1,5-Dipolar Cycloaddition Reactions. Semicarbazone Bromides, 5-Alkyl (or aryl)amino-1,3,4-oxadiazole-2-carboxylic Acids and their Esters

Ciuseppe Werber, Francesco Buccheri, Renato Noto and Manlio Gentile

Istituto di Chimica Organica, Facoltà di Scienze dell'Università, Via Archirafi 20, Palermo, Italy

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The synthesis of the title compounds from semicarbazones of glyoxylic ester is reported.

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In connection with our studies on the decarboxylation of 5-amino-1,3,4-oxadiazole-2-carboxylic acid (1) and of 5-amino-1,3,4-thiadiazole-2-carboxylic acid (2) we have in progress the rate measurements of hydrolysis of some esters of 5-amino-1,3,4-oxadiazoles-2-carboxylic acids *N*-substituted and of decarboxylation of the corresponding acids to gain information on the effects of the *N*-substitution on the reaction rates. We also intend to undertake a kinetic investigation of the cyclization reaction of semicarbazonic bromides **2a-d** to esters **3a-d**.

In this paper we report the synthesis of the compounds **2a-d**, **3a-d**, **4a-d**, **5a-d** and **6a-d**, necessary to our kinetic studies through 1-5 cycloaddition reaction. Compounds **3a-d** have been synthesized by treating the corresponding substituted semicarbazones **1a-d** with the bromine-sodium acetate reagent. Operating at room temperature we have been able to obtain the intermediate semicarbazone bromides (**2a-d**), which by the action of triethylamine furnished the required esters **3a-d** (see Scheme I). The semicarbazones **1a-d** gave with the above mentioned reagent directly **3a-d** by refluxing. The esters **3a-d** by hydrolysis with sodium hydroxide furnished the acids **4a-d**. These are rather unstable as they easily undergo decarboxylation on standing at room temperature, yielding the corresponding 1,3,4-oxadiazoles **5a-d**. However, when reacted with diazomethane in diethyl ether, as they are isolated, one readily obtains the corresponding methyl esters **6a-d**, which in turn can be hydrolyzed giving acids **4a-d** or decarboxylation products **5a-d**.

The proposed structures are supported by elemental analyses and spectral data (nmr) (3).

EXPERIMENTAL

All melting points (Kofler) are uncorrected. Ir spectra (nujol mull) were obtained with a Perkin-Elmer Infracord 137 Spectrophotometer, nmr spectra were recorded on a Jeol C-60 H Spectrometer (TMS as internal reference).

General Procedure of Preparation of Semicarbazones **1a-d**.

To 0.02 mole of the appropriate semicarbazide dissolved in water (for the 4,4-diphenylsemicarbazide ethanol-water 1:1 was employed) was added 0.03 mole of ethyl glyoxylate. After standing ten hours, the resulting precipitate was removed by filtration, dried and recrystallized from the solvent indicated in Table I.

General Procedure of Preparation of Semicarbazonic Bromides **2a-d**.

To a solution or suspension of the appropriate semicarbazone (0.01227 mole) in 17.5 ml. of acetic acid, at room temperature (for **2b** at 0°), were added 4 g. of anhydrous sodium acetate and, dropwise and with stirring, a cooled solution of bromine (0.01282 mole in 6 ml. of acetic acid). The reaction mixture was allowed to stand at room temperature for 1 hour (for **2b** at 0°) and then diluted with water. For **2a** and **2b**, the solution was extracted

