1,3-Dipolar Cycloaddition Synthesis of 3-Bromo-5-substituted Isoxazoles, Useful Intermediates for the Preparation of Pharmacologically Active Compounds

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Received June 3, 1986

Bromonitrile oxide **2**, generated from easily available dibromoformaldoxime **1**, reacts with monosubstituted acetylenic derivatives **4** to give 3-bromo-5-substituted isoxazoles **5** in high yield. The experimental conditions necessary to overcome difficulties such as the low reactivity of acetylenic dipolarophiles and the high tendency to dimerization of bromonitrile oxide **2**, are discussed; the regioselectivity of this 1,3-dipolar cycloaddition is also studied. The obtained improvements in the synthesis of some pharmacologically active compounds are reported.

J. Heterocyclic Chem., **24**, 43 (1987).

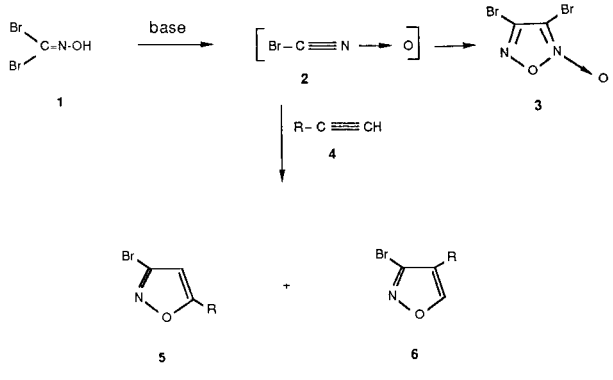
3-Bromoisoxazoles play a significant role as intermediates for the preparation of pharmacologically active derivatives; nevertheless few examples are described in the literature depending on the remarkable difficulties inherent in the already known synthesis.

The first reported approach to obtain 3-bromoisoxazoles involves the rearrangement of 2-nitrovinylfurane with hydrobromic acid [1]; ß-nitroketone, originated from the cleavage of furan, reacts with hydrobromic acid to give the isoxazole ring as demonstrated by Fusco and co-workers [2]. The yields are generally low and moreover ß-nitroketones very often present synthetic problems.

The second and most direct synthesis is that of Cabiddu and co-worker [3] who employ a 1,3-dipolar cycloaddition reaction between alkynylmagnesium bromides and dibromoformaldoxime **1** in order to construct the 3-bromoisoxazole ring. Monosubstituted alkynes are available starting materials, but the synthesis yields poorly and with limitations inherent in the Grignard reagents.

Not long ago a new and practical preparation of dibromoformaldoxime **1** was developed during the investigations targeted towards the obtainment of analogues of the antitumor antibiotic Acivicin [4]. In this synthesis the use of an excess of bromonitrile oxide **2** yields the formation of a large amount of undesired dibromofuroxan **3** derived from the dipole dimerization. The interest in the series of 3-bromo-5-substituted isoxazoles **5** [5] urged us to study a simple and inexpensive commercial scale preparation (Scheme 1).

Scheme 1



1 2 3 4 5 6

The difficulty contained in our synthetic strategy based on a 1,3-dipolar cycloaddition, has been to reconcile the low reactivity of monosubstituted acetylenes **4** as dipolarophiles [6] with the short time of complete dimerization of non isolable bromonitrile oxide **2**. Furthermore the presence of dibromofuroxan **3** in the crude mixture has to be avoided because of its dangerousness [7] and the difficult purification of the desired isoxazoles **5**. On that basis we have verified that a very slow addition of a dibromoformaldoxime **1** solution together with the use of an inorganic base in heterogeneous phase, results in a reduction of the dipole dimerization. Carrying out in such a way the cycloaddition, the reaction mixture always contains a very small quantity of bromonitrile oxide **2** in the presence of a large excess of an acetylenic derivative **4**.

The optimal dipole: dipolarophile ratio has been investigated by hplc study (Table 1). It is interesting to note with a 1:1 ratio the furoxan is still present in troublesome quantities while its almost complete absence is accomplished with the use of 1:5 ratio. We have recognized that a 1:2 ratio is sufficient to obtain desired isoxazoles **5** in excellent yields together with a negligible and non troublesome quantity of dimer.

