A Novel Synthesis of 3-Bromo-1,2,4-oxadiazoles

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Received June 15, 1988

A novel synthesis of 3-bromo-1,2,4-oxadiazoles by 1,3-dipolar cycloaddition between bromocyanogen oxide and alkyl and aryl nitriles is described.

J. Heterocyclic Chem., **26**, 23 (1989).

3-Halo-1,2,4-oxadiazoles **7** and **8** are useful intermediates which have been used for the preparation of 3-hydroxy **12**, 3-alkoxy **13**, 3-amino **14** [1,2] and 3-azido **15** [3] derivatives by nucleophilic displacement of halide ion. We required a method for the preparation of 3-cyano-1,2,4-oxadiazoles **16** and thus reaction between cyanide ion and the bromo compounds **8** appeared to be a potential synthetic route to these compounds. 3-Halo-1,2,4-oxadiazoles **7** and **8** may be obtained from 3-amino-1,2,4-oxadiazoles **17** by diazotisation followed by treatment with halide ion [1,2]. However, 1,3-dipolar cycloaddition between bromocyanogen oxide and nitriles suggested a more facile route to these derivatives. Bromo and chloro cyanogen oxides **3** and **4** are readily prepared by treatment of dihaloformaldoximes **1** and **2** with base, but dimerisation occurs to form 1,2,5-oxadiazole oxides **5** and **6** unless they are trapped by dipolarophiles. Reaction with alkenes gave 3-haloisoxazolines **9** and **10** [4-7] whereas with alkynes 3-bromoisoxazoles **11** were obtained [8].

We have now shown that generation of bromocyanogen oxide in excess alkyl or aryl nitriles with or without solvent gives 3-bromo-1,2,4-oxadiazoles **8** in moderate to good yields (35-79%), Table 1. The by-product 3,4-dibromo-1,2,5-oxadiazole 2-oxide **6** (5-10%) contaminated the crude

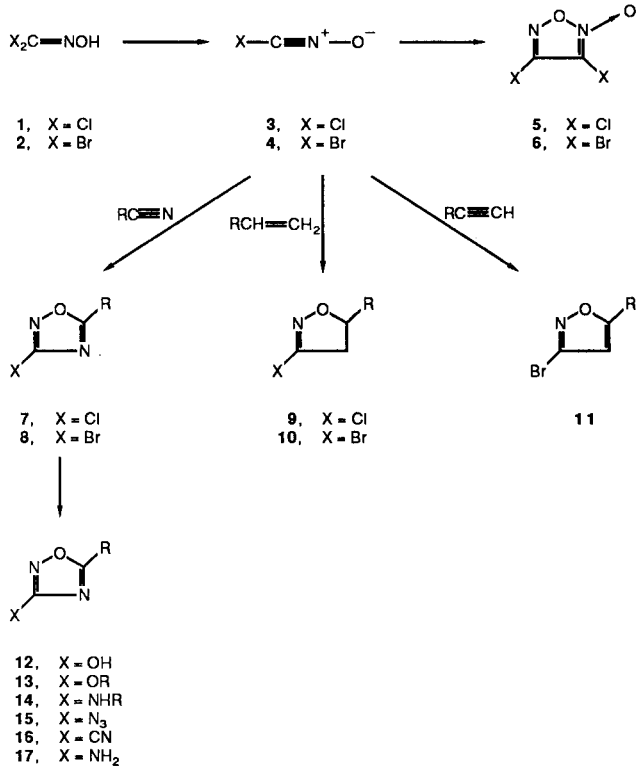

Table 1

3-Bromo-1,2,4-oxadiazoles **8**

Compound	R	Method	Yield % [a]	Bp, °C/torr [b] or mp °C	Molecular Formula	Analysis, % Calcd./Found C	H	N	EIMS [e] Base Peak; M+·
8a	$(CH_3)_2CH$	A	64	30/0.2	$C_5H_7BrN_2O$	31.44	3.69	14.66	191 (M + H)+ [f]
						31.63	3.71	14.64	
8b	$(CH_2)_2CH$	A	48	45/0.3	$C_5H_5BrN_2O$	31.77	2.67	14.82	81, 188 (42%)
						30.11	2.43	14.39 [g]	
8c	$CO_2C_2H_5$	B	79	80/0.5	$C_5H_5BrN_2O_3$	27.17	2.28	12.67	29, 220 (11%)
						27.33	2.25	12.62	
8d	$C_6H_5CH_2$	A	35	130/0.3	$C_9H_7BrN_2O$	45.22	2.95	11.72	91, 238 (44%)
						44.82	2.94	11.67	
8e	C_6H_5	A	40	50-51 [c]	$C_8H_5BrN_2O$				225 (M + H)+ [f]
8f	4-NO_2-C_6H_4	B	38	149-150	$C_8H_4BrN_3O_3$	35.58	1.49	15.56	269 (M+·)
						35.64	1.58	15.54	
8g	$ClCH_2$ [d]	A	48	70/0.4	$C_3H_2BrClN_2O$				198 (M+·)
8h	$BrCH_2$	B	40	55/0.2	$C_3H_2Br_2N_2O$	14.90	0.83	11.58	161, 240 (33%)
						15.28	0.87	11.63	

[a] Non optimised yields. [b] Kugelrohr. [c] Lit [2] mp 51°. [d] Contains ~10% of bromomethyl compound. [e] ^{79}Br ions quoted. [f] C.I. [g] Satisfactory analysis was not obtained for this compound.