SCHEME I

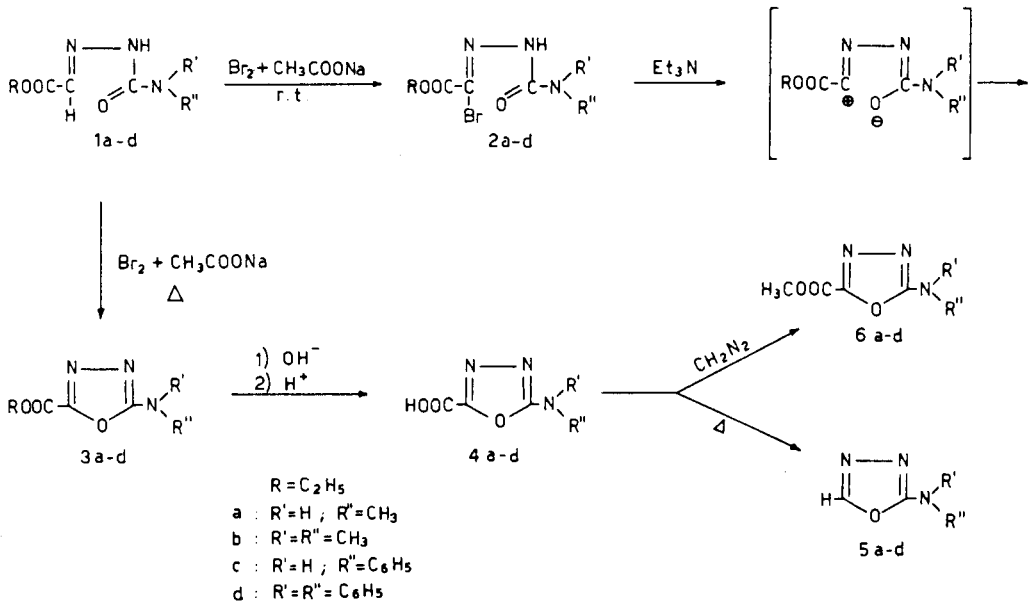

Table I

Physical Data

Compound	Yield %	M.p. (solvent) or b.p.	Formula	Analyses			
1a	86	167-168 (water)	$C_6H_{11}N_3O_3$	Calcd.:	C, 41.61;	H, 6.40;	N, 24.27
				Found:	C, 41.73;	H, 6.53;	N, 24.35
1b	92	162-163 (ethyl/ acetate)	$C_7H_{13}N_3O_3$	Calcd.:	C, 44.91;	H, 7.00;	N, 22.45
				Found:	C, 44.62;	H, 7.23;	N, 22.71
1c	91	177-178 (ethanol) (a)	$C_{11}H_{13}N_3O_3$	Calcd.:	C, 56.16;	H, 5.57;	N, 17.86
				Found:	C, 56.52;	H, 5.87;	N, 17.80
1d	90	206-207 (ethanol)	$C_{17}H_{17}N_3O_3$	Calcd.:	C, 65.58;	H, 5.50;	N, 13.50
				Found:	C, 65.80;	H, 5.51;	N, 13.72
2a	82	133-134 (carbon/ tetrachloride)	$C_6H_{10}BrN_3O_3$	Calcd.:	C, 28.59;	H, 4.00;	N, 16.67; Br, 31.70
				Found:	C, 28.40;	H, 3.94;	N, 16.75; Br, 31.80
2b	62	117-119 (benzene)	$C_7H_{12}BrN_3O_3$	Calcd.:	C, 31.59;	H, 4.54;	N, 15.79; Br, 30.03
				Found:	C, 31.50;	H, 4.48;	N, 15.63; Br, 29.84
2c	98	169-170 (ethanol)	$C_{11}H_{12}BrN_3O_3$	Calcd.:	C, 42.05;	H, 3.85;	N, 13.38; Br, 25.44
				Found:	C, 42.08;	H, 3.90;	N, 13.55; Br, 25.68
2d	97	163-165 (benzene)	$C_{17}H_{16}BrN_3O_3$	Calcd.:	C, 52.32;	H, 4.13;	N, 10.77; Br, 20.48
				Found:	C, 52.47;	H, 4.05;	N, 10.90; Br, 20.29
3a	84	160-161 (benzene)	$C_6H_9N_3O_3$	Calcd.:	C, 42.10;	H, 5.30;	N, 24.55
				Found:	C, 42.16;	H, 5.45;	N, 24.45
3b	88	141 (1.6 mm Hg)	$C_7H_{11}N_3O_3$	Calcd.:	C, 45.40;	H, 5.99;	N, 22.69
				Found:	C, 45.59;	H, 5.91;	N, 22.76
3c	91	164-165 (ethyl/ acetate)	$C_{11}H_{11}N_3O_3$	Calcd.:	C, 56.65;	H, 4.75;	N, 18.02
				Found:	C, 56.76;	H, 5.02;	N, 18.13