Table 1

HPLC Study for the Cycloaddition between **1** and **4c**

Molar ratio **1:4c**	**5c** weight %	**3** weight %	**5c** yield, % [a]
1:5	99.8	0.2	90
1:3	98.1	1.2	89
1:2	97.9	2.1	87
1:1	76.5	23.5	75
2:1	63.3	36.7	90 [b]

[a] Yields calculated from **1**. [b] Yield calculated from **4c**.

As reported for the cycloaddition reactions [6] the choice of the solvent is not determinant thus we have turned to a solvent such as ethyl acetate usable in a large scale synthesis. In any case a small amount of water makes the reaction proceed easier. The cycloaddition is carried out at room temperature for a number of hours.

In a field of 1,3-dipolar cycloadditions the orientation problems are far from being thoroughly understood; generally most nitrile oxides react in a high regioselectivity with terminal alkynes giving practically pure 5-substituted isoxazoles. With some dipolarophiles we have observed the formation of small but detectable amounts of 4-substituted derivatives **6** (Table 2).

Wade and co-workers [8] studying the cycloaddition between dichloroformaldoxime and olefinic dipolarophiles, proposed an interesting mechanistic hypothesis involving an attractive interaction of the halogen of the nitrile oxide with appropriate allylic hydrogens, favoring the obtainment of the minor 4-substituted isomer. According to this theory our data show that detectable amounts of 4-substituted isoxazoles **6** are obtained when acidic hydrogens on the side chain of acetylenic compounds **4** can interact with the bromine of nitrile oxide **2**. In order to complete the regioselectivity studies, we have experimented with the use of ethyl propiolate **4b** as the dipolarophile; as expected [6], a notable increase (30%) of 4-substituted isomer **6h** has been obtained.

Table 2

Regioselectivity of Cycloaddition Reaction [a]

Compounds	Ratio [b]	^{1}H-NMR [c] of Isoxazole hydrogens, δ (ppm)
5a:6a	93:7	6.43:8.53
5b:6b	94:6	6.33:8.43
5c:6c	94:6	6.33:8.40
5d:6d	93:7	6.36:8.43
5e:6e	93:7	6.33:8.43
5f:6f	87:13	6.46:8.50
5h:6h	70:30	7.10:9.04

[a] Compound **5g** has been obtained highly regioselective. [b] Estimated by integration of isoxazole hydrogens. [c] Conditions: deuteriochloroform with TMS as the internal standard.

(3-Bromo-5-isoxazolyl)alkanols **5a-f** New Synthesis of the "Key Intermediate" for Broxaterol [5].

Among alkynylmagnesium bromides employed by Cabiddu and co-worker [3] for a cycloaddition with dibromoformaldoxime **1**, there is the properly protected propargyl alcohol which gives **5a** in poor yield (29%). The experimental conditions of our synthetic method allow the preparation of (3-bromo-5-isoxazolyl)alkanols **5a-f** in good yield without any protection of acetylenic alcohols **4a-f**.

4-Substituted isomers **6a-f** obtained in small amounts (Table 2) have not been isolated; 5-substituted compounds **5a-f** can be purified either by fractionated distillation or by column chromatography. Analytical data of these derivatives are presented in Table 3; ^{1}H-nmr of new compounds **5b-f** are reported in Table 5.

Compounds **5c-e** are oxidized to corresponding ketones **7a-c** (Scheme 2) with chromic anhydride in acetic acid in

Table 3

3-Bromo-5-Substituted Isoxazoles **5**

Compound	R	Yield, %	Bp, °C/torr or mp, °C	Molecular Formula	Analysis, % Calcd./Found C	H	N	Br
5a [3]	CH_2OH	88	100/1.2	$C_4H_4BrNO_2$	26.99	2.26	7.87	44.90
					26.81	2.14	7.91	44.81
5b	CH_2CH_2OH	85	105/1.0	$C_5H_6BrNO_2$	31.27	3.15	7.29	41.62
					31.40	3.08	7.36	41.40
5c	$CHOHCH_3$	87	90/0.4	$C_5H_6BrNO_2$	31.27	3.15	7.29	41.62
					31.12	3.18	7.40	41.78
5d	$CHOHC_2H_5$	86	95/0.6	$C_6H_8BrNO_2$	34.97	3.91	6.80	38.78
					34.90	3.83	6.91	38.92
5e	$CHOHC_3H_7n$	84	105/1.0	$C_7H_{10}BrNO_2$	38.20	4.58	6.36	36.31
					38.36	4.68	6.28	36.10
5f	$CHOHCOOC_4H_9n$	82	170/0.8	$C_9H_{12}BrNO_4$	38.87	4.35	5.04	28.73
					38.63	4.21	5.20	28.81
5g [9]	C_6H_5	92	72-73	C_9H_6BrNO	48.24	2.70	6.25	35.66
					48.40	2.81	6.12	35.48
5g	$COOC_2H_5$	68	47-48	$C_6H_6BrNO_3$	32.75	2.75	6.37	36.32
					32.83	2.90	6.28	36.16

