Table III. Proton Magnetic Resonance Peaks of Hydrazones V and VII in DMSO-d_6

compd	R	peaks (δ) CH=N	OH	NH	R
V	CH_3	8.30	11.15	12.20	2.01, 2.20[a]
	C_6H_5	8.60	11.25	12.03	
	p-HO-C_6H_4	8.55	11.27	11.80	10.13 (OH)
	p-$CH_3C_6H_4$	8.57	11.27	11.92	2.37 (CH_3)
	p-O_2N-C_6H_4[b]	8.37			
	p-H_2N-C_6H_4	8.55	11.50	11.68	5.78 (NH_2)
	p-t-C_4H_9-C_6H_4	8.63	11.38	12.00	1.33 (t-Bu)
	p-CH_3O-C_6H_4	8.67	11.48	12.00	3.88 (OCH_3)
	m-Cl-C_6H_4	8.62	11.18	12.08	
	m-F-C_6H_4	8.67	11.23	12.10	
	m-Br-C_6H_4	8.60	11.17	12.08	
	4-C_5H_4N	8.68	11.15	12.20	8.78 (2H, pyridyl)
	2-C_4H_3O	8.60	11.50		
	2-C_4H_3S	8.60	11.13	11.98	
VII	C_6H_5	9.45	12.10	12.73	
	p-HO-C_6H_4	9.50	12.00	12.93	10.30 (OH)

[a] Two singlet peaks integrate to three H, indicating compound to be mixture of geometrical isomers. [b] Solvent: trifluoroacetic acid-d.

and to this was added a solution of pyridoxal hydrochloride (2.04 g, 0.01 mol) and anhydrous sodium acetate (0.90 g, 0.11 mol) in water (100 mL). The mixture was boiled under reflux for 30 min, cooled, and filtered. The solid hydrazone was washed in the filter with water and dried in a vacuum desiccator overnight. The hydrazone was essentially pure, neither melting point nor NMR spectrum showing any change when the compound was recrystallized from 95% ethanol.

B. From Salicylaldehyde or 2-Hydroxy-1-naphthaldehyde. A solution of the aldehyde (1.22 g, 0.01 mol) and acetic acid (2 mL) in 95% ethanol (50 mL) was added to a solution of the acylhydrazide (0.01 mol) in 50% aqueous ethanol (125 mL). The mixture was boiled under reflux, concentrated, cooled, and filtered, and the solid hydrazone dried for 3 days in a vacuum desiccator. The melting point and NMR spectrum of the hydrazone were not altered by recrystallization from 95% ethanol.

