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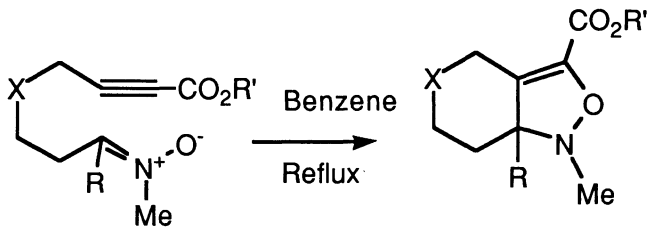
Unexpected Thermal Rearrangement of *N*-[1-Methyl-6-(methoxycarbonyl)-5-hexynylidene]methylamine *N*-Oxide

Han-Young KANG,* Yong Seo CHO, Hun Yeong KOH, and Moon Ho CHANG*
Drug Synthesis Lab, Korea Institute of Science and Technology
P. O. Box 131 Cheongryang, Seoul 131-650, Korea

N-[1-Methyl-6-(methoxycarbonyl)-5-hexynylidene]methylamine *N*-oxide, a ketonitrone which was prepared from the reaction between methyl 7-oxooct-2-ynoate and *N*-methylhydroxylamine rearranged thermally into two isomeric bicyclic compounds instead of the expected intramolecular [3+2] cycloadduct. Also an aldonitrone, *N*-[6-(methoxycarbonyl)-5-hexynylidene]methylamine *N*-oxide provided the corresponding rearranged product.

In connection with our research interests in [3+2] cycloaddition of nitrones,[1] we have recently reported[2] that intramolecular [3+2] nitrone addition to an alkyne is facile when the tether chain length is appropriate, that is, the cycloaddition is successful in case that six-membered rings fused to isoxazolidines can be formed as shown in the following equation (1). In the course of examining on the scope and limitations of this intramolecular [3+2] nitrone-alkyne cycloaddition,[3] we had occasion to look into the reactions of nitrones having shorter tethers which would provide five(or smaller, if possible)-membered cycles fused to the isoxazolidine (Scheme 1).

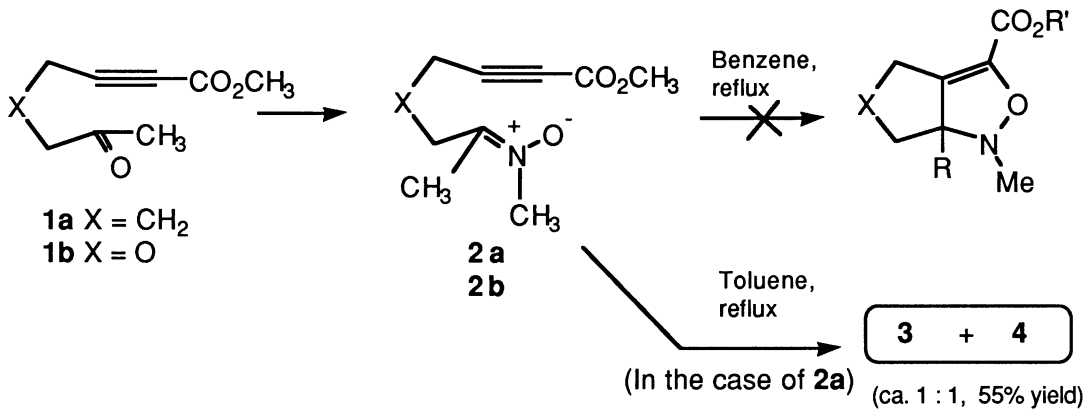


(1)

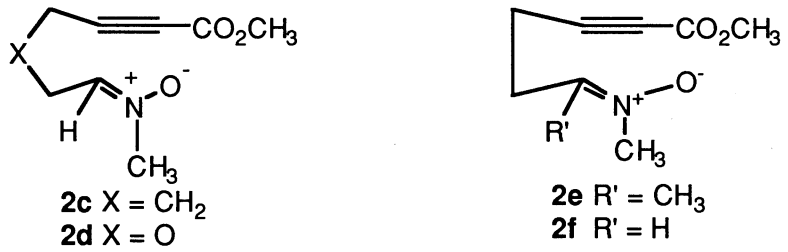
R = H, Me; R' = Me, Benzyl, p-Nitrobenzyl; X = CH_2, O

