4647, (1978).

14. J. J. Tufariello, Sk. Asrof Ali, and H. O. Klingele, submitted for publication.

15. Similar results have recently been noted for the reaction of 1 with methyl acrylate; M. Joucla and J. Hamelin, J. Chem. Res., (M), 3532 (1978).

16. This stereochemical assignment is made by an NMR comparison with the acrylate adducts described herein and recorded in ref. 15. Both chemical shift and coupling constant data are utilized.

17. E. J. Fornefeld and A. Pike, J. Org. Chem., 44, 835 (1979).

(Received in USA 26 June 1979)