Registry No. I·HCl, 65-22-5; II (R = CH_3), 15871-96-2; II (R = C_6H_5), 72343-06-7; II (R = p-HO-C_6H_4), 116324-84-6; II (R = p-CH_3-C_6H_4), 116324-85-7; II (R = p-O_2N-C_6H_4), 116324-86-8; II (R = p-H_2N-C_6H_4), 116324-87-9; II (R = p-t-C_4H_9-C_6H_4), 116324-88-0; II (R = p-CH_3O-C_6H_4), 116324-89-1; II (R = m-Cl-C_6H_4), 116324-90-4; II (R = m-F-C_6H_4), 116324-91-5; II (R = m-Br-C_6H_4), 116324-92-6; II (R = 4-C_5H_4N), 737-86-0; II (R = 2-C_4H_3O), 105402-29-7; II (R = 2-C_4H_3S), 96712-66-2; IV, 90-02-8; V (R = CH_3), 5941-05-9; V (R = C_6H_5), 3232-37-9; V (R = p-HO-C_6H_4), 82859-76-5; V (R = p-CH_3-C_6H_4), 82859-74-3; V (R = p-O_2N-C_6H_4), 50366-20-6; V (R = p-H_2N-C_6H_4), 50366-22-8; V (R = p-t-C_4H_9-C_6H_4), 82859-75-4; V (R = p-CH_3O-C_6H_4, 100969-61-7; V (R = m-Cl-C_6H_4), 116324-93-7; V (R = m-F-C_6H_4), 116324-94-8; V (R = m-Br-C_6H_4), 116324-95-9; V (R = 4-C_5H_4N), 495-84-1; V (R = 2-C_4H_3O), 92982-43-9; V (R = 2-C_4H_3S), 96818-57-4; VI, 708-06-5; VII (R = CH_3), 34334-87-7; VII (R = C_6H_5), 15017-21-7; VII (R = p-HO-C_6H_4), 69733-97-7; VII (R = p-CH_3-C_6H_4), 82859-80-1; VII (R = p-O_2N-C_6H_4), 95523-63-0; VII (R = p-H_2N-C_6H_4), 116324-96-0; VII (R = p-t-C_4H_9-C_6H_4), 68758-85-0; VII (R = p-CH_3O-C_6H_4), 40111-51-1; VII (R = m-Cl-C_6H_4), 116324-97-1; VII (R = m-F-C_6H_4), 116324-98-2; VII (R = m-Br-C_6H_4), 116324-99-3; VII (R = 4-C_5H_4N), 796-42-9; VII (R = 2-C_4H_3O), 60947-25-3; VII (R = 2-C_4H_3S), 116325-00-9; $CH_3CONHNH_2$, 1068-57-1; $C_6H_5CONHNH_2$, 613-94-5; p-HO-$C_6H_4CONHNH_2$, 5351-23-5; p-CH_3-$C_6H_4CONHNH_2$, 3619-22-5; p-O_2N-$C_6H_4CONHNH_2$, 636-97-5; p-H_2N-$C_6H_4CONHNH_2$, 5351-17-7; p-t-C_4H_9-$C_6H_4CONHNH_2$, 43100-38-5; p-CH_3O-$C_6H_4CONHNH_2$, 3290-99-1; m-Cl-$C_6H_4CONHNH_2$, 1673-47-8; m-F-$C_6H_4CONHNH_2$, 499-55-8; m-Br-$C_6H_4CONHNH_2$, 39115-96-3; 4-$C_5H_4NCONHNH_2$, 54-85-3; 2-$C_4H_3OCONHNH_2$, 3326-71-4; 2-$C_4H_3SCONHNH_2$, 2361-27-5; Fe, 7439-89-6.

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Supplementary Material Available: Elemental analyses (C, H, N) for all compounds (3 pages). Ordering information given on any current masthead page.

Cycloaddition Reactions of 2,4,6-Trimethoxybenzonitrile Oxide with Disubstituted Acetylenes. 3

Sultan T. Abu-Orabi,* Ibrahim Jibril, Reham Obiedat, and Lina Hatamleh

Chemistry Department, Yarmouk University, Irbid, Jordan

Cycloaddition reactions of 2,4,6-trimethoxybenzonitrile oxide with dimethyl acetylenedicarboxylate, diethyl acetylenedicarboxylate, di-*tert*-butyl acetylenedicarboxylate, and diphenylacetylene were used for the synthesis of polyfunctional isoxazole ring systems.

One of the most general methods for the preparation of various isoxazole and 2-isoxazoline derivatives is the cycloaddition reaction of nitrile oxide with substituted acetylenes (*3–7*) and substituted ethylenes (*8–10*), respectively. In connection with our continuing interest in the synthesis of polyfunctional heterocyclic compounds such as isoxazole and 2-isoxazolines (*1*, *2*), we have examined herein the cycloaddition reactions of 2,4,6-trimethoxybenzonitrile oxide (**1**) with disubstituted acetylenes which provide polyfunctional isoxazoles as shown in Scheme I. This type of synthesis is the first example using a benzonitrile oxide bearing a substitutent more