The intramolecular cycloaddition of **2a** and **2c** failed to provide the expected cycloadducts when heated at reflux in benzene, while the successful cycloadditions shown in the equation (1) were observed for the nitrones with longer tether chains under the same condition as mentioned above.[4] Prolonged exposure to this condition simply resulted in gradual decompositon of the nitrones. Nitrone **2a** under forcing condition (reflux in toluene), however, yielded two products in 55% combined yield. The ratio of two products (**3** : **4**) was

approximately 1:1. Similarly, aldonitrone **2c** when heated at reflux in toluene afforded a product (**5**) in lower yield (ca. 20%). Incorporation of an oxygen atom into the tether chain (**2b** and **2d**) led to decomposition when heated to reflux in either benzene or toluene. So did further shortening of the tether length (**2e** and **2f**).



Scheme 1.

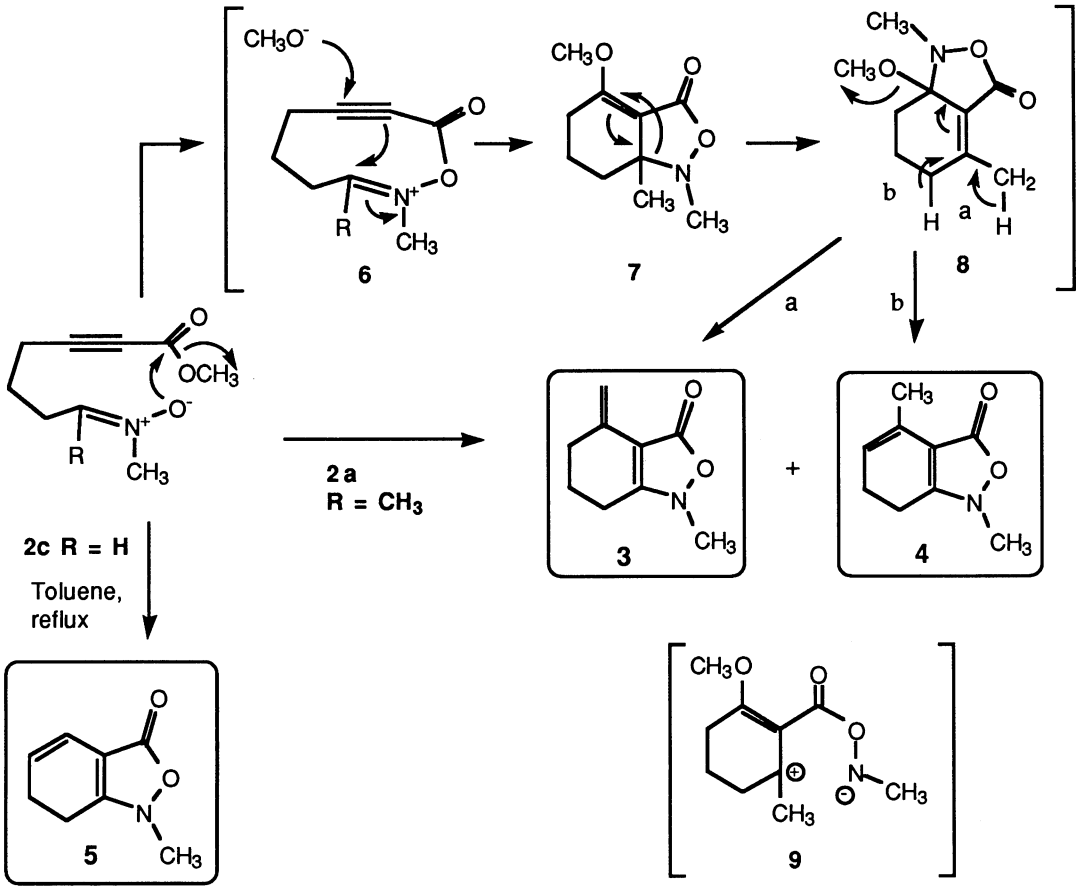


The structures of these isolated products were deduced to be the bicyclic compounds **3**, **4**, and **5** depicted in Scheme 2 from spectroscopic[5] and X-ray analyses. According to these data including DEPT and COSY spectral analyses, it was quite obvious that products **3** and **4** were structural isomers and, of course, not the expected cycloaddition products. Also isomerization between **3** and **4** occured on standing chromatographically purified **3** and **4**, and this isomerization process was accelerated upon addition of catalytic amount of acids. Although much information was available from the routine spectral analysis, unambiguous structural assignment of the products was not trivial. A conclusive evidence for the correct structures of the products came from the X-ray analysis of **3** (Fig. 1).

X-Ray data[6,7] reveal that product **3** has a bicyclic structure, and on the basis of this structure, **4** and **5** should have the stuctures shown in Scheme 2. Therefore, the intramolecular [3+2] nitrone-alkyne cycloadditon was prohibited due to steric constraints and consequently nitrone **2a** (and **2c**) undertook a different reaction course.

