THE 5-ALKOXYMETHYL-, 5-ALKYLTHIOMETHYL-, AND 5-DIALKYLAMINOMETHYL-ISOXAZOLES

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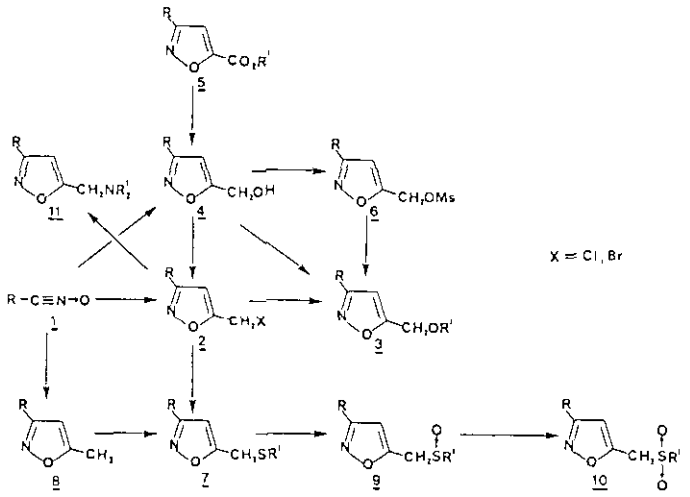
Abstract - A variety of methods were used for the preparation of the 5-alkoxymethyl-, 5-alkylthiomethyl-, and 5-dialkylaminomethyl-isoxazoles. A novel method for the separation of the isomeric mixture of 3-(5-)methoxymethyl-5-(3-)methylisoxazoles (obtained by the reaction of 1-methoxypentane-1,3-dione with hydroxylamine), based on the difference in reactivity with n-butyllithium, is described. Methods for the preparation of 5-alkylthiomethylisoxazoles from the 5-methylisoxazoles; and 5-alkoxymethylisoxazoles from the 5-hydroxymethylisoxazoles are also reported.

In continuing studies directed towards the synthesis of heterocyclic compounds with potential biological activity, we have investigated the lithiation reactions of various 5-alkoxymethylisoxazoles, 3; 5-alkylthiomethylisoxazoles, 7; and 5-dialkylaminomethylisoxazoles, 11. The methods used for the preparation of these isoxazoles are reported in this publication, and the results of our studies on the lithiation reactions of these compounds are discussed in the following paper. The reactions used to prepare many of the compounds are summarized in Scheme I.

SCHEME I



The dipolar cycloaddition[1] of nitrile oxides[2], 1 (either isolated or generated in situ) with an appropriately substituted acetylene gave the 5-bromomethylisoxazole, 2; or the 5-hydroxymethylisoxazoles, 4. The 5-bromomethylisoxazoles on reaction with an alkoxide, a thioalkoxide, or a dialkylamine gave the appropriate 5-alkoxymethylisoxazole, 3; the 5-alkylthiomethylisoxazole, 7; or the 5-dialkylaminomethylisoxazole, 11.

The 5-hydroxymethylisoxazoles, 4, could also be obtained by the LAH reduction of 5-carboalkoxyisoxazoles, 5. These alcohols, 4, are alkylated to the 5-alkoxymethylisoxazoles, 3. Alternatively, the 5-hydroxymethylisoxazoles, 4, can be converted to the 5-chloromethylisoxazoles, 2, which can be used as a precursor to compounds 3, 7, and 11. It was, however, found that a better route providing high yields (over 75%) of the 5-alkoxymethylisoxazoles, 3, is via the mesylate, 6.

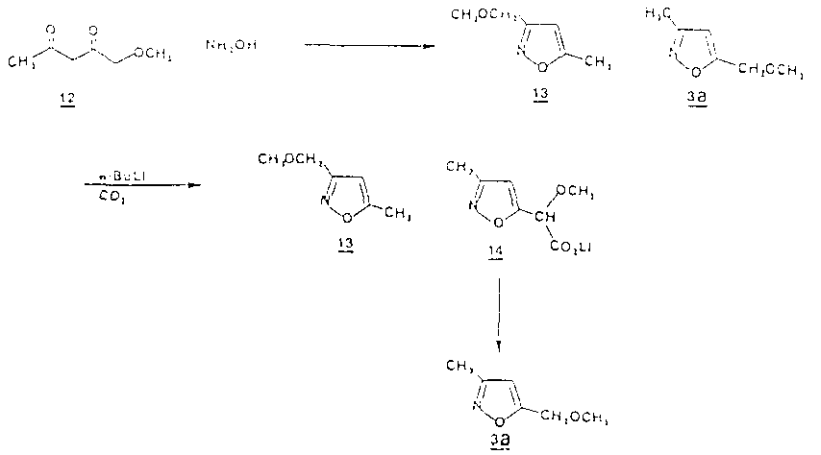
A very convenient method for the preparation of the 5-alkylthiomethylisoxazoles, 7, was by way of the 5-methylisoxazoles, 8[3,4]. The lithiation of these compounds 8 (R=aryl or alkyl), as described by us[5], and confirmed by Gainer and co-workers[6], proceeds exclusively at the C-5 methyl group to give the 5-lithiomethylisoxazoles. These compounds react with dimethyldisulfide producing the 5-methylthiomethylisoxazoles, 7, in excellent yields. Bravo and Gaviraghi used a similar approach with methylsulfenyl chloride as the reagent.[7] In view of the volatility, reactivity, and instability of methylsulfenyl chloride (which must be prepared just prior to use), the use of dimethyldisulfide is preferable for these reactions.