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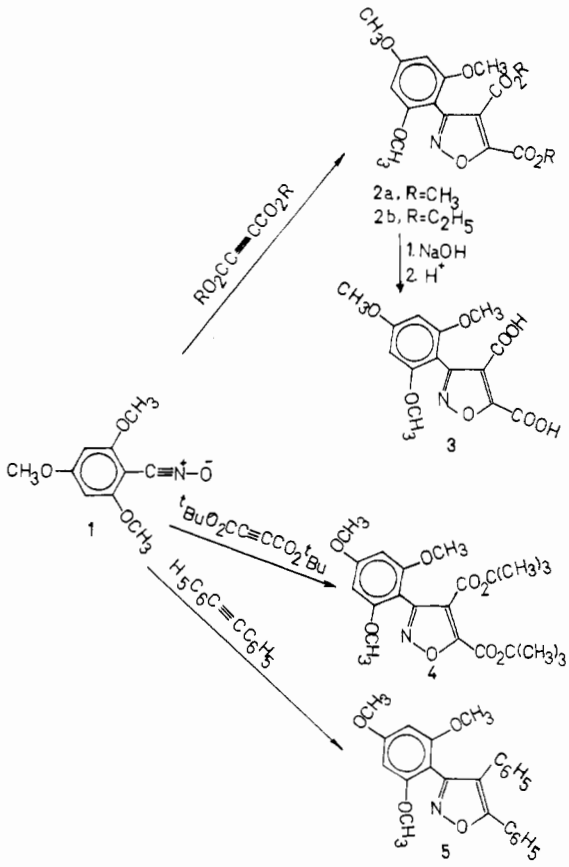
Scheme I



activating than the methyl group.

Experimental Section

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Pye-Unicam SP 3-300 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Bruker WP 80 SY spectrometer using tetramethylsilane as an internal standard and shifts (δ) are reported in ppm. Mass spectra data were obtained by using VG Analytical 7070 E organic mass spectrometer operating at an ionizing voltage of 70 eV. Elemental analysis were performed at M-H-W Laboratories, Phoenix, AZ. 2,4,6-Trimethoxybenzonitrile oxide was prepared according to the method reported by Grundmann (*11*).

Preparation of Dimethyl 3-(2,4,6-Trimethoxyphenyl)-4,5-Isoxazoledicarboxylate (2a). To a solution of 3.15 g (15 mmol) of freshly prepared 2,4,6-trimethoxybenzonitrile oxide in 50 mL of tetrahydrofuran was added 2.15 g (15 mmol) of dimethyl acetylenedicarboxylate. The resulting mixture was heated under reflux for 4 h. After removal of the solvent, the residue was recrystallized from methanol–petroleum ether to give 4.10 g (78%) of **2a**, mp 119–120 °C; ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 6 H), 3.75 (s, 3 H), 3.85 (s, 3 H), 4.0 (s, 3 H), 6.17 (s, 2 H); IR (NaBr) 1735 cm^{-1} (C=O); *m/e* 352 ($M^+ + 1$, 18), 351 (M^+ for $C_{16}H_{17}NO_8$, 96), 292 ($M^+-CO_2CH_3$, 100), 233 ($M^+-2CO_2CH_3$, 46), 209 ($M^+-CH_3O_2CC{\equiv}CCO_2CH_3$, 25).

Diethyl 3-(2,4,6-Trimethoxyphenyl)-4,5-Isoxazoledicarboxylate (2b). To a solution of 2.5 g (12 mmol) of 2,4,6-trimethoxybenzonitrile oxide in 40 mL of tetrahydrofuran was added 2.04 g (12 mmol) of diethyl acetylenedicarboxylate. The resulting mixture was heated under reflux for 4 h. After removal of the solvent, the residue was recrystallized from methanol–petroleum ether to give 3.65 g (81%) of **2b**, mp 75–77 °C; ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 3 H J = 7 Hz), 1.42 (t, 3 H, J = 7 Hz), 3.73 (s, 6 H), 3.85 (s, 3 H), 4.20 (q, 2 H, J = 7 Hz), 4.46 (q, 2 H, J = 7 Hz), 6.17 (s, 2 H); IR (NaBr) 1715 cm^{-1} (C=O); *m/e* 380 (M^++1, 10), 379 (M^+ for $C_{18}H_{21}NO_8$, 49), 306 ($M^+-CO_2CH_3$, 100), 233 ($M^+-2CO_2C_2H_5$, 23), 209 ($M^+-C_2H_5O_2CC{\equiv}CCO_2C_2H_5$, 2).

