DME in a 25-mL three-necked flask fitted with a 2 syrum stopper, drying tube, magnetic stirrer and nitrogen inlet was added, under nitrogen, 3 mL of 1 M "Super Hydride". The mixture was stirred under nitrogen for 1 h, poured into 50 mL of water, and extracted with ether. The combined ether extracts were dried (Na_2SO_4) and concentrated, and the residue was chromatographed (preparative TLC, silica gel 60 F-254, 95:5 chloroform/ethyl acetate) to give 71 mg (50%) of quinaldine, identical in every respect with an authentic sample.

Under the same conditions, isoquinoline was obtained in 30% yield from (1-(1-isoquinolinyl)-4-tosylimidazole and "Super Hydride", except that oxygen was bubbled through the reaction mixture for 4 h prior to the workup.

Displacement of the 4-Tosylimidazolyl Substituent by a Wittig Reagent. Synthesis of 1-Styrylisoquinoline. Sodium hydride (50%, 0.192 g, 4 mmol), methyltriphenylphosphonium bromide (1.07 g, 3 mmol) and dry DME (40 mL) were added with stirring to a three-necked flask under nitrogen, and the mixture was heated under reflux for 2 h. To the cooled solution was then added 0.35 g (1 mmol) of 1-(1-isoquinolinyl)-4-tosylimidazole (under nitrogen), and the mixture was heated under reflux for 13 h. Benzaldehyde (0.6 g) was then added, and the mixture was heated under reflux for 12 h. It was then cooled and poured into 100 mL of water, and the aqueous solution was extracted with chloroform. The combined chloroform extracts were evaporated to dryness, the residue was dissolved in ether and filtered, and the filtrate was concentrated. Chromatography of the residue over silica gel with chloroform gave 150 mg (69%) of 1-styrylisoquinoline (mp 109–110 °C), identical in every respect with an authentic sample.

Displacement of the 5-Phenyl-1-tetrazolyl Substituent by a Wittig Reagent. Synthesis of 1-Ethylisoquinoline. To a stirred suspension of ethyltriphenylphosphonium iodide (4.6 g, 11 mmol) in 75 mL of dry DME under nitrogen at −40 °C was added 4.6 mL (11 mmol) of *n*-butyllithium (2.4 M). The reaction mixture was stirred for 2 h, and then a solution of 1.37 g (5.0 mmol) of **4** in 10 mL of dry DME was added. The reaction mixture was heated under reflux for 48 h and cooled, and a solution of 1.06 g (10 mmol) of sodium carbonate in 20 mL of water was added. The resulting solution was heated for 3 h under reflux and concentrated to a small volume under reduced pressure, and 50 mL of chloroform and 20 mL of saturated aqueous sodium chloride solution were added. The chloroform layer was separated and extracted with 5% aqueous HCl (4 × 50 mL). The combined acidic extracts were made alkaline with solid NaOH and extracted with ether (3 × 100 mL), and the combined ether extract was dried (Na_2SO_4) and evaporated to give a viscous oil. Distillation then gave 210 mg (28%) of 1-ethylisoquinoline as a colorless oil (picrate, mp 209–210 °C), identical with an authentic sample.

Registry No. **1**, 57761-77-0; **2**, 80781-06-2; **3**, 5454-05-7; **4**, 80781-07-3; **5** (Het = 4-pyridyl), 16705-92-3; **5** (Het = 2-methyl-4-quinolinyl), 80781-08-4; **5** (Het = 1-isoquinolinyl), 35257-15-9; **5** (Het = 2,6-dimethyl-4-pyrimidinyl), 80781-09-5; **6** (Het = 4-pyridyl), 80781-10-8; **6** (Het = 2-methyl-4-quinolinyl), 80781-11-9; **6** (Het = 1-isoquinolinyl), 80781-12-0; **6** (Het = 2,6-dimethyl-4-pyrimidinyl), 80781-13-1; **9**, 36680-19-0; 4-benzamidopyridine, 5221-44-3; 4-(*p*-nitrobenzamido)pyridine, 13160-58-2; sodium azide, 26628-22-8; 2-benzamidopyridine, 4589-12-2; 1-benzamidoisoquinoline, 33357-47-0; triethyl orthoformate, 122-51-0; 4-ethoxypyridine, 33399-46-1; 4-ethoxyquinaldine, 46272-56-4; 1-ethoxyisoquinoline, 66728-96-9; 1-ethoxyisoquinoline picrate, 80781-14-2; 2,6-dimethyl-4-ethoxypyridine, 4595-72-6; 2,6-dimethyl-4-ethoxypyridine picrate, 4679-06-5; 4-(*n*-butylthio)pyridine, 26891-64-5; 4-(*n*-butylthio)pyridine picrate, 53708-25-1; 4-(*n*-butylthio)quinaldine, 80781-15-3; 1-(*n*-butylthio)isoquinoline, 80781-16-4; 2,6-dimethyl-4-(*n*-butylthio)pyrimidine, 80781-17-5; 4-(phenylthio)quinaldine, 80781-18-6; 1-(phenylthio)isoquinoline, 19653-18-0; 2,6-dimethyl-4-(phenylthio)pyrimidine, 77752-56-8; quinaldine, 91-63-4; isoquinoline, 119-65-3; methyltriphenylphosphonium bromide, 1779-49-3; benzaldehyde, 100-52-7; ethyltriphenylphosphonium iodide, 4736-60-1; 1-ethylisoquinoline, 7661-60-1; 1-ethylisoquinoline picrate, 79172-39-7; 4-pyridinamine, 504-24-5; 4-amino-2-methylquinoline, 6628-04-2; 1-aminoisoquinoline, 1532-84-9; 4-amino-2,6-dimethylpyrimidine, 461-98-3; $TsCH_2NC$, 36635-61-7; NaOEt, 141-52-6; $NaSC_4H_9$-*n*, 4779-86-6; NaSPh, 930-69-8; $LiHBEt_3$, 22560-16-3.