Formation of **3** and **4** (also **5**) deserves explanation. One plausible mechanism for the formation could involve the initial attack of oxygen in nitrones **2a** (and **2c**) at the ester carbonyl carbon and the following rearrangement (Scheme 2). It is well documented that nitrones can behave as oxygen nucleophlies.[8] This attack would lead to the formation of a

nine-membered cyclic intermediate **6**.



Scheme 2.

The rearrangement leading to the isolated bicyclic products (**3** and **4**) would be initiated with the Michael type addition of methoxide to the alkyne bond accompanied by a transannular addition to the carbon-nitrogen double bond in nitrone functionality. The resultant bicyclic intermediate **7** would be transformed to **8**, which would then undergo deprotonation with elimination of methanol to produce **3** and **4** (Scheme 2). The rearrangement of **7** to **8** might proceed via an ionic intermediate **9** formed by the C-N bond cleavage. This cleavage could be facilitated due to stabilization of the resultant tertiary carbocation and nitrogen anion by methoxyvinyl and oxycarbonyl moieties, respectively.[9] The formation of **5** from **2c** could be similarly explained.

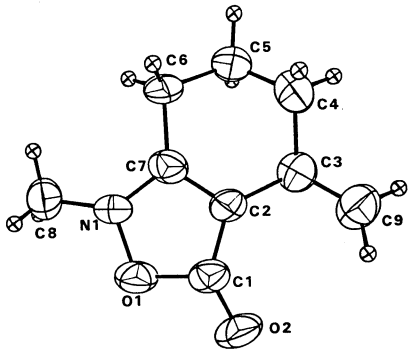


Fig. 1. X-Ray Crystal Structure of **3**.

References

1) a) K. B. Tossell, "Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis, Novel Strategies in Synthesis," VCH, New York (1987); b) E. Bruer "Nitrones, Nitronates and Nitroxides," ed by S. Patai and Z. Rappoport, Wiley, New York (1989), Chap. 2; c) P. N. Confalone and E. Huie, *Org. React.*, **36**, 1 (1988).

2) H.-Y. Kang, Y. S. Cho, H. Y. Koh, and M. H. Chang, *Tetrahedron Lett.*, **32**, 0000 (1991) in press.

3) Before our study on the intramolecular [3+2] nitrone-alkyne cycloaddition, only one relevant report was available. See, N. A. Le Bel, *J. Am. Chem. Soc.*, **92**, 5278 (1970).

