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Synthesis of Macrocarbocycles Utilizing Intramolecular 1,3-Dipolar Cycloaddition of Nitrile Oxides. Synthesis of (±)-Muscone

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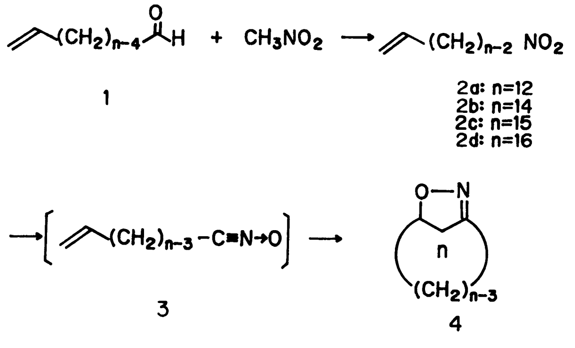
Synopsis. Intramolecular 1,3-dipolar cycloaddition of nitrile oxides generated from *ω*-nitro-1-alkenes gave isoxazoline-fused macrocarbocycles (ring size 12, 14, 15, and 16) in fair to good yields. The 15-membered derivative was converted into (±)-muscone.

In connection with a total synthesis of macrocyclic natural products, we examined intramolecular 1,3-dipolar cycloaddition of silyl nitronates and nitrile oxides generated from *ω*-nitroalkyl acrylates, and achieved the synthesis of macrolides, (±)-pyrenophorin and (±)-A26771B.[1,2] In this note we will describe intramolecular 1,3-dipolar cycloaddition of nitrile oxides generated from *ω*-nitro-1-alkenes.[3]

The nitro alkenes **2** were easily prepared from the corresponding aldehydes **1** by the method of Wollenberg and Mille[4] in good yields. Intramolecular 1,3-dipolar cycloaddition was carried out using dilute solution of **2** in benzene or toluene (concentration=1 mmol of **2**/400 ml of solvent) in the presence of 10 equiv of *p*-chlorophenyl isocyanate and triethylamine.[5] We examined the effects of reaction temperature and time using **2c** (Table 1, Run 4—8).

When reaction was carried out in refluxing benzene the reaction was relatively slow and after 15—25 h, desired cyclic compound **4c** was obtained in 31—44% yield (Run 4 and 5). Then the reaction was carried out in refluxing toluene for 15 h. Surprisingly the yield of **4c** dropped to 18% and a large amount (40%) of starting material (**2c**) was recovered. This result suggests that dehydration of nitro compounds with triethylamine and isocyanate is supressed at that temperature presumably because of the instability of *aci*-nitro form at high temperature (Run 6). According to this assumption, the reaction was carried out at 50 °C for 18 h in order to generate the nitrile oxide completely and then at 110 °C for 18 h to give better yield (63%) of **4c** (Run 7). However when the intramolecular addition step was carried out at higher temperature (140 °C) the yield dropped slightly, probably because of decomposition of the product at that temperature. Intramolecular 1,3-



Scheme 1.

Table 1. Intramolecular 1,3-dipolar cycloaddition of nitrile oxides (**3**) derived from **2**

Run	Nitro Olefin	Solvent	Temp and Time	Ring Size	Yield **4**/%
1	**2a**	A	80 °C 18 h	12	21
2	**2b**	A	80 °C 20 h	14	44
3		B	50 °C 18 h and 110 °C 18 h		38
4	**2c**	A	80 °C 15 h	15	31
5		A	80 °C 25 h		44
6		B	110 °C 15 h		18
7		B	50 °C 18 h and 110 °C 18 h		63
8		C	30 °C 20 h and 140 °C 10 h		47
9	**2d**	B	50 °C 18 h and 110 °C 18 h	16	60

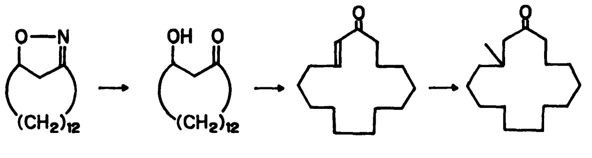
Solvent A: Benzene, B: Toluene, C: Xylene.