Reactions at High Pressures. [3 + 2] Dipolar Cycloaddition of Nitrones with Vinyl Ethers†

Carl Michael Dicken and Philip DeShong*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Received December 10, 1981

The [3 + 2] dipolar cycloaddition of a nitrone and an electron-rich depolarophile can be induced by high-pressure as well as by thermal reaction conditions, and the high-pressure conditions lead to altered stereoselectivities in the cycloaddition.

In recent years, the thermal [3 + 2] dipolar cycloaddition of nitrones with electron-deficient dipolarophiles (i.e., acrylates, styrenes, dienes, etc.) has been extensively utilized as a key feature in the total synthesis of structurally diverse natural products.[1] On the other hand, the synthetic potential offered by cycloadditions of nitrones and electron-rich olefins (i.e., vinyl ethers, enamines, etc.) has been neglected. Following the pioneering studies of Huisgen and his co-workers,[2] there has been limited research in this area of nitrone chemistry.[3] We viewed the cycloadduct (**5**) resulting from the dipolar cycloaddition of nitrone **1** and ethyl vinyl ether (**3**) as a masked β-amino aldehyde which could be released by reduction of the N,O bond and chose to incorporate this approach to β-amino aldehydes as a critical element in a synthetic project. Unfortunately, we were almost immediately confronted with a limitation to the approach: many nitrones are not

† This paper is dedicated to George Büchi on the occasion of his 60th birthday.

(1) Tufariello, J. *J. Acc. Chem. Res.* **1979**, *12*, 396–403 and references cited therein.

(2) Huisgen, R.; Grashey, R.; Seidl, H.; Hauck, H. *Chem. Ber.* **1968**, *101*, 2559–2567. See also: Black, D. S. C.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, 205–221.

(3) Inouye, Y.; Watanabe, Y.; Takahashi, S.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3762–3764. Fisera, L.; Kova, J.; Poliacikova, J. *Heterocycles* **1979**, *12*, 1005–1008. Samuilov, Y. D.; Solo'eva, S. E.; Konovalov, A. I. *J. Org. Chem. USSR (Engl. Transl.)* **1980**, *16*, 1061–1065. Nomura, Y.; Furusaka, F.; Takenchi, Y. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1740.

0022-3263/82/1947-2047$01.25/0

Table I. [3 + 2] Dipolar Cycloadditions of Nitrones and Electron-Rich Dipolarophiles

nitrone	dipolarophile	pressure, bar	temp, °C	time, h	yield of cycloadduct,[a] %	ratio of stereoisomers[b]
1	3	1	80	72	78	50:50 (5a/5b)
1	3	1000	25	72	0	
1	3	2000	25	72	25[c] (>95)[g]	50:50 (5a/5b)
1	3	4000	25	96	10[c] (>95)[g]	57:43 (5a/5b)
1	3	2000	50	6	83	(5a/5b)
1	4	1	115	72	51	50:50[d] (7a/7b)
1	4	2000	25	48	50[c] (90)[g]	33:67[d,e] (7a/7b)
2	3	1	120	96	42[f]	67:33 (8a/8b)
2	3	2000	25	90	17[c,h]	58:42 (8a/8b)
9	3	1	80	24	0[f]	
9	3	2000	50	24	83	100:0[d] (10)
11	3	1	80	6	92	0:100[d] (12b)
11	3	4000	50	6	92	0:100[d] (12b)

[a] Isolated yield of the mixture of stereoisomers. [b] Ratio determined by GC analysis unless stated otherwise. [c] The unreacted nitrone was recovered in approximately quantitative yield from the reaction mixture. [d] Ratio obtained by isolation of the separate isomers. [e] The mixed fractions from chromatography display an abundance of 7b. [f] Trace of nitrone remained in the reaction mixture. [g] Yield based upon consumed nitrone. [h] The yield was improved to almost quantitative after a reaction period of ~3 weeks.

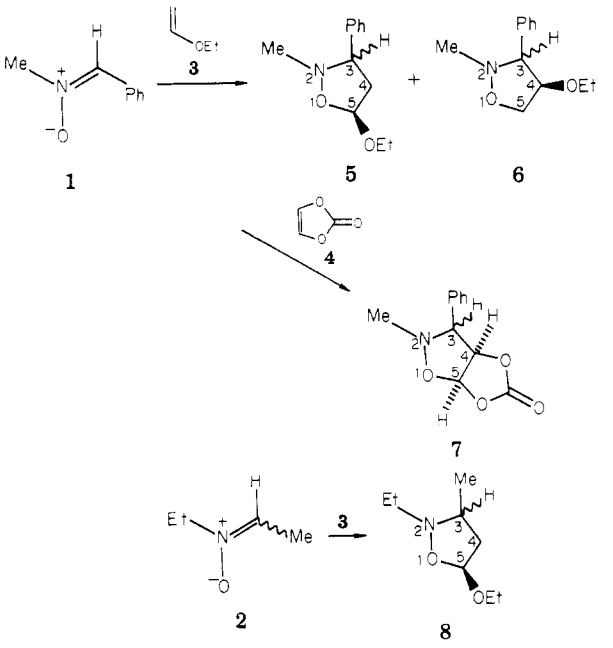
stable to the prolonged heating (usually >24 h) required to obtain cycloaddition with electron-rich olefins, resulting in a lowered yield of cycloadduct. At this juncture, rather than relinquish the approach entirely, we sought alternate conditions to effect cycloaddition which would not lead to nitrone decomposition. This paper reports the results of this study: first, that high-pressure reaction conditions can be employed to effect [3 + 2] cycloadditions at *room temperature* in yields generally exceeding those of the thermal conditions and, second, that the *stereoselectivity of the cycloaddition* is altered by the shift from thermal to high-pressure conditions.