The 5-alkylthiomethylisoxazoles, 7, are readily oxidized by reagents such as peracetic acid or m-chloroperbenzoic acid, to the respective sulfoxides, 9; or sulfones, 10, the stoichiometry of the reaction determining the product formed.

In the case of those compounds, 7, where R=$COOC_2H_5$, further modifications of this C-3 group to R=COOH, $CONH_2$, CN, $CON(CH_3)_2$, and CH_2OH, were brought about by standard methods.

Treating 1-methoxypentane—1,3-dione, 12 (Scheme 2) with hydroxylamine gave a mixture of 3-methoxymethyl-5-methylisoxazole, 13[6], and 3-methyl-5-methoxymethylisoxazole, 3a, in the ratio 62:38, as determined by glc and from the pmr spectrum.

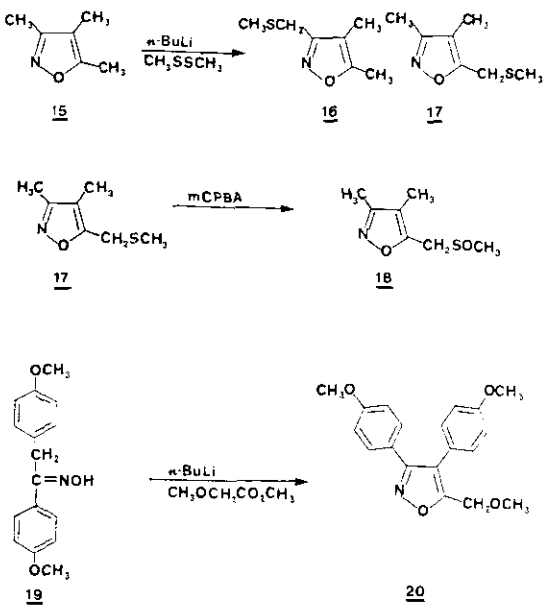
SCHEME 2



Although this mixture can be resolved by silica gel column chromatography, a novel method of separation for isomers of this type, based on the difference in the reactivity of these isomers to n-butyllithium, was investigated. When the mixture of isomers 13 and 3a was treated with n-butyllithium (an amount equivalent to compound 3a), *exclusive reaction with 3a occurred, treatment with* carbon dioxide producing an essentially quantitative yield of 14, mixed with the unreacted 13. Washing the concentrated reaction mixture with ether separated the 13 (ether soluble) from the salt 14 (ether insoluble). Distillation of the residue from the ether soluble fraction gave pure 13 as a colourless liquid.[6] The lithium salt, 14, on conversion to the free acid, followed by heating (particularly in presence of cupric oxide) gave pure 3a as a colourless liquid. Compounds 3a and 13 were readily distinguished by their pmr spectra.

3-Methylpentane-2,4-dione,[8] on reaction with hydroxylamine gave 3,4,5-trimethylisoxazole, 15 (Scheme 3).

SCHEME III



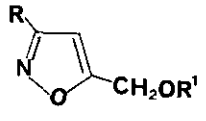
15 16 17 17 18 19 20

When 3,4,5-trimethylisoxazole, 15, was treated with n-butyllithium and dimethyldisulfide and the product chromatographed on silica gel, there was obtained a 6.8% overall yield of the pure compound 16, and a 37.2% overall yield of the pure compound 17, the structural assignments being made from the pmr spectral characteristics. Oxidation of 17 with 1 equivalent of peracetic acid or m-chloroperbenzoic acid gave 18.

5-Methoxymethyl-3,4-di-(p-methoxyphenyl)isoxazole, 20, was made by a modification of the method of Beam and co-workers.[9] The oxime of deoxyanisoin, 19, on treatment with two equivalents of n-butyllithium, followed by reaction with methyl methoxyacetate gave 5-methoxymethyl-3,4-di-(p-methoxyphenyl)isoxazole, 20.

Table 1 summarizes the data on the 5-(aryloxy)- and 5-alkoxymethylisoxazoles; Table 2 summarizes the data on the 5-alkylthiomethylisoxazoles, their sulfoxides and sulfones; and Table 3 lists the miscellaneous compounds prepared.