Table 2

NMR Spectra of Compounds **8**

Compound	^{1}H NMR [a] δ ppm	^{13}C NMR [a] δ ppm C-3	C-5	Other
8a	1.40 (d, 6H, J = 7 Hz, CH_3), 3.35 (sept, 1H, J = 7 Hz, CH)	149.7	186.5	19.9 (q, CH_3), 28.2 (d, CH)
8b	1.2-1.4 (m, 4H, CH_2CH_2), 2.35 (m, 1H, CH)	149.6	184.2	8.0 (t, CH_2), 10.9 (d, CH)
8c	1.45 (t, 3H, J = 6 Hz, CH_3), 4.50 (q, 2H, J = 6 Hz, OCH_2)	150.5	153.2	14.1 (q, CH_3), 64.5 (t, CH_2), 168.6 (s, CO)
8d	4.38 (s, 2H, CH_2), 7.2-7.5 (m, 5H, Ph)	149.9	181.5	33.1 (t, CH_2), 128.3 (d), 129.5 (d), 129.8 (d), 134.0 (s) (Ph)
8e	7.5-8.1 (m, 5H, Ph)	150.6	177.8	123.8 (s), 128.9 (d), 130.3 (d), 134.6 (d) (Ph)
8f	8.3-8.6 (m, 4H, Ar-H)	151.0	176.3	125.4 (d), 129.1 (s), 130.4 (d), 151.7 (s) (Ar)
8g	5.04 (s, 2H, CH_2Cl) [b]	150.0	177.5	33.8 (t, CH_2)
8h	4.57 (s, 2H, CH_2Br)	150.1	177.8	17.1 (t, CH_2)

[a] Recorded in acetone-d_6 on a Bruker FT (250 MHz) spectrometer. [b] Peak also at 4.58 δ due to presence of CH_2Br compound.

products which were purified by distillation or chromatography. The chloromethyl compound **8g** was prepared as an example which could undergo chain extension, and the presence of bromide ion in the reaction mixture caused halide exchange to occur generating ~10% bromomethyl compound.

The ^{1}H and ^{13}C nmr spectra of the oxadiazoles **8** are collated in Table 2.

Attempts to obtain the nitriles **16** by reaction of the bromo compounds **8** with potassium cyanide were unsuccessful.

EXPERIMENTAL

Melting points (uncorrected) were determined with a Buchi apparatus. A Bruker FT (250 MHz) spectrometer was used to determine nuclear magnetic resonance spectra. Mass spectra were recorded on a Finnegan Mat TSQ70 spectrometer. Chemical ionisation mass spectra were recorded using methane as the ionising gas.

Method A.

3-Bromo-5-phenyl-1,2,4-oxadiazole **8e**.

A solution of dibromoformaldoxime [4] (20 g, 0.1 mole) in benzonitrile (30 ml) was added very slowly (over 2 hours) to a stirred solution of sodium bicarbonate (33 g, 0.39 mole) in benzonitrile (20 ml) at 80°. The mixture was allowed to cool, water (150 ml) and dichloromethane (100 ml) were added and the organic phase separated. The extract was washed with saturated sodium bicarbonate, dried over sodium sulphate and concentrated. Analysis (glc) of the benzonitrile solution indicated a 94:6 mixture of product **8a** and by-product **6**. The benzonitrile was removed by distillation and the residue distilled (Kugelruhr) to afford 3-bromo-5-phenyl-1,2,4-oxadiazole **8e** (8.8 g, 40%) as a colourless crystalline solid mp 50-51°, lit [2] mp 51°.

Other compounds in Table 1 were prepared similarly and purified by distillation or column chromatography.

Method B.

3-Bromo-5-ethoxycarbonyl-1,2,4-oxadiazole **8c**.

Dibromoformaldoxime (6.0 g, 30 mmoles) was added in small portions over 45 minutes to a stirred solution of ethyl cyanoformate (6.6 g, 60 mmoles) in toluene (10 ml) containing sodium bicarbonate (8.0 g, 95 mmoles) in suspension at 90°. The mixture was stirred at 90° for 3 hours, diluted with ethyl acetate (80 ml) and poured into water (100 ml). The organic layer was separated, washed with water and dried (sodium sulfate). Analysis (glc) indicated a 90:10 mixture of product **8c** and dimer **6**. The solution was evaporated and the residue chromatographed on silica with ethyl acetate-hexane to give the product as an oil (5.3 g, 79%) bp 80°/0.5 torr.

Other compounds in Table 1 were similarly prepared and purified by distillation or column chromatography.

Acknowledgement.

We thank P. V. Byway for mass spectral data and Dr. D. J. Kennedy for nmr spectra.

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