In this report, the high-pressure conditions employed[4] do not exceed pressures of 4 kbar. There is a practical reason for this limitation. As seen in the Table I, at pressures greater than 4 kbar (room temperature), no cycloadduct was formed. At these higher pressures, the cycloaddition was aborted, and starting nitrone was recovered quantitatively.[5] The extension of this work to more extreme pressures is currently being undertaken in this laboratory.

We chose initially to investigate the model systems comprised of nitrones **1** and **2** as the dipolar components and ethyl vinyl ether (**3**) and vinylidene carbonate (**4**) as the dipolarophiles (Scheme I). These were chosen because (1) authentic samples of both stereoisomers of the cycloadducts **5**, **7**, and **8** were available and (2) the cycloadducts were known to be stable to the reaction conditions.[6] Therefore, the potential for secondary reactions or rearrangements interfering with the interpretation of the results was diminished.

When a solution of nitrone **1** in ethyl vinyl ether (**3**) was pressurized[7] to 2.0 kbar at room temperature for 72 h, a 25% yield of cycloadduct **5**[8,9] was obtained. Under thermal

Scheme I[a]



[a] a, α-H at C-3; b, β-H at C-3.

conditions (80 °C, 72 h), a 78% yield of the cycloadduct was isolated (Table I). At first glance, it would appear that the more effective cyclization method involved thermal conditions; however, this was not the case. In the thermal reaction, no nitrone **1** could be recovered from the reaction mixture, whereas under the high-pressure conditions, unreacted nitrone could be recovered almost quantitatively. Therefore, to improve the yield of **5** in the high-pressure reaction, it was only necessary to extend the reaction time accordingly.

A significant improvement in the yield of **5** occurred if the reaction mixture was heated gently. When the cycloaddition of **1** with **3** was conducted at 2.0 kbar (50 °C) for 6 h, cycloadduct **5** was obtained in 83% yield. It should be noted that even though neither of the high-pressure reactions employed led to significantly higher yields of

(4) A referee has pointed out that our original designation of these conditions (1–4 kbar) as "ultrahigh-pressure conditions" was probably unwarranted.

(5) Some of the possible reasons for this phenomenon are dimerization of the nitrone, precipitation of the nitrone under the reaction conditions, or solidification of the reaction medium. Dimerization of the nitrone seems to be the most logical explanation. Both acyclic and cyclic nitrones are known to dimerize,[23] and this reaction should be accelerated by high-pressure conditions. A referee has pointed out that the solubility of the nitrone should have changed by no more than a factor of 2 at high pressures and therefore probably played no role in the reaction.

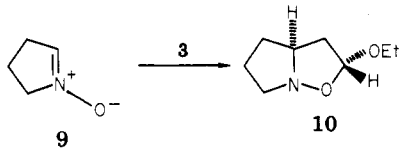
(6) DeShong, P. R.; Dicken, C. M., manuscript in preparation.

(7) The high-pressure apparatus will be described in detail elsewhere (manuscript in preparation).

(8) All compounds isolated gave satisfactory analytical data (IR, NMR, mass spectra, etc.)

(9) The preferential formation of **5** (and **8**) has been predicted by perturbation molecular orbital (PMO) theoretical studies: Houk, K. N.; Sims, J.; Duke, R. E., Jr.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287–7301. Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *Ibid.* **1973**, *95*, 7301–7315.

Scheme II



9 10

cycloadduct than the corresponding thermal sequences, the conditions did allow cycloaddition of nitrones with ethyl vinyl ether to proceed at temperatures which do not normally lead to decomposition of sensitive nitrones.

Analogous results were obtained from the reaction of nitrone **2**[10] and ethyl vinyl ether. High-pressure cycloaddition (25 °C/2.0 kbar/90 h) resulted in a 17% yield of **8**[8] (and a virtually quantitative recovery of unreacted nitrone). By extending the reaction time (~3 weeks) an almost quantitative yield of **8** was obtained. Cycloadduct **8** could also be obtained (in 42% yield) after 96 h at 120–125 °C, but little unreacted nitrone could be recovered (Table I). Therefore, to obtain the highest yields of cycloadduct **8**, we found it necessary to employ the high-pressure conditions.

A more dramatic example of the effectiveness of the high-pressure-induced cycloaddition involved nitrone **9** and **3** (Scheme II). No cycloadduct was obtained when nitrone **9** was heated to 80 °C in excess ethyl vinyl ether. On the other hand, 50 °C/2.0 kbar/24 h was sufficient to result in the formation of **10** from **9** and **3** in 83% yield. This is an example of a case in which the nitrone can withstand the thermal conditions, but the cycloadduct (**10**)[6,21] cannot; without resorting to high pressures, it would be impossible to obtain **10**.