TABLE 1. THE 5-ALKOXYMETHYLISOXAZOLES*

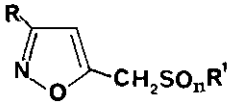


No.	R	R^1	bp °C/mm	Yield %	pmr spectrum, 60 MHz, ($CDCl_3$)
3a	CH_3	CH_3	36-37/0.2	92.3	2.33(s,3H,$\underline{CH_3}$); 3.47 (s,3H,$O\underline{CH_3}$); 4.48 (s,2H,$\underline{CH_2}O$); 6.07 (s,1H,=$\underline{CH}$).
3b	CH_3	C_2H_5	38-39/0.1	78	1.20(t,J=6.0 Hz,3H,$CH_2\underline{CH_3}$); 2.27(s,3H,$\underline{CH_3}$); 3.50(q,J=6.0 Hz,2H,$\underline{CH_2}CH_3$); 4.52(s,2H,$\underline{CH_2}O$); 6.00(s,1H,=$\underline{CH}$).
3c	CH_3	n-C_3H_7	48-49/0.5	80	0.92(t,J=5.0 Hz,3H,$CH_2\underline{CH_3}$); 1.58(Sixtet, J_1=J_2=5.0 Hz, $CH_2\underline{CH_2}CH_3$); 2.30(s,3H,$\underline{CH_3}$); 3.47(t,J=5.0 Hz,$O\underline{CH_2}CH_2CH_3$); 4.57(s,2H,$\underline{CH_2}O$); 6.07(s,1H,=$\underline{CH}$).
3d	CH_3	n-C_4H_9	53-54/0.1	75	0.90(t,J=6.0 Hz,3H,$CH_2\underline{CH_3}$); 1.17-1.70(m,4H,-$\underline{CH_2}$-); 2.32(s,3H,$\underline{CH_3}$); 3.48(t,J=6.0 Hz,$O\underline{CH_2}CH_2$); 4.53(s,2H,$\underline{CH_2}O$); 6.03(s,1H,=$\underline{CH}$).
3e	CH_3	n-C_5H_{11}	68-71/0.1	78	0.86(ill-defined t,3H,$CH_2\underline{CH_3}$); 1.03-1.83(m, 6H,-$\underline{CH_2}$-); 2.31(s,3H,$\underline{CH_3}$); 3.48(t,J=6.0 Hz,2H,$O\underline{CH_2}CH_2$); 4.55(s,2H,$\underline{CH_2}O$);6.07(s,1H, =$\underline{CH}$).
3f	CH_3	n-C_6H_{13}	75-80/0.1	80	0.85(ill-defined t,3H,$CH_2\underline{CH_3}$); 1.10-1.90(m,8H,-$\underline{CH_2}$-); 2.30(s,3H,$\underline{CH_3}$); 3.48(t,J=5.0 Hz,2H,$O\underline{CH_2}CH_2$); 4.53(s,2H, $\underline{CH_2}O$);6.05(s,1H,=$\underline{CH}$).
3g	CH_3	n-C_8H_{17}	94-95/0.1	80	0.88(ill-defined t,3H,$CH_2\underline{CH_3}$); 1.08-1.88(m, 12H,-$\underline{CH_2}$-); 2.32(s,3H,$\underline{CH_3}$); 3.52(t,J=6.0 Hz,2H,$O\underline{CH_2}CH_2$); 4.58(s,2H,$\underline{CH_2}O$);6.10(s,1H, =$\underline{CH}$).
3h	CH_3	$(CH_2)_2N(CH_3)_2$	78-80/0.1	75	2.26(s,6H,$N\underline{CH_3}$); 2.43(t,J=5.0 Hz,2H, $CH_2\underline{CH_2}N$); 3.53(t,J=5.0 Hz,2H,$O\underline{CH_2}CH_2$); 4.53(s,2H,$\underline{CH_2}O$); 6.00(s,1H,=$\underline{CH}$).
3i	CH_3	$(CH_2)_2SCH_3$	85-87/0.1	76	2.13(s,3H,$\underline{CH_3}$);2.30(s,3H,$S\underline{CH_3}$); 2.67(t,J=6.0 Hz,2H,$CH_2\underline{CH_2}S$); 3.37(t,J=6.0 Hz,2H,$O\underline{CH_2}CH_2$); 4.60(s,2H,$\underline{CH_2}O$);6.07(s,1H, =$\underline{CH}$).
3j	CH_3	$(CH_2)_2SO_2CH_3$	154-162/0.2[a]	94	2.36(s,3H,$\underline{CH_3}$); 3.06(s,3H,$SO_2\underline{CH_3}$); 3.26(t,J=6.0 Hz,2H, $CH_2\underline{CH_2}O$); 3.93(t,J=6.0 Hz,2H,$SO_2\underline{CH_2}CH_2$); 4.60(s,2H,$\underline{CH_2}O$); 6.08(s,1H,=$\underline{CH}$).

3k	C_6H_5	CH_3	100-102/0.05	95.6	3.46(s,3H,OCH_3); 4.55(s,2H,CH_2O); 6.53(s,1H,=CH); 7.40-7.86(m,5H,C_6H_5).
3l	2,6-$Cl_2C_6H_3$	CH_3	138-140/0.1	98	3.52(s,3H,OCH_3); 4.63(s,2H,CH_2O); 6.33(s,1H,=CH); 7.42(m,3H,$C_6H_3Cl_2$).
3m	2,6-$Cl_2C_6H_3$	n-C_4H_9	139/0.08	94	0.90(t,J=5.0 Hz,3H,CH_2CH_3); 1.10-1.86(m,4H,-$(CH_2)_2$-); 3.53(t,J=6.0 Hz,2H,OCH_2CH_2); 4.67(s,2H,CH_2O); 6.33(s,1H,=CH);7.40(m, 3H,$C_6H_3Cl_2$).