Table 4

(3-Bromo-5-isoxazolyl)alkanones **7**

Compound	R_1	Yield, %	Mp, °C or bp, °C/torr	Molecular Formula	Analysis, % Calcd./Found C	H	N	Br
7a [5]	CH_3	82	65-66	$C_5H_4BrNO_2$	31.61 31.49	2.12 2.18	7.37 7.35	42.06 42.12
7b	C_2H_5	83	36-37 70/0.5	$C_6H_6BrNO_2$	35.32 35.40	2.96 3.01	6.87 6.95	39.17 39.09
7c	n-C_3H_7	88	80/0.5	$C_7H_8BrNO_2$	38.56 38.52	3.70 3.63	6.42 6.45	36.65 36.67

good yields. Analytical data of these compounds are reported in Table 4. The ^{1}H-nmr of new derivatives **7b-c** are presented in Table 5.

SHEME 2

5a-e 7a-c

Table 5

^{1}H-NMR Data of New Compounds

Compounds	δ (ppm) Deuteriochloroform [a]
5b	3.05 (t, 2H), 3.96 (t, 2H), 6.33 (s, 1H)
5c	1.60 (d, 3H), 5.00 (q, 1H), 6.33 (s, 1H)
5d	1.06 (t, 3H), 1.90 (m, 2H), 4.80 (t, 1H), 6.36 (s, 1H)
5e	0.83-2.20 (m, 7H), 4.90 (t, 1H), 6.33 (s, 1H)
5f	0.70-2.00 (m, 7H), 4.30 (t, 2H), 5.36 (d, 1H), 6.46 (s, 1H)
5h	1.43 (t, 3H), 4.50 (q, 2H), 7.10 (s, 1H)
6h	1.37 (t, 3H), 4.42 (q, 2H), 9.04 (s, 1H)
7b	1.25 (t, 3H), 3.03 (q, 2H), 7.02 (s, 1H)
7c	1.03 (t, 3H), 1.80 (m, 2H), 2.96 (t, 2H), 7.03 (s, 1H)

[a] TMS as the internal standard.

Derivatives **7a-c** can be purified either by crystallization or by column chromatography. In particular product **7a**, obtained in a two-step synthesis with an overall yield of 73%, is the "key intermediate" of Broxaterol [5] a new selective β_2-adrenergic drug developed in our laboratories. The preceding preparation of ketone **7a** is carried out in a six-step synthesis with an overall yield of 11%.

3-Bromo-5-phenylisoxazole, Anthelmintic Compound [9]. New Synthesis.

Among the anthelmintic isoxazoles published by Carr and co-workers [9], 3-bromo-5-phenyl derivative **5g** is one of the most interesting compounds. The reported synthesis starts from ß-nitroketone, yielding 15% of the desired isoxazole **5g**. The reaction between phenylacetylene **4g** and dibromoformaldoxime **1**, under our conditions, gives compound **5g** in highly regioselective fashion and in 92% of yield. Analytical data of derivative **5g** are presented in Table 3.

3-Bromo-5-isoxazolecarboxylic Acid Ethyl Ester **5h** and 3-Bromo-4-isoxazolecarboxylic Acid Ethyl Ester **6h**.