We have also studied the cycloaddition of nitrone **1** and vinylidene carbonate (**4**) to give adduct **7**[8] in ~50% isolated yield (not optimized) under both sets of reaction conditions. Although neither cycloaddition method was superior to the other in yield of **7** produced, *the ratio of* ***7a*** */* ***7b*** *produced during the cycloaddition was distinctly dependent upon the reaction conditions employed* (Table I). Thermal cycloaddition gave a 1:1 mixture of **7a/7b**; while at high pressure the ratio of **7a/7b** was >2:1.[8] Thus, even though the high-pressure conditions did not lead to an increased yield of cycloadduct, they did result in improved stereoselectivity for the cycloaddition.

The ratio of stereoisomers has varied as the pressure was increased in each of the nitrone cycloadditions we have studied (see Table I). Although the changes are small in magnitude and reflect rather small energy differences in transition-state energies (generally <1 kcal/mol), it is still obvious that pressure can play a significant role in influencing the stereochemical outcome of the cycloaddition. We are presently engaged in further experiments to determine the full potential of pressures as a means of influencing the stereochemistry in this and other cycloaddition reactions.

The results reported in this paper complement those of Dauben,[11] Gladysz,[12] and others,[13] who have found that Diels–Alder reactions of unreactive dienes (e.g, furans, etc.) readily occur at elevated pressures. A group of Russian workers have also reported the pressure-induced dipolar cycloaddition of nitronic esters to steroidal dipolarophiles.[14] As in the case of these cycloadditions, the dipolar reaction was expected to have a large, negative activation volume and thus be accelerated by pressure.[15] This report confirms that prediction.

In conclusion, we have shown that the [3 + 2] dipolar cycloaddition of a nitrone and an electron-rich dipolarophile can be induced by high-pressure as well as thermal reaction conditions and that the high-pressure conditions lead to altered stereoselectivities in the cycloaddition. In due course, we will report on the utilization of cycloadducts such as **5**, **7**, and **8** for the total synthesis of natural products and on other high-pressure-induced cycloaddition reactions.

Experimental Section

Melting points were taken in Kimax soft-glass capillary tubes by using a Thomas-Hoover Uni-Melt capillary melting point apparatus (Model 6406 K) equipped with a calibrated thermometer.

Proton magnetic resonance (NMR) spectra were recorded on Varian Associates analytical NMR spectrometers (Model EM-360) or a Bruker WP-200 or WP-360 Super Con spectrometer. Proton chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard. Coupling constants (J values) are given in hertz, and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Infrared spectra were recorded on a Perkin-Elmer Model 197, Model 267, or Model 580 diffraction grating spectrophotometer. Peak positions are given in reciprocal centimeters and are listed as very strong (vs), strong (s), medium (m), or weak (w). Mass spectral data were obtained on a KRATOS MS-950 double-focusing high-resolution spectrometer or on a Finnigan 3200 twin EI and CI quadrapole mass spectrometer equipped with a Digital Equipment Corp. PDP 8/I computer. The chemical ionization carrier gas was methane unless specified otherwise. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, IL.

Gas chromatography (GC) was performed on a Varian Model 920 or Model 3200 gas chromatograph equipped with a thermal-conductivity detector using the following columns: 5 ft × 0.25 in., 30% SE-30 on Gas Chrom Q, 100–120 mesh; 5 ft × 0.25 in., 1.5% OV-101 on Chrom G, 100–120 mesh (stainless-steel columns). Peak areas in GC analysis have been corrected for differences in response factors for each compound.

Thin-layer chromatography (TLC) was performed on 0.25-mm Merck silica-coated glass plates, with the compounds being identified in one or more of the following manners: UV (λ = 253.7 nm, unless noted otherwise), iodine, and/or sulfuric acid charring.

Preparative layer chromatography (PLC) was performed on 0.25-, 0.50-, or 2.0-mm Merck silica-coated glass plates, with the compounds being identified as above.

Flash chromatography was performed by using thick-walled glass columns and "medium-pressure" silica (Merck, 32–63 μm) according to the method of Still.[20]

All reaction solvents were distilled from $CaCl_2$ before use unless noted otherwise. The deuterated NMR solvent contained 99.0–99.8% deuterium in the indicated position and was obtained from Merck and Co., Inc. The Me_4Si was for use in NMR and was obtained from Stohler Isotope Chemicals (catalog no. D 327 S).

(10) Heicklen, J.; Olofson, R. A.; Bhatki, K. S.; Schmitthenner, H. J. *Org. Prep. Proced. Int.* **1979**, *11*, 249–251.
(11) Dauben, W. G. Krabbenhoft, H. O. *J. Am. Chem. Soc.* **1976**, *98*, 1992–1933. Dauben, W. G.; Krabbenhoft, H. O. *J. Org. Chem.* **1977**, *42*, 282–287. Dauben, W. G.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1974**, *96*, 3664–3666.
(12) Gladysz, J. A.; Lu, S. J.; Tomasello, J. A. V; Yu, U. S. *J. Org. Chem.* **1977**, *42*, 4170–4172.
(13) Jurczak, J.; Tkacz, M. *J. Org. Chem.* **1979**, *44*, 3347–3352.
(14) Kamernitzky, A. V.; Levina, I. S.; Mortikova, E. I.; Shitkin, V. M.; El'Yanov, B. S. *Tetrahedron* **1977**, *33*, 2135–2139.
(15) Whalley, E. *Adv. Phys. Org. Chem.* **1964**, *2*, 93–162. Vol. 2, Academic le Noble, W. J. *Prog. Phys. Org. Chem.* **1967**, *5*, 207–330. Jenner, G. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 137–143.
(16) *Chem. Abstr.* **1968**, *69*, 86809.
(17) Sevaratore, A. Ph.D. Thesis, State University of New York at Buffalo, 1979.
(18) NMR decoupling work was done by Alan Freyer and Dr. Lloyd Jackman.
(19) Elemental analyses were performed by Micro-Tech Labs, Inc., Skokie, IL.
(20) Mitra, A; Kahn, M.; Still, W. *J. Org. Chem.* **1978**, *43*, 2923.
(21) Cycloadduct **10** decomposed when heated at 80 °C in ethyl vinyl ether.