*Elemental Analyses of these compounds were within acceptable limits.
[a]Kugelrohr distillation; air bath temperature.

TABLE 2. THE 5-ALKYLTHIOMETHYLISOXAZOLES* (SULFOXIDES AND SULFONES)



7 n=0
9 =1
10 =2

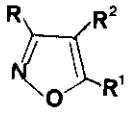
No.	R	R^1	bp °C/mm	Yield %	pmr spectrum, 60 MHz, ($CDCl_3$)
7a	CH_3	CH_3	100-102/9	87	2.16(s,3H,CH_3); 2.30(s,3H,SCH_3); 3.73(s,2H,CH_2S);6.05(s,1H,=CH).
7b	C_6H_5	CH_3	118/0.05	91.5	2.20(s,3H,SCH_3); 3.77(s,2H,CH_2S); 6.46(s,1H,=CH); 7.33-7.88(m,5H,C_6H_5).
7c	2,6-$Cl_2C_6H_3$	CH_3	153-155/0.1	94	2.23(s,3H,SCH_3); 3.53(s,2H,CH_2S); 6.28(s,1H,=CH); 6.97-7.43(m,3H,$C_6H_3Cl_2$).
7d	C_2H_5OOC	CH_3	98-100/0.05	68	1.40(t,J=6.0 Hz,3H,CH_2CH_3); 2.15(s,3H, SCH_3); 3.67(s,2H,CH_2S); 4.53(q,J=6.0 Hz,2H, CH_2CH_3); 6.63(s,1H,=CH).
7e	HOOC	CH_3	120-122(mp)	63.4	2.20(s,3H,SCH_3); 3.90(s,2H,CH_2S); 6.68(s,1H,=CH); 12.90(s,1H,COOH).[a]
7f	H_2NCO	CH_3	142-143(mp)	94.7	2.15(s,3H,SCH_3); 3.88(s,2H,CH_2S); 6.65(s,1H,=CH); 7.67 & 7.85 (broad s, 2H,$CONH_2$).[a]
7g	$(CH_3)_2NCO$	CH_3	134-140/0.2[c]	99	2.29(s,3H,SCH_3); 3.17(s,3H,NCH_3); 3.33(s,3H,NCH_3) 3.83(s,2H,CH_2S); 6.47(s,1H,=CH).
7h	$CH_2SO_2CH_3$	CH_3	oil-decomp. on distr.	70	2.20(s,3H,SCH_3); 3.13(s,3H,SO_2CH_3); 3.60(s,2H,CH_2S); 5.27(s,2H,CH_2SO_2); 6.37(s,1H,=CH).
7i	$HOCH_2$	CH_3	116-118/0.25	66.7	2.20(s,3H,SCH_3); 3.80(s,3H,CH_2S); 3.86(s,1H,OH); 4.72(s,2H,CH_2OH); 6.28(s,1H,=CH).

7j	NC	CH_3	68-71/0.25	74	2.25(s,3H,SCH_3); 3.92(s,2H,CH_2S); 6.63(s,1H,=CH).
9a	CH_3	CH_3	59-60(mp)	76	2.35(s,3H,CH_3); 2.63(s,3H,$SOCH_3$); 3.78(s,2H,CH_2SO); 6.23(s,1H,=CH).
9b	C_6H_5	CH_3	110-112(mp)	95	2.63(s,3H,$SOCH_3$); 4.15(s,2H,CH_2SO); 6.70(s,1H,=CH); 7.37-7.87(m,5H,C_6H_5).
9c	2,6-$Cl_2C_6H_3$	CH_3	150-152(mp)	88.5	2.67(s,3H,$SOCH_3$); 4.30(s,2H,CH_2SO); 6.55(s,1H,=CH); 7.48(s,3H,$C_6H_3Cl_2$).
9d	C_2H_5OOC	CH_3	60-61(mp)	74.8	1.40(t,J=6.0 Hz,3H,CH_2CH_3); 2.60(s, 3H,$SOCH_3$); 4.20(s,2H,CH_2SO);4.46(q, J=6.0 Hz,2H,CH_2CH_3); 6.85(s,1H,=CH).
10a	CH_3	CH_3	103-105(mp)	95	2.40(s,3H,CH_3); 3.00(s,3H,SO_2CH_3); 4.46(s,2H,CH_2SO_2); 6.42(s,1H,=CH).
10b	C_6H_5	CH_3	162-163(mp)	95.2	3.15(s,3H,SO_2CH_3); 4.97(s,2H,CH_2SO_2); 7.10(s,1H,=CH); 7.45-8.00(m,5H,C_6H_5).[b]
10c	2,6-$Cl_2C_6H_3$	CH_3	182-184(mp)	80	3.13(s,3H,SO_2CH_3); 5.03(s,2H,CH_2SO_2); 6.80(s,1H,=CH); 7.60(s,3H,$C_6H_3Cl_2$).
10d	C_2H_5OOC	CH_3	99-101(mp)	89	1.35(t,J=6.0 Hz,3H,CH_2CH_3); 3.13(s,3H, SO_2CH_3); 4.42(q,J=6.0 Hz,2H,CH_2CH_3); 5.07(s,2H,CH_2SO_2); 7.03(s,1H,=CH).
10e	HOOC	CH_3	184-186(mp)	88.5	3.15(s,3H,SO_2CH_3); 5.03(s,2H,CH_2SO_2); 6.97(s,1H,=CH).[b]

*Elemental Analyses of these compounds were within acceptable limits.

a) $CDCl_3$ & DMSO-d_6 as solvent; b) DMSO-d_6 as solvent; c) Kugelrohr distillation; air bath temperature.

