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CONVERSION OF 2-ISOXAZOLINES TO ISOXAZOLES

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Abstract—A convenient and easy conversion of 2-isoxazolines to isoxazoles is described. The reaction proceeds *via* N-bromosuccinimide bromination and subsequent dehydrobromination with bases, and has considerable application both to alkyl- and aryl-mono and 3,5-disubstituted 2-isoxazolines.

THE two methods most commonly used for the synthesis of isoxazoles are (a) the cyclization of β-diketones or