Unless noted otherwise, the ground-glass glassware and syringes used in all the reactions described below were washed thoroughly and dried in an oven at 150 °C. The glassware was assembled while still hot and maintained under an anhydrous, inert atmosphere of nitrogen or argon.

The high-pressure apparatus consisted of a hydraulically pressurized autoclave containing castor oil. Pressures were determined directly from a gauge attached to the autoclave. The autoclave was heated by means of a heating tape regulated by a thermocouple. The reaction vessel consisted of heat-sealed Teflon tubing. Details of the reaction vessel and apparatus will be published elsewhere.[7]

α-Phenyl-*N*-methylnitrone (*Z* Isomer, 1). The procedure in the literature[16] was modified. Freshly distilled benzaldehyde (8.03 g, 76.0 mmol) was added to a 250-mL round-bottomed flask containing *N*-methylhydroxylamine hydrochloride (8.03 g, 96.1 mmol) in methylene chloride (120 mL). Sodium bicarbonate (20.05 g) was added to the flask, and the reaction mixture was refluxed at 80 °C for 12 h. When the mixture cooled, the sodium bicarbonate was filtered and washed with methylene chloride, and the solvent was removed by evaporation. Yellow crystals remained which were recrystallized from hexane–dichloromethane: 7.54 g (73%); mp 84–86 °C (lit.[22] mp 82–84 °C); ^{1}H NMR ($CDCl_3$) 3.81 (s, 3 H), 7.39 (dd, 4 H), 8.22 (dd, 2 H); IR (CCl_4) 1415 (vs), 1170 (vs), 950 (vs).

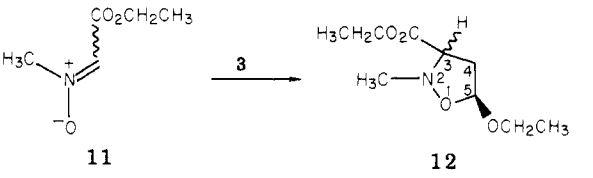
α-Methyl-*N*-ethylnitrone (2). The procedure of Heicklen et al. was followed.[10] Distilled *N*,*N*-diethylhydroxylamine (2.23 g, 25 mmol) was added via a syringe into a rapidly stirred suspension of dry silver oxide (11.6 g, 50 mmol) in 50 mL of anhydrous diethyl ether maintained at 0 °C under N_2. After 1 h, the reaction mixture was filtered through Celite, dried over Na_2SO_4, and evaporated to give a quantitative yield of **2**. Nitrone **2** was purified further by distillation at 25–30 °C (1 mm) into a liquid N_2 trap: clear oil; 2.00 g (92% yield); ^{1}H NMR ($CDCl_3$) 1.4 (t, 3 H, J = 7 Hz), 1.9 (d, 3 H, J = 6 Hz), 3.8 (q, 2 H, J = 7 Hz), 6.9 (q, 1 H, J = 6 Hz); IR (CCl_4) 3000–2900 (vs), 1600–1500 (s), 1450–1400 (vs), 1200–1150 (vs), 1050–1000 (vs); mass spectrum, m/z (relative intensity) 87 (M^+, 100), 72 (21), 71 (26), 59 (51), 56 (89). A 9:1 ratio of E/Z isomers (^{1}H NMR) was obtained.

Pyrrolidine 1-Oxide (9). The (*E*)-nitrone **9** was prepared by the method of Tufariello.[17] Yellow mercuric oxide (30 g, 0.130 mmol) was added to a solution of 5.0 g (56 mmol) of *N*-hydroxypyrrolidine in 250 mL of methylene chloride under N_2 at 0 °C. After 1 h, 3.0 g of anhydrous $MgSO_4$ was added and the mixture stirred for 1 h. The resulting suspension was filtered through a Celite pad, and the mercury salts were washed with CH_2Cl_2. The solvent was removed in vacuo at 0 °C. The crude oil was used without further purification: 2.5 g (51%); ^{1}H NMR ($CDCl_3$) 2.2 (m, 2 H), 2.8 (m, 2 H), 3.9 (m, 2 H), 6.8 (m, 1 H).