TABLE 3. MISCELLANEOUS ISOXAZOLES*



NO	R	R^1	R^2	BP °C/MM	YIELD %	PMR SPECTRUM, 60 MHZ ($CDCL_3$)
2a	C_2H_5OOC	CH_2Br	H	98-100/0.25	66.4	1.45(t,J=7.0 Hz,3H,CH_2CH_3);4.46(q, J=7.0 Hz, 2H,CH_2CH_3); 4.58(s,2H, CH_2Br); 6.77(s,1H,=CH).
4	CH_3	CH_2OH	H	78-80/0.75	85	2.27(s,3H,CH_3); 4.70(s,2H,CH_2OH); 5.00(broad s,1H,OH);6.12(s,1H,=CH).
11a	2,6-$Cl_2C_6H_3$	$CH_2N(CH_3)_2$	H	154-155/0.9	48.5	2.40(s,6H,NCH_3); 3.75(s,2H,CH_2N); 6.27(s,1H,=CH); 7.40(s,3H,$C_6H_3Cl_2$).

13	CH_3OCH_2	CH_3	H	72-74/9	62	2.40(s,3H,$\underline{CH_3}$); 3.37(s,3H,$O\underline{CH_3}$); 4.48(s,2H,$\underline{CH_2}O$); 6.07(s,1H,=$\underline{CH}$).
15	CH_3	CH_3	CH_3	165-167/atm.	56.7	1.87(s,3H,$\underline{CH_3}$); 2.22(s,3H,$\underline{CH_3}$); 2.30(s,3H,$\underline{CH_3}$).
16	CH_3SCH_2	CH_3	CH_3	57-58/0.2	6.8	1.98(s,3H,$\underline{CH_3}$); 2.08(s,3H,$S\underline{CH_3}$); 2.35(S,3H,$\underline{CH_3}$); 3.62(s,2H,$\underline{CH_2}S$).
16b	CH_3SOCH_2	CH_3	CH_3	101-103(mp)	81	2.03(s,3H,$\underline{CH_3}$); 2.36(s,3H,$\underline{CH_3}$); 2.67(s,3H,$SO\underline{CH_3}$); 3.94 and 4.12 (AB type d of d; 13.0 Hz; 2H,$\underline{CH_2}SO$).
16c	$CH_3SO_2CH_2$	CH_3	CH_3	146-147(mp)	77.6	2.03(s,3H,$\underline{CH_3}$); 2.40(s,3H,$\underline{CH_3}$); 3.13(s,3H,$SO_2\underline{CH_3}$); 4.70(s,2H, $\underline{CH_2}SO_2$).[a]
17	CH_3	CH_2SCH_3	CH_3	64-65/0.1	37.2	1.98(s,3H,$\underline{CH_3}$); 2.16(s,3H,$\underline{CH_3}$); 2.27(s,3H,$S\underline{CH_3}$); 3.72(s,2H,$\underline{CH_2}S$).
18	CH_3	CH_2SOCH_3	CH_3	96-97(mp)	90	2.07(s,3H,$\underline{CH_3}$); 2.30(s,3H,$\underline{CH_3}$); 2.66(s,3H,$SO\underline{CH_3}$); 4.13(s,2H,$\underline{CH_2}SO$).
20	p-$CH_3OC_6H_4$	CH_2OCH_3	p-$CH_3OC_6H_4$	206-208/0.1	43.2	3.47(s,3H,$O\underline{CH_3}$); 3.83(s,3H, $C_6H_4O\underline{CH_3}$); 3.86(s,3H,$C_6H_4O\underline{CH_3}$); 4.46(s,2H,$\underline{CH_2}O$); 6.80-7.57 (2 set of d of d, J=9.0 Hz & 9.0 Hz, 8H, $C_6\underline{H_4}OCH_3$).

*Elemental Analyses of these compounds were within acceptable limits

a) DMSO-d_6 as solvent

EXPERIMENTAL

Representative examples are described.