Table 2. Spectral and physical data of **4a**—**d**

Compound	NMR ($CDCl_3$), δ	IR (KBr), cm^{-1}	Mp, θ_m/°C
4a	1.30 (14H, broad s), 1.20—1.82 (2H, m), 2.80 (2H, t) 2.14—2.54 (2H, m), 4.26—4.85 (1H, m)	1610 (C=N)	85.5—86.5
4b	1.34 (20H, broad s), 2.26—2.70 (2H, m), 2.80 (1H, d), 2.83 (1H, d), 4.46—4.96 (1H, m)	1605 (C=N)	67.0—68.5
4c	1.43 (22H, broad s), 2.13—2.63 (2H, m), 2.63—2.97 (2H, m), 4.33—4.93 (1H, m)	1615 (C=N)	81.0—82.0
4d	1.82 (24H, broad s), 2.13—2.63 (2H, m), 2.63—2.97 (2H, m), 4.32—4.81 (1H, m)	1610 (C=N)	88.5—90.0

dipolar cycloaddition of alkenenitrile oxides having different chain length was also examined. Nitroalkenes **2b** and **2d**, gave the expected cyclic compounds **4b** and **4d** in 44 and 60% yields, respectively. In the case of **2a** however, the reaction was complex and **4a** was isolated only in 21% yield. The structures of **4a**—**d** were confirmed by spectral (NMR, IR, and Mass) data and elemental analyses. Their NMR and IR spectral data along with their melting points are listed in Table 2.

In the course of the synthetic studies of macrolides, we have shown that isoxazoline derivatives were easily converted to α,β-unsaturated ketones in high yields by hydrogenolysis under acidic conditions and subsequent dehydration.[1,2,6] Then transformation of the isoxazoline derivative **4c** to (±)-muscone *via* enone **6** was examined. Although hydrogenolysis of **4c** under acidic conditions in the presence of Pd-C showed formation of some by-products, use of PtO_2 as a catalyst gave better results. After hydrogenolysis of **4c** in acetic acid-water under atmospheric pressure of hydrogen at room temperature for 2 d, the resulted crude **5** was treated with methanesulfonyl chloride and triethylamine to give **6** in 45% overall yield from **4c**, which was converted to (±)-muscone **7** in 79% yield by known method.[7]



4c **5** **6** **7**

Scheme 2.

Experimental

A Typical Procedure of Intramolecular 1,3-Dipolar Cycloaddition: Nitroalkene **2c** (255 mg, 1 mmol), *p*-chlorophenyl isocyanate (1.52 g, 10 mmol), and triethyamine (4 ml, 10 mmol) were dissolved in 400 ml of dry toluene. The solution was stirred at 50 °C for 18 h and then heated under reflux for 18 h. To the reaction mixture was added isopropylamine (1 ml) at 0 °C and stirred at that temperature for 20 min. After filtration through short pad of celite, the solution was concentrated *in vacuo* and the residue was purified by column chromatography (benzene: ether=50:1) to give 149 mg of **4c**.

trans-*2-Cyclopentadecenone (6)*: A solution of **4c** (66 mg) dissolved in acetic acid (3 ml) and water (0.5 ml) was stirred under H_2 for 2 d in the presence of PtO_2. After removal of catalyst by filtration, solvent was removed under reduced pressure. To the residue dissolved in dry CH_2Cl_2 (2 ml) were added MsCl (124 mg, 1.07 mmol) and triethylamine (0.37 ml, 2.65 mmol) at 0 °C under argon. After 16 h, a small amount of MeOH was added dropwise to the reaction mixture. The mixture was diluted with ether and precipitated salt was removed by filtration. After removal of solvent, the residue was purified by column chromatography (hexane:ether=10:1) to give **6** (28 mg, 45%): IR (NaCl) 1685, 1655 cm^{-1} (C=O) and 1627 cm^{-1} (C=C); NMR (60 MHz, $CDCl_3$) δ=1.05—1.93 (20H, m), 2.07—2.70 (4H, m), 6.10 (2H, d, J=16 Hz), 6.68 (1H, dt, J=16 and 6 Hz).

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