α-(Carboethoxy)-*N*-methylnitrone (11; *E* and *Z* Mixture). The procedure of Inouye[3] et al. was followed. *N*-Methylhydroxylamine hydrochloride (3.60 g, 43.1 mmol), calcium chloride (3.00 g), and sodium bicarbonate (10.50 g) were stirred in ether (50 mL) at 0 °C. Ethyl glyoxylate (4.50 g, 44.1 mmol) was added, and the reaction mixture was stirred for 1.5 h. The solid was filtered, and the filtrate was evaporated in vacuo. White crystals of the addition product were obtained: mp 72–78 °C; ^{1}H NMR ($CDCl_3$) 1.3 (t, 3 H), 4.3 (q, 2 H), 4.4 (br s, 3 H), 4.7 (s, 1 H). The crystals were dissolved in toluene and evaporated in vacuo (4×) to yield a yellow oil: 4.2 g (75%); ^{1}H NMR ($CDCl_3$) 1.3 (t, 3 H), 3.9 (s, 3 H, *Z* isomer), 4.2 (s, 3 H, *E* isomer), 4.2 (q, 2 H, both isomers), 7.1 (s, 1 H, *Z* isomer), 7.2 (s, 1 H, *E* isomer); IR (CCl_4) 3000–2800 (s), 1750–1700 (vs), 1400–1300 (s), 1200–1100 (vs). A 3.5:1 ratio of E/Z isomers was obtained.

Phenylisoxazolidines 5a,b. Thermal Conditions. α-Phenyl-*N*-methylnitrone (1; 1.00 g, 7.4 mmol) was dissolved in an excess of freshly distilled ethyl vinyl ether (25.0 mL, 161 mmol), and the solution was placed in a thick-walled glass reaction tube and sealed. The tube was heated at 80 °C for 72 h. After cooling, excess vinyl ether was removed by evaporation under high vacuum. The resulting reaction mixture was chromatographed (CH_2Cl_2) to remove unreacted nitrone followed by bulb-to-bulb distillation at 145 °C (1 mm) to give a yellow oil (1.19 g, 78%). On the basis of GC (SE-30 column/140 °C) and NMR analysis, the reaction mixture contained a 50:50 mixture of cis/trans isomers (**5a**/**5b**) (retention times of 4.0 and 5.4 min, respectively). The isomers were separated by column chromatography (120 g; 10:1 hexane/EtOAc). The isomer with the higher R_f was the cis isomer (**5a**) while the isomer with the lower R_f was the trans isomer (**5b**). Cis isomer: clear oil; ^{1}H NMR ($CDCl_3$) 1.25 (t, 3 H, J = 7 Hz), 2.32 (ddd, 1 H, J = 3, 10, 13 Hz), 2.55 (s, 3 H), 2.86 (ddd, 1 H, J = 6, 10, 13 Hz), 3.34 (t, 1 H, J = 10 Hz), 3.45 (dq, 1 H, J = 7, 14 Hz), 3.93 (dq, 1 H, J = 7, 14 Hz), 5.15 (dd, 1 H, J = 3, 6 Hz), 7.33 (m, 5 H)[18]; IR (CCl_4) 3100–3000 (m), 3000–2800 (vs), 1455 (s), 1370 (s), 1100 (vs); mass spectrum, m/z (relative intensity) 207 (M^+, 4), 161 (36), 118 (100), 77 (75). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; H, 6.76. Found: C, 69.44; H, 8.10; H, 6.69).[19] Trans isomer: clear oil; ^{1}H NMR ($CDCl_3$) 1.23 (t, 3 H, J = 7 Hz), 2.41 (ddd, 1 H, J = 5, 9, 13 Hz), 2.57 (ddd, 1 H, J = 1, 6, 13 Hz), 2.78 (s, 3 H), 3.48 (dq, 1 H, J = 7, 10 Hz), 3.86 (dq, 1 H, J = 7, 10 Hz), 4.03 (dd, 1 H, J = 6, 9 Hz), 5.16 (d, 1 H, J = 5 Hz), 7.30 (m, 5 H);[18] IR (CCl_4) 3100–3000 (m), 3000–2800 (vs), 1455 (s), 1370 (s), 1100 (vs); mass spectrum, m/z (relative intensity) 207 (M^+, 9), 161 (100), 134 (63), 118 (53), 77 (48). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.37; H, 8.10; N, 6.77.[19]

Scheme III[a]



11 12

[a] a, α-H at C-3; b, β-H at C-3.

Isoxazolidines 7a,b. Thermal Conditions. A toluene solution of nitrone **1** (0.406 g, 3.0 mmol) and vinylidene carbonate (0.386 g, 4.5 mmol) was heated at reflux for 72 h. Evaporation of the solvent and chromatography of the resulting brown residue gave **7a**/**7b** (1:1) in 51% yield. Cis isomer (**7a**): mp 116–118 °C; ^{1}H NMR ($CDCl_3$) 271 (s, 3 H), 3.58 (d, J = 4 Hz, 1 H), 5.20 (dd, J = 4, 5 Hz, 1 H), 6.20 (d, J = 5 Hz, 1 H), 7.2–7.5 (m, 5 H); IR (CH_2Cl_2) 3060–2850 (m), 1800 (s), 1480 (m), 1450 (m), 1370 (m), 1170 (s), 1110 (s), 1080 (s), 1070 (s), 760 (s), 700 (s). Trans isomer (**7b**): oil; ^{1}H NMR ($CDCl_3$) 2.49 (s, 3 H), 4.34 (s, 1 H), 5.31 (d, J = 5.5 Hz, 1 H), 6.19 (d, J = 5.5 Hz, 1 H), 7.0–7.3 (m, 5 H); IR (CH_2Cl_2) 3050–2850 (m), 1805 (s), 1590 (m), 1455 (m), 1380 (m), 1320 (m), 1175 (s), 1090 (s), 1000 (s); mass spectrum, m/z (relative intensity) 221 (M^+, 35), 134 (71), 131 (74), 118 (100), 103 (32), 91 (72), 77 (76).