3-Carbethoxy-5-bromomethylisoxazole, 2a

Propargyl bromide (55.8 g of an 80% solution in toluene, 0.375 mole) was added over a 15 min period to an ice-cold stirred solution of ethyl chloroximeacetate[10] (34.9 g, 0.25 mole) in ether (150 ml). After stirring for 10 min at 0°C, a solution of triethylamine (38.3 ml, 0.275 mole) in ether (100 ml) was added dropwise over a 5.5 h period maintaining the temperature between 1°C and 4°C. The reaction mixture was stirred for an additional 20 min at 0°C, filtered to remove the triethylamine hydrochloride, and washed the solid with ether. The combined filtrate was washed with brine (2 x 100 ml), then dil hydrochloric acid (100 ml), dried ($MgSO_4$), filtered and concentrated to give 44.4 g of the crude product. Distillation gave 38.9 g (66.4%) of a clear liquid bp 98-100°C/0.25 mm.

Note: This compound is a powerful vesicant.

3-(2,6-Dichlorophenyl)-5-bromomethylisoxazole, 2.

Cold propargyl bromide (89.3 g of an 80% solution in toluene, 0.6 mole) was added slowly to a cold, stirred solution of crude 2,6-dichlorophenylnitrile oxide[11,12] (prepared from 95 g, 0.5 mole of

2,6-dichlorobenzaldoxime) in carbon tetrachloride (500 ml). The reaction mixture was stirred in an ice bath and allowed to reach room temperature overnight. The solution was concentrated on a rotary evaporator and then under vacuum when 124.9 g (81% from oxime) of an oil which crystallized, was obtained. This crude product was used in the subsequent reactions.

3-(2,6-Dichlorophenyl)-5-dimethylaminomethylisoxazole, 11a.

Dimethylamine (6.75 g of a 40 weight % solution in water, 0.15 mole) was added slowly to an ice-cold, stirred, solution of 3-(2,6-dichlorophenyl)-5-bromomethylisoxazole (15.35 g, 0.05 mole) in ether (250 ml). After a few minutes a white solid began to separate from the reaction mixture which was stirred at 0°C for 2 h. Cold molar sodium hydroxide (75 ml) was then added and stirring continued in the ice-bath for 20 min. The layers were separated and the organic layer washed with water, dried ($MgSO_4$), and concentrated to give 14.1 g of the crude product. Stirred the crude product with ether and filtered and dried the off-white solid, weighing 3.9 g [The spectral data and analysis of this solid indicates that it is probably the quart-ammonium N,N-dimethyl-N,N-bis-[3-(2,6-dichlorophenyl)-isoxazol-5-methyl]ammonium bromide]. The ether solution was concentrated to give 9.8 g of an oil, which on distillation gave 6.7 g (48.5%) of the desired product as a clear oil, bp 154-155°C/0.9 mm.

3-(2,6-Dichlorophenyl)-5-methoxymethylisoxazole, 3l

Sodium (0.85 g, 37 mmol) was dissolved in methanol (125 ml), and the solution cooled to room temperature. A solution of 3-(2,6-dichlorophenyl)-5-bromomethylisoxazole (11.35 g, 37 mmol) in methanol (25 ml) was added and the reaction mixture stirred at room temperature overnight, by which time a tlc indicated complete reaction. The reaction mixture was concentrated and the residue taken up in ether (100 ml). The ether extract was washed with water, dried ($MgSO_4$), and concentrated to give 9.5 g of an oil, which on distillation gave 9.35 g (98%) of the desired compound, bp 138-140°C/0.1 mm.

3-(2,6-Dichlorophenyl)-5-methylthiomethylisoxazole, 7c

n-Butyllithium (190 ml of a 2.1 molar solution in n-hexane, 0.4 mole) was added to THF (750 ml) at -70°C in a nitrogen atmosphere. Methyl mercaptan was bubbled into this solution for 15 min, maintaining the temperature below -55°C. After the addition allowed the reaction mixture to warm to room temperature (about 1 h) and stirred for an additional hour at room temperature. During the last half hour removed the excess methyl mercaptan by bubbling nitrogen through the reaction mixture.
The lithium methylmercaptide solution was cooled to 0°C, and a solution of 3-(2,6-dichlorophenyl)-5-bromomethylisoxazole (107.95 g, 0.35 mole), in THF (125 ml) - cooled to 0°C - was added over a 5 min period to the stirred solution. The stirred reaction mixture was allowed to reach ambient temperature, and stirred an additional 2 h, and then concentrated. The residue was taken up in ethyl

acetate (400 ml). The extract was washed with water and brine, dried ($MgSO_4$), and concentrated to give 95.04 g of an oil. Distillation gave 90.3 g (94%) of the desired compound as a clear oil, bp 153-155°C/0.5 mm.

3-(2,6-Dichlorophenyl)-5-methylsulfoxidemethylisoxazole, 9c

A solution of m-chloroperbenzoic acid (85% pure, 0.88 g, 4.4 mmol) in methylene chloride (10 ml) was added to a solution of 3-(2,6-dichlorophenyl)-5-methylthiomethylisoxazole (1.08 g, 4 mmole) in methylene chloride (10 ml) in an ice-bath, and the mixture was stirred at 0°C for 0.5 h and then at room temperature for 1 h. The reaction mixture was washed sequentially with 5% aqueous sodium bisulfite, with aqueous sodium bicarbonate, with water, and then dried ($MgSO_4$), filtered and concentrated to give 1.25 g of the crude sulfoxide. Recrystallization from benzene gave 1.0 g (88.5%) of white crystals, mp 150-152°C.