3-(2,4,6-Trimethoxyphenyl)-4,5-Isoxazoledicarboxylic Acid (3). A solution of 10 mmol of **2a** or **2b** in 50 mL of 15% NaOH solution was heated under reflux for 4 h. The solution was acidified with diluted HCl solution then extracted with diethyl ether and dried over anhydrous $CaCl_2$. After removal of the ether, the product was recrystallized from water to give 2.80 g (87%) of product **3**, mp 134–136 °C; ^{1}H NMR (DMSO-d_6) δ 3.68 (s, 6 H), 3.84 (s, 3 H), 6.31 (s, 2 H), 12.96 (s, 2 H); *m/e* 324 (M^+ + 1, 1), 279 (M^+-CO_2, 24), 235 (M^+-2CO_2, 39), 209 (M^+–HOOCC≡CCOOH, 100).

Di-tert-butyl 3-(2,4,6-Trimethoxyphenyl)-4,5-Isoxazoledicarboxylate (4). To a solution of 3.15 g (15 mmol) of 2,4,6-trimethoxybenzonitrile oxide in 50 mL of tetrahydrofuran was added 3.4 g (15 mmol) of di-*tert*-butyl acetylenedicarboxylate. The resulting mixture was heated under reflux for 5 h. After removal of the solvent, the residue was recrystallized from methanol–petroleum ether to yield 4.6 (70%) of **4**, mp 120–121 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9 H), 1.61 (s, 9 H), 3.73 (s, 6 H), 3.85 (s, 3 H), 6.17 (s, 2 H); IR (NaBr) 1720 cm^{-1} (C=O); *m/e* 436 (M^+ + 1, 16), 435 (M^+ for $C_{22}H_{29}NO_8$, 63), 379 ($M^+-C_4H_9$, 13), 323 ($M^+-2C_4H_9$, 97), 278 ($M^+-CO_2C_4H_9-C_4H_9$, 43), 234 ($M^+-2CO_2C_4H_9$, 37), 209 ($M^+-C_4H_9O_2CC{\equiv}CCO_2C_4H_9$, 25), 57 ($C_4H_9^+$, 100).

3-(2,4,6-Trimethoxyphenyl)-4,5-diphenylisoxazole (5). To a solution of 3.55 g (17 mmol) of 2,4,6-trimethoxybenzonitrile oxide in 50 mL of tetrahydrofuran was added 3.05 g (17 mmol) of diphenylacetylene. The resulting mixture was heated under reflux for 7 h. After removal of the solvent, the product was recrystallized from methanol–petroleum ether to produce 3.9 g (59%) of product **5**, mp 140–142 °C; ^{1}H NMR ($CDCl_3$) δ 3.58 (s, 6 H), 3.78 (s, 3 H), 6.08 (s, 2 H), 7.20–7.56 (m, 10 H); *m/e* 388 (M^+ + 1, 3), 387 (M^+ for $C_{24}H_{21}NO_4$, 49), 310 ($M^+-C_6H_5$, 100), 233 ($M^+-2C_6H_5$, 71), 209 ($M^+-C_6H_5C{\equiv}CC_6H_5$, 14).

Elemental analyses (C, H, N) for compounds **2a–5** in agreement with theoretical values were obtained and submitted for review.

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Registry No. **1**, 2904-59-8; **2a**, 115914-38-0; **2b**, 115914-39-1; **3**, 115914-40-4; **4**, 115914-41-5; **5**, 115914-42-6; $CH_3O_2CC{\equiv}CCO_2CH_3$, 762-42-5; $C_2C_5O_2CC{\equiv}CCO_2C_2H_5$, 762-21-0; t-$BuO_2CC{\equiv}CCO_2$-t-Bu, 66086-33-7; $C_6H_5C{\equiv}CC_6H_5$, 501-65-5.

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