Methylisoxazolidines 8a,b. Thermal Conditions. By use of the procedure described above, isoxazolidines **8a**/**8b** were prepared from α-methyl-*N*-ethylnitrone (**2**; 0.190 g, 2.2 mmol) and ethyl vinyl ether (15.0 mL, 96.6 mmol). After a standard workup and chromatography, **8** was obtained as a yellow oil (0.14 g, 42%). On the basis of GC (OV-101/110 °C) and NMR analysis the product contained a 2:1 mixture of isomers (retention times: 3.5 min for major isomer, 3.9 min for minor isomer). PLC separation of the isomers (2.0-mm plate, 5:1 hexane/EtOAc, four elutions) gave the cis isomer (major): ^{1}H NMR ($CDCl_3$) 1.23 (m, 9 H), 1.63 (m, 1 H), 1.90 (m, 1 H), 2.59 (m, 2 H), 2.96 (m, 1 H), 3.47 (m, 1 H), 5.08 (m, 1 H);[18] IR (CCl_4) 3000–2800 (vs), 1450–1400 (s), 1250 (vs), 1100–1000 (vs). Trans isomer (minor): ^{1}H NMR ($CDCl_3$) 1.26 (m, 9 H), 1.67 (m, 2 H), 2.34 (m, 2 H), 2.94 (m, 1 H), 3.46 (m, 1 H), 3.74 (m, 1 H), 5.12 (d, 1 H);[18] IR (CCl_4) 3000–2800 (s), 1450–1400 (m), 1250 (vs), 1100–1000 (vs).

Attempted Preparation of Isoxazolidine 10 under Thermal Conditions. Nitrone **9** (2.5 g, 29.4 mmol) was dissolved in 25.0 mL of ethyl vinyl ether (**3**), and the solution was heated in a sealed tube at 80 °C for 24 h. Polymerization ensued, and no low molecular weight material could be obtained.

(Carboethoxy)isoxazolidine (12b). Thermal Conditions. By use of the procedure above, isoxazolidine **12b** was prepared from α-(carboethoxy)-*N*-methylnitrone **11** (0.70 g, 5.3 mmol) and ethyl vinyl ether (25 mL, 161 mmol) (Scheme III). Flash chromatography and bulb-to-bulb distillation of the reaction mixture

(22) Boyle, L.; Peagram, M.; Whitham, C. *J. Chem. Soc. B* **1971**, 1728–1731.

(23) Brown, R. F. C.; Clark, V. M.; Todd, A. *Proc. Chem. Soc., London* **1957**, 97. Thesing, J; Maya, H. *Chem. Ber.* **1956**, *89*, 2159.

[115 °C (1 mm)] gave isoxazolidine **12** as a yellow oil (1.06 g, 92%). On the basis of GC (OV-101/130 °C) and NMR analysis the product consisted of one isomer (retention time 3.4 min) which was assigned the trans configuration (**12b**): ^{1}H NMR ($CDCl_3$) 1.21 (t, 3 H, J = 7 Hz), 1.29 (t, 3 H, J = 7 Hz), 2.55 (dd, 1 H, J = 8, 8 Hz), 2.71 (ddd, 1 H, J = 5, 8, 8 Hz), 2.95 (s, 3 H), 3.48 (dq, 1 H, J = 7, 10 Hz), 3.75 (dd, 1 H, J = 8, 8 Hz), 3.81 (dq, 1 H, J = 7, 10 Hz), 4.21 (q, 2 H, J = 7 Hz), 5.20 (d, 1 H, J = 5 Hz);[18] IR (CCl_4) 3000–2800 (s), 1750–1700 (vs), 1450–1400 (s), 1200–1150 (vs), 1100–1000 (vs); mass spectrum, m/z (relative intensity) 203 (M^+, 5), 157 (5), 130 (100), 102 (17), 84 (24).

General Procedure for High-Pressure Reaction of Nitrones and Ethyl Vinyl Ether (3). A solution of the nitrone in ethyl vinyl ether (~0.3 M) was sealed in Teflon tubing and placed in the high-pressure autoclave. The reaction vessel was pressurized and heated (when required). After the autoclave was cooled (where appropriate), the pressure was relieved, and the vessel was removed. Purification and analysis of the product mixture was accomplished as outlined above. Cycloadducts **5ab**, **8a**, **8b**, **10**, and **12b** were obtained from the respective nitrones in the yields described in the Table.

Isoxazolidines 7a,b. High-Pressure Conditions. A solution of nitrone **1** (0.102 g, 0.75 mmol) and vinylidene carbonate (0.130 g, 1.5 mmol) in 5 mL of CH_2Cl_2 was sealed in teflon Tubing and pressurized to 2000 kbar for 48 h. Purification of the reaction mixture by column chromatography (CH_2Cl_2) yielded isoxazolidine **7a** (17%), isoxazolidine **7b** (33%), and unreacted nitrone **1** (40%), respectively.

Acknowledgment. This research was generously supported by the Naval Sea Systems Command under contract with The Pennsylvania State University, Applied Research Laboratory, and the donors of the Petroleum Research Fund, administered by the American Chemical Society. We also acknowledge the support of Dr. William White and Judy Garland, who have made the facilities of the Materials Research High Pressure Laboratory available to us, Dr. R. Minard for mass spectra, and Alan Freyer for FT NMR spectra. Partial support for the purchase of a Bruker WP-200 from the National Science Foundation is also gratefully acknowledged. Helpful discussions with Joe Perez are also acknowledged.