3-(2,6-Dichlorophenyl)-5-methylsulfonylmethylisoxazole, 10c

Repeating the above reaction using double the amount of m-chloroperbenzoic acid, and a 2 h reaction time at room temperature gave an 80% yield of the sulfone, which was recrystallized from ethyl acetate as white crystals, mp 182-184°C.

3-(5-)Methoxymethyl-5-(3-)methylisoxazole, 3a and 13

A mixture of 1-methyloxypentane-1,3-dione (130 g, 1 mole) and hydroxylamine hydrochloride (84 g, 1.2 mole) in water (500 ml) was stirred at room temperature for 4 h, then cooled in an ice-bath and carefully neutralized with aqueous sodium hydroxide (48 g, 1.2 mole in 250 ml water). The oily layer was separated and the aqueous layer continuously extracted with ether overnight. The oil and ether extract were dried ($MgSO_4$), filtered and the ether removed by distillation. Distillation of the residue gave 101 g of a colourless liquid, bp 76-79°C/9 mm. The glc and pmr spectrum indicated that the product was a mixture of 62% 3-methoxymethyl-5-methylisoxazole, 13, and 38% of 3-methyl-5-methoxymethylisoxazole, 3a.

Separation of 3-methoxymethyl-5-methylisoxazole, 13, from 3-methyl-5-methoxymethylisoxazole, 3a.

n-Butyllithium (37 ml of a 2.17 molar solution in n-hexane, 0.08 mole - 40% stoichiometry), was added slowly to a well stirred solution of the isomeric mixture 13 and 3a obtained as described above (25.4 g, 0.2 mole) in dry THF (300 ml) in a nitrogen atmosphere, the temperature being maintained below -65°C. The amber coloured reaction mixture was stirred at -75°C for an additional 30 min and then poured, with stirring into excess, well powdered dry ice. The reaction mixture was allowed to reach ambient temperature and then concentrated. The residue was washed well with ether and the resulting solid separated by filtration.

The combined ethereal layer was concentrated and distilled to give 13 g of a colourless oil, bp 72-74°C/9 mm whose pmr spectrum (see Table 3, compound 13) indicated it was the 3-methoxymethyl-5-methylisoxazole, 13.

The lithium salt, the ether insoluble solid, was taken up in water and acidified to pH 2 with dil hydrochloric acid. The solution became dark purple. Saturated the aqueous solution with salt and extracted with ethyl acetate. The combined ethyl acetate layers were dried and concentrated to give 9.5 g of a dark coloured oil. Distillation of this oil (either alone or in presence of cupric oxide), under reduced pressure resulted in evolution of gas and distillation of a clear mobile oil. Redistillation gave 5 g of 3-methyl-5-methoxymethylisoxazole, 3a, bp 36-37°C/0.2 mm.

3-Methyl-5-methoxymethylisoxazole, 3a, from 3-methylisoxazole-5-methanol, 4.

Sodium hydride (20.85 g of 56% in oil, 486.7 mmole), was washed with hexane and added portionwise over 30 min in a nitrogen atmosphere, to a stirred solution of 3-methylisoxazol-5-methanol, 4 (50 g, 442.5 mmole) in dry THF (500 ml) cooled in an ice-bath. Stirring was continued at 0°C for an additional 2 h. Methyl iodide (41 ml, 665 mmole) was added dropwise over a 30 min period and stirring was continued for an additional 2 h at room temperature. The reaction mixture was allowed to stand and the supernatant organic layer decanted. The salt was washed with ether (2 x 100 ml). The combined organic layers were concentrated and the residue was distilled to give 51.9 g (92.3%) of 3-methyl-5-methoxymethylisoxazole, 3a, as a colourless oil, bp 36-37°C/0.2 mm.

3-Methyl-5-octyloxymethylisoxazole, 3g.

A mixture of 3-methylisoxazol-5-methanol (11.3 g, 0.1 mole) and mesyl chloride (12.65 g, 0.11 mole) in methylene chloride (60 ml) was stirred in an ice-brine bath and the temperature maintained at -8°C. A solution of triethylamine (15.3 g - 21.2 ml, 0.15 mole) in methylene chloride (30 ml) was added slowly and the mixture stirred for an additional 2 h, and allowed to warm to room temperature. The reaction mixture was washed quickly with brine (2 x 25 ml), dried ($MgSO_4$), and concentrated to give the crude mesylate, 19 g, which was used as such.

A solution of 1-octanol (1.3 g, 0.1 mole) in THF (15 ml) was cooled to 0°C in a nitrogen atmosphere, and sodium hydride (0.5 g of 56% in oil, 0.105 mole - prewashed with hexane) added. Stirring was continued at 0°C for an additional hour. To this solution, a solution of the mesylate described above (1.92 g, 0.1 mole) in THF (5 ml), was added over 5 min, and stirring continued at 0°C for 1 h, at which time the tlc showed no starting material. The reaction mixture was concentrated, the residue stirred with water and methylene chloride and the organic layer separated. The organic layer was dried ($MgSO_4$), filtered and concentrated, and the residue was distilled to give 1.8 g (86%) of a colourless oil, bp 94-95°C/0.1 mm.