The reaction between ethyl propiolate **4h** and dibromoformaldoxime **1** gives in high yield (97%) the mixture of 3-bromo-5-isoxazolecarboxylic acid ethyl ester **5h** and 3-bromo-4-isoxazolecarboxylic acid ethyl ester **6h** (respectively 70% and 30%). Whereas the slight presence of minor isomers **6a-f** in (3-bromo-5-isoxazolyl)alkanols **5a-f** could only be detected by ^{1}H-nmr data (Table 2), in this case the considerable amount of derivative **6h** led us to isolate both isomers by column chromatography. The molar ratio obtained from pure isomers **5h** and **6h**, confirms that the ratio calculated by ^{1}H-nmr is correct. Analytical data of compound **5h** are reported in Table 3; ^{1}H-nmr of derivatives **5h** and **6h** are presented in Table 5.

EXPERIMENTAL

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Boiling points are also uncorrected; fractionated distillations were carried out by means of a Fischer Spaltrohr-System apparatus. The ^{1}H-nmr spectra were recorded with a Varian EM-360L.

1-(3-Bromo-5-isoxazolyl)ethanol (**5c**).

A solution of dibromoformaldoxime **1** (240 g, 1.183 moles) in ethyl acetate (250 ml) is added dropwise during 6 hours at room temperature to a stirred mixture of 3-butyl-2-ol **4c** (165.8 g, 2.366 moles) and potassium bicarbonate (355.3 g, 3.549 moles) in ethyl acetate (4450 ml) and water (44.5 ml). After stirring for 18 hours, water (1200 ml) is added; the organic layer is separated, washed twice with water and dried. After evaporation of the solvent under reduced pressure, the residue is purified by distillation (bp 88-90°; 0.4 torr) obtaining pure **5c** (197.5 g, 87%).

Compounds **5a-f** are similarly prepared.

1-(3-Bromo-5-isoxazolyl)ethanone (**7a**).

A solution of chromic anhydride (136 g, 1.36 moles) in acetic acid (1768 ml) and water (176.8 ml) is added dropwise during 2 hours to a stir-

red solution of **5c** (239 g, 1.183 moles) in acetic acid (1673 ml) cooling at 15°. After stirring for 40 hours, the solvent is removed under reduced pressure. The residue is poured into water (3500 ml) and treated with sodium bicarbonate to neutralization. The aqueous layer is extracted with ethyl acetate (3500 ml) which is washed with water and dried. After evaporation of the solvent under reduced pressure, the solid residue (200 g) is crystallized from isopropyl alcohol (200 ml) to give pure **7a** (184.3 g, 82%, mp 65-66°).

Compounds **7b-c** are similarly prepared.

3-Bromo-5-phenylisoxazole (**5g**).

A solution of dibromoformaldoxime **1** (40.6 g, 0.2 mole) in ethyl acetate (50 ml) is added dropwise during 6 hours at room temperature to a stirred mixture of phenylacetylene **4g** (40.9 g, 0.4 mole) and potassium bicarbonate (60.1 g, 0.6 mole) in ethyl acetate (750 ml) and water (7.5 ml). After stirring overnight, water (200 ml) is added; the organic layer is separated, washed twice with water and dried. After evaporation of the solvent under reduced pressure, the residue is crystallized from *n*-hexane to give pure **5g** (41.2 g, 92%, mp 72-73°).

3-Bromo-5-isoxazolecarboxylic Acid Ethyl Ester (**5h**) and 3-Bromo-4-isoxazolecarboxylic Acid Ethyl Ester (**6h**).

A solution of dibromoformaldoxime **1** (20.3 g, 0.1 mole) in ethyl acetate (25 ml) is added dropwise during 6 hours at room temperature to a stirred mixture of ethyl propiolate **4h** (19.6 g, 0.2 mole) and potassium bicarbonate (30.0 g, 0.3 mole) in ethyl acetate (375 ml) and water (37.5 ml). After stirring for 18 hours, water is added; the organic layer is separated, washed twice with water and dried. After evaporation of the solvent under reduced pressure, the residue is purified by distillation (bp 80°, 0.5 torr) obtaining the pure mixture of **5h** and **6h** (21.3 g, 97%). The two isomers are separated by column chromatography (silica gel 1065 g, eluent *n*-hexane:methyl-*t*-butyl ether 95:5) giving pure **5h** (14.9 g, mp 47-48°) and pure **6h** (6.4 g, mp 43-44°).

Anal. Calcd. for $C_6H_6BrNO_3$ (**6h**): C, 32.75; H, 2.75; N, 6.37; Br, 36.32. Found: C, 32.49; H, 2.80; N, 6.40; Br, 36.52.

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