Registry No. 1, 81206-51-1; (*E*)-**2**, 81206-52-2; (*Z*)-**2**, 81206-53-3; **3**, 109-92-2; **4**, 872-36-6; **5a**, 81206-54-4; **5b**, 81206-55-5; **7a**, 81206-56-6; **7b**, 81244-92-0; **8a**, 81206-57-7; **8b**, 81206-58-8; **9**, 24423-88-9; **10**, 81206-59-9; (*E*)-**11**, 81206-60-2; (*Z*)-**11**, 81206-61-3; **12b**, 81206-62-4; benzaldehyde, 100-52-7; *N*-methylhydroxylamine hydrochloride, 4229-44-1; *N*,*N*-diethylhydroxylamine, 3710-84-7; *N*-hydroxypyrrolidine, 5904-62-1.

Diels–Alder Reactions of (Trifluoromethyl)ethene and (Trifluoromethyl)styrenes with Functionalized Butadienes

Iwao Ojima,* Momoko Yatabe, and Takamasa Fuchikami

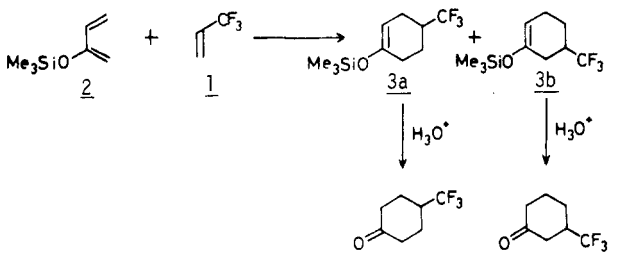
Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan

Received September 25, 1981

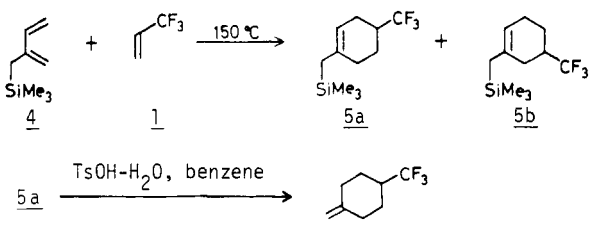
The Diels–Alder reactions of (trifluoromethyl)ethene (**1**) with 2-(trimethylsiloxy)buta-1,3-diene (**2**), 2-[(trimethylsilyl)methyl]-1,3-butadiene (**4**), and 1-methoxy-3-(trimethylsiloxy)buta-1,3-diene (**6**) were carried out to give the corresponding [4 + 2] cycloadducts in 17–38% yields. It was found that the former two cycloadducts were a mixture of para (major) and meta (minor) isomers, while the latter was the para isomer exclusively. Similarly, β-(trifluoromethyl)-4-(methoxycarbonyl)styrene (**9**) and β-(trifluoromethyl)-4-nitrostyrene (**10**) were allowed to react with **4** and **6**, giving the corresponding [4 + 2] cycloadducts in 56–90% yields. The regioselectivity of the reaction on using **6** as the diene turned out to be extremely high, leading to the formation of only one regioisomer. The substituent effect of the trifluoromethyl group in the Diels–Alder reaction in terms of regioselectivity is discussed.

Recently, it has been shown that the introduction of a trifluoromethyl group into a biologically active compound often brings about unique physiological activities.[1] For introduction of the trifluoromethyl group into a carbon skeleton, trifluoromethylation,[2] direct fluorination,[3] and halogen exchange reactions[4] are possible methods. However, such methods are sometimes accompanied by low reactivity and low selectivity. On the other hand, the use of a proper building block which already has the trifluoromethyl group in it is another promising approach. From this point of view, we chose (trifluoromethyl)ethene and (trifluoromethyl)styrenes as fundamental building blocks and dienophiles for Diels–Alder reaction in the present study. Although only one report described the Diels–Alder reaction of (trifluoromethyl)ethene (**1**), the dienes employed in the reaction were restricted to symmetrical dienes, i.e., cyclopentadiene, butadiene, and anthracene.[5] In order to look at the regioselectivity of the

Scheme I



Scheme II



(1) For example: (a) Smith, F. A. CHEMTECH **1973**, 422. Filler, R. *Ibid.* **1974**, 752. (b) Lin, T.-S.; Chai, C.; Prusoff, W. H. *J. Med. Chem.* **1976**, *19*, 915.

(2) For example: (a) Haszeldine, R. N.; Mir, I.-D.; Tipping, A. E.; Wilson, A. G. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1170. (b) McLoughlin, V. C. R.; Thrower, J. *Tetrahedron* **1969**, *25*, 5921. (c) Kobayashi, Y.; Kumadaki, I. *Tetrahedron Lett.* **1969**, 4095.

(3) For example: (a) Tyczkowski, E. A.; Bigelow, L. A. *J. Am. Chem. Soc.* **1955**, *77*, 3007. (b) Attaway, J. A.; Groth, R. H.; Bigelow, L. A. *Ibid.* **1959**, *81*, 3599.

(4) For example: (a) Henne, A. L.; Hinkamp, J. B. *J. Am. Chem. Soc.* **1945**, *67*, 1197. (b) Yagupol'skii, L. M.; Marents, M. S. *Zh. Obshch. Khim.* **1954**, *24*, 887; *Chem. Abstr.* **1955**, *49*, 8172*d*.

0022-3263/82/1947-2051$01.25/0