3-Methyl-5-methylthiomethylisoxazole, 7a.

n-Butyllithium (625 ml of a 1.6 molar solution in n-hexane, 1 mole) was added slowly to a stirred, *cold (-70°C) solution of 3,5-dimethylisoxazole (97.1 g, 1 mole) in dry THF* (900 ml) in a nitrogen atmosphere. The clear yellow solution was stirred at -75°C for 1 h. This solution was added slowly under nitrogen to a stirred, cold (-75°C) solution of dimethyldisulfide (110 ml, 1.2 mole) in dry THF (900 ml) in a nitrogen atmosphere over a 30 min period maintaining the temperature of the reaction mixture below -65°C. Stirred an additional 15 min at -75°C, then allowed to reach room temperature. At about -25°C a solid came out of solution. Concentrated the reaction mixture and extracted the residue with ether (1.5 l). The ether extract was washed with water (2 x 300 ml), dried ($MgSO_4$), and concentrated to give 146.5 g of a yellow mobile oil. Distillation using a Vigreaux column gave 124.5 g (87%) of the desired compound as a colourless oil, bp 100-102°C/9 mm.

3,4,5-Trimethylisoxazole, 15.

A mixture of 3-methylpentane-2,4-dione[9] (145 g, 1.27 mole), hydroxylamine hydrochloride (88.4 g, 1.27 mole), and water (900 ml) was stirred at room temperature overnight. The reaction mixture was extracted with methylene chloride (4 x 150 ml), and the combined organic layers dried ($MgSO_4$), filtered and concentrated to give 145.7 g of an oil. Distillation using a Vigreaux column gave 80 g (56.7%) of the desired compound, bp 165-167°C.

3-Methylthiomethyl-4,5-dimethylisoxazole, 16, and 3,4-dimethyl-5-methylthiomethylisoxazole, 17.

Starting with 3,4,5-trimethylisoxazole (33.3 g, 0.3 mole), the reaction as described for the preparation of 3-methyl-5-methylthiomethylisoxazole, 7a, was repeated. The crude product (48.1 g) was distilled and the fraction, bp 53-54°C/0.08 mm, 29.4 g (62.4%) was chromatographed on Silica CC-7 using hexane to hexane-ethyl acetate 9:1 gradient elution, to give 3.2 g (6.8%) of 3-methylthiomethyl-4,5-dimethylisoxazole, 16, as a colourless oil, bp 57-58°C/0.2 mm, and 17.5 g (37.2%) of 3,4-dimethyl-5-methylthiomethylisoxazole, 17, as a colourless oil, bp 64-65°C/0.1 mm.

3,4-Di-(p-methoxyphenyl)-5-methoxymethylisoxazole, 20.

n-Butyllithium (90 ml of a 2.22 molar solution in n-hexane, 0.198 mole) was added over a 30 min period, in a nitrogen atmosphere, to a stirred, ice-cold solution of desanisoin oxime (26.77 g, 0.099 mole), in dry THF (350 ml). Stirred for an additional 35 min at 0°C and then added a solution of methyl methoxyacetate (10.3 g, 0.099 mole) in THF (50 ml) over a 15 min period. The resulting red solution was stirred at 0°C for 1 h, and 3 N hydrochloric acid (400 ml) was added to the cooled solution, after which it was heated to reflux for 1 h. Concentrated the reaction mixture and dissolved the residue in hot ethanol. After allowing to cool overnight, a yellow solid, 1.6 g, whose

spectral characteristics resembled desoxyanisoin crystallized out. The filtrate was concentrated and gave 30.1 g of a thick wax whose pmr spectrum indicated that cyclization was not complete. The residue was dissolved in benzene (250 ml), P_2O_5 (14 g, 0.2 mole) was added and the mixture was stirred well and heated under reflux for 1 h, giving a light orange solution and a black gum. The orange solution was filtered hot and concentrated giving 24 g of a yellow oil, which on distillation gave 14 g (43.2%) of a colourless oil, bp 206-208°C/0.1 mm.

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REFERENCES

1. R. Huisgen, Angew. Chem. (Int.), 1963, 2, 565.
2. C. Grundmann and P. Grunanger, The Nitrile Oxides, Springer-Verlag, N.Y. (1971).
3. A.O. Fitton and R.K. Smalley, Practical Heterocyclic Chemistry, Academic Press, New York, 1968, p. 28.
4. R.G. Micetich, Can. J. Chem., 1970, 48, 467.
5. R.G. Micetich, Can. J. Chem., 1970, 48, 2006.
6. J. Gainer, G.A. Howarth, W. Hoyle, S.M. Roberts, and H. Suschitzky, J. Chem. Soc., 1976, 994.
7. P. Bravo and G. Gaviraghi, J. Het. Chem., 1977, 14, 37.
8. A.W. Johnson, E. Markham and R. Price, Org. Syn., 1962, 42, 75.
9. C.F. Beam, M.C.D. Dyer, R.A. Schwarz, and C.R. Hauser, J. Org. Chem., 1970, 35, 1806.

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