4) To a solution of ketone **1** (or aldehyde) in benzene was added a solution of *N*-methylhydroxylamine in methanol. After stirring at room temperature for ca. 30 min, the solution was concentrated. The residue was dissolved in benzene (or toluene) and heated at reflux for 2–3 h.

5) Spectral and physical data for compound **3**, **4**, and **5** are as follows. **3**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.80–1.97 (2H, quint, J = 6 Hz), 2.35–2.40 (2H, t, J = 6 Hz), 2.45–2.55 (2H, t, J = 6 Hz), 3.31 (3H, s), 4.91 (1H, s), 5.66 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.0, 162.7, 133.5, 107.3, 100.0, 37.5 (NCH_3), 30.9 (CH_2), 22.4 (CH_2), 22.0 (CH_2); DEPT no CH; IR (KBr) 1665, 1492, 1374, 1334 cm^{-1}; UV λ_{max}^{MeOH} = 282 nm; MS (*m*/*z*, rel intensity) 165 (M^+, 21), 79 (90), 42 (85), 39 (100); HRMS Found: 165.0800. Calcd for $C_9H_{11}NO_2$ 165.07897; mp 79–81 °C; Anal. Found: C, 65.50; H, 6.71; N, 8.37%. Calcd for $C_9H_{11}NO_2$: C, 65.49; H, 6.71; N, 8.48%.
4: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.98–2.00 (3H, q, J = 1.8 Hz), 2.34–2.42 (2H, m), 2.51–2.57 (2H, m), 3.34 (3H, s), 5.14–5.18 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.5, 162.7, 127.2, 114.9, 98.6, 36.8 (NCH_3), 22.4 (CH_2), 20.4 (CH_2), 17.6 (CH_3); IR (KBr) 1708, 1560, 1437, 1377 cm^{-1}; UV λ_{max}^{MeOH} = 307 nm; MS (*m*/*z*, rel intensity) 165 (M^+,100), 79 (55), 55 (39), 39 (38); HRMS Found: 165.0799. Calcd for $C_9H_{11}NO_2$: 165.07897; mp 99–100 °C; Anal. Found: C, 65.49; H, 6.70; N, 8.42%. Calcd for $C_9H_{11}NO_2$: C, 65.49; H, 6.71; N, 8.48%.
5: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.46–2.51 (2H, m), 2.60–2.66 (2H, m), 3.35 (3H, s), 5.55–5.58 (1H, m). 6.21 (1H, br d, J = 9.6Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.5, 162.8, 120.8, 117.5, 98.5, 37.6 (NCH_3), 22.8 (CH_2), 20.6 (CH_2); IR (KBr) 1718. 1568, 1414 cm^{-1}; UV λ_{max}^{MeOH} = 305 nm; MS (*m*/*z*, rel intensity) 151 (M^+,33), 106 (74), 66 (80), 55 (55), 39 (100); mp 63–65 °C; Anal. Found: C, 63.80; H, 6.12; N, 9.35%. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27%.

6) Crystal data for **3** : $C_9H_{11}NO_2$, FW = 165.194; monoclinic, space group $P2_1$; a = 7.544(1), b = 6.2980(8), c = 8.3073(9) Å; β = 99.38(1)°; V = 428.4(1) Å^3; Z = 2; d(calcd) = 1.28 g/cm^3, Crystal size 0.25 x 0.33 x 0.40 mm^3. The final R (R_w) value was 0.0544(0.0579) for 379 (I>3σ(I)) reflections.

7) We thank Dr. Jong Hwa Jeong of the Inorganic Chemistry Lab of Korea Institute of Science and Technology(KIST) for the X-ray crystal structure determination of **3**.

8) Ref. 1b , pp. 202–208; S. A. Lang, Jr. and Y.-i. Lin, "Comprehensive Hetrocyclic Chemistry," ed by A. R. Katrizky and C. W. Rees, Pergamon, Oxford (1984), Vol. 6, Chap. 4.16, p. 113.

9) The authors appreciate the referee's comments on the mechanism for the formation of **3**.

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