3d	74	146-148 (benzene/ ligroin)	$C_{17}H_{15}N_3O_3$	Calcd.:	C, 66.01;	H, 4.89;	N, 13.59
				Found:	C, 65.85;	H, 4.96;	N, 13.71
4a	91	93 dec ($NaHCO_3$/ HCl 1:1)	$C_4H_5N_3O_3$	Calcd.:	C, 33.57;	H, 3.52;	N, 29.37
				Found:	C, 33.65;	H, 3.66;	N, 29.35
4b	63	75 dec ($NaHCO_3$/ HCl 1:1)	$C_5H_7N_3O_3$	Calcd.:	C, 38.22;	H, 4.49;	N, 26.74
				Found:	C, 37.84;	H, 4.15;	N, 26.95
4c	74	64-66 dec ($NaHCO_3$/ HCl 1:1)	$C_9H_7N_3O_3$	Calcd.:	C, 52.68;	H, 3.44;	N, 20.48
				Found:	C, 52.40;	H, 3.25;	N, 20.50
4d	94	73 dec ($NaHCO_3$/ HCl 1:1)	$C_{15}H_{11}N_3O_3$	Calcd.:	C, 64.05;	H, 3.94;	N, 14.94
				Found:	C, 63.78;	H, 4.15;	N, 15.00
5a	70	71-72 (ligroin)	$C_3H_5N_3O$	Calcd.:	C, 36.36;	H, 5.09;	N, 42.41
				Found:	C, 36.43;	H, 5.05;	N, 42.58
5b	84	98-99 (1.6 mm Hg)	$C_4H_7N_3O$	Calcd.:	C, 42.47;	H, 6.24;	N, 37.15
				Found:	C, 42.50;	H, 6.12;	N, 37.35
5c	68	153-154 (ethanol/ water) (b)	$C_8H_7N_3O$	Calcd.:	C, 59.62;	H, 4.38;	N, 26.07
				Found:	C, 59.70;	H, 4.41;	N, 26.27
5d	92	122-123 (ethanol/ water)	$C_{14}H_{11}N_3O$	Calcd.:	C, 70.87;	H, 4.67;	N, 17.71
				Found:	C, 70.90;	H, 4.70;	N, 17.54
6a	75	211-213 (ethanol)	$C_5H_7N_3O_3$	Calcd.:	C, 38.22;	H, 4.49;	N, 26.74
				Found:	C, 37.98;	H, 4.35;	N, 26.70
6b	88	93-95 (benzene/ ligroin)	$C_6H_9N_3O_3$	Calcd.:	C, 42.10;	H, 5.30;	N, 24.55
				Found:	C, 41.96;	H, 5.20;	N, 24.60
6c	90	231-233 (ethanol)	$C_{10}H_9N_3O_3$	Calcd.:	C, 54.79;	H, 4.14;	N, 19.17
				Found:	C, 54.85;	H, 4.30;	N, 19.06
6d	94	168-169 (ethanol)	$C_{16}H_{13}N_3O_3$	Calcd.:	C, 65.08;	H, 4.44;	N, 14.23
				Found:	C, 65.20;	H, 4.29;	N, 14.20

(a) In reference 4 a m.p. of 176° was reported. (b) In reference 5 a m.p. of 152-153° was reported.

Table II

Proton Magnetic Resonance Parameters

Compound	Solvent	Chemical Shift, ppm δ
1a	Deuteriochloroform	1.34 (t, 3H, J = 7.1 Hz, O-CH_2-CH_3), 2.92 (d, 3H, J = 4.7 Hz, NH-CH_3), 4.29 (q, 2H, J = 7.1 Hz, O-CH_2-CH_3), 6.44 (br s, 1H, *NH*-CH_3), 7.27 (s, 1H, CH), 11.13 (br s, 1H, NH)
1b	Deuteriochloroform	1.28 (t, 3H, J = 7.1 Hz, O-CH_2-CH_3), 3.05 [s, 6H, $N(CH_3)_2$], 4.21 (q, 2H, J = 7.1 Hz, O-CH_2-CH_3), 7.59 (s, 1H, CH), 10.80 (br s, 1H, NH)
1c	Deuteriochloroform	1.36 (t, 3H, J = 7.2 Hz, O-CH_2-CH_3), 4.34 (q, 2H, J = 7.2 Hz, O-CH_2-CH_3), 6.69 (s, 1H, CH), 7.23-7.64 (m, 5H, ArH), 8.25 (br s, 1H, *NH*-C_6H_5) 10.81 (br s, 1H, NH)
1d	Dimethylsulfoxide-d_6	1.23 (t, 3H, J = 7.1 Hz, O-CH_2-CH_3), 4.17 (q, 2H, J = 7.1 Hz, O-CH_2-CH_3), 7.28 (s, 10 H, 2 x ArH), 7.51 (s, 1H, CH), 10.84 (br s, 1H, NH)
2a	Deuteriochloroform	1.38 (t, 3H, J = 7.2 Hz, O-CH_2-CH_3), 2.94 (d, 3H, J = 4.5 Hz, NH-CH_3), 4.37 (q, 2H, J = 7.2 Hz, O-CH_2-CH_3), 6.25 (br s, 1H, *NH*-CH_3), 8.60 (br s, 1H, NH)
2b	Deuteriochloroform	1.37 (t, 3H, J = 7.1 Hz, O-CH_2-CH_3), 3.11 [s, 6H, $N(CH_3)_2$], 4.36 (q, 2H, J = 7.1 Hz, O-CH_2-CH_3), 8.52 (br s, 1H, NH)
2c	Deuteriochloroform	1.42 (t, 3H, J = 7.1 Hz, O-CH_2-CH_3), 4.34 (q, 2H, J = 7.1 Hz, O-CH_2-CH_3), 7.07-7.70 (m, 5H, ArH), 8.09 (br s, 1H, *NH*-C_6H_5), 8.63 (br s, 1H, NH)
2d	Deuteriochloroform	1.38 (t, 3H, J = 7.2 Hz, O-CH_2-CH_3), 4.37 (q, 2H, J = 7.2 Hz, O-CH_2-CH_3), 7.25-7.52 (m, 10 H, 2 x ArH), 8.12 (br s, 1H, NH)
3a	Acetone-d_6	1.32 (t, 3H, J = 7.2 Hz, O-CH_2-CH_3), 2.98 (d, 3H, J = 4.5 Hz, NH-CH_3), 4.34 (q, 2H, J = 7.2 Hz, O-CH_2-CH_3), 7.02 (br s, 1H, *NH*-CH_3)
3b	Carbon tetrachloride	1.38 (t, 3H, J = 7.1 Hz, O-CH_2-CH_3), 3.12 [s, 6H, $N(CH_3)_2$], 4.32 (q, 2H, J = 7.1 Hz, O-CH_2-CH_3)
3c	Dimethylsulfoxide-d_6	1.34 (t, 3H, J = 7.1 Hz, O-CH_2CH_3), 4.37 (q, 2H, J = 7.1 Hz, O-CH_2-CH_3), 6.90-7.65 (m, 5H, ArH)
3d	Deuteriochloroform	1.37 (t, 3H, J = 7.2 Hz, O-CH_2-CH_3), 4.41 (q, 2H, J = 7.2 Hz, O-CH_2-CH_3), 7.00-7.50 (m, 10 H, 2 x ArH)
4a,5a	Dimethylsulfoxide-d_6	2.81 (d, 3H, J = 4.5 Hz, NH-CH_3), 7.38 (br s, 1H, *NH*-CH_3), 8.89 (s, 1H, CH)
4b,5b	Carbon tetrachloride	3.00 [s, 6H, $N(CH_3)_2$], 7.91 (s, 1H, CH)
4c,5c	Dimethylsulfoxide-d_6	6.70-7.72 (m, 5H, ArH), 8.71 (s, 1H, CH), 10.38 (br s, 1H, *NH*-C_6H_5)
4d,5d	Deuteriochloroform	7.34 (s, 10 H, 2 x ArH), 7.99 (s, 1H, CH)
6a	Dimethylsulfoxide-d_6	2.91 (d, 3H, J = 4.5 Hz, NH-CH_3), 3.94 (s, 3H, O-CH_3), 8.20 (br s, 1H, *NH*-CH_3)
6b	Deuteriochloroform	3.24 [s, 6H, $N(CH_3)_2$], 4.00 (s, 3H, O-CH_3)
6c	Dimethylsulfoxide-d_6	3.97 (s, 3H, O-CH_3), 6.85-7.70 (m, 5H, ArH)
6d	Deuteriochloroform	3.97 (s, 3H, O-CH_3), 7.07-7.60 (m, 10 H, 2 x ArH)

with chloroform and after drying (magnesium sulfate), the organic solution was concentrated under reduced pressure and the residue collected. For **2c** and **2d** the mixture was filtered. The products were recrystallized from the appropriate solvent (see Table I).

If the mixture of reaction was refluxed for 2 minutes, compounds **3a-d** were obtained directly.

Cyclization of Semicarbazone Bromides **2a-d**.

To a solution of the semicarbazone bromide (0.01 mole) in benzene was added triethylamine (0.02 mole) and the mixture was refluxed for 15 minutes. The solvent was evaporated to dryness under reduced pressure and then, after dilution with water, the product was collected and recrystallized from the solvent indicated in Table I.

Hydrolysis of **3a-d** and of **6a-d**.

To solution or suspension of the ester (0.01 mole) in water (10 ml.) were added at room temperature, 6 ml. of 10% sodium hydroxide for **3a**, **6a**, **3b** and **6b**; 40 ml. of 5% sodium hydroxide for **3c**, **6c**, **3d** and **6d** (the suspension of **3d** and **6d** was heated until solution). After cooling, the solution was acidified with hydrochloric acid 1:1 and the product collected and washed with ice-water was purified (see Table I).

Decarboxylation of **4a-d**.

The suspension of the appropriate acid (0.01 mole) in ethanol (25 ml.) was heated for 10 minutes and after removing the solvent the residue was recrystallized (distilled for **4b**) from the solvent indicated in Table I.

Methylation of **4a-d** with Diazomethane.

To a suspension of the appropriate acid (0.005 mole) in ether (20 ml.), an excess of ethereal diazomethane was added. After standing 24 hours, the solvent was evaporated and the residue collected and recrystallized from the solvent indicated in Table I.

REFERENCES AND NOTES

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(3) The nmr spectra of the acids in DMSO-d_6 solvent are identical with those of the corresponding decarboxylation products; clearly, decarboxylation occurs readily upon dissolving these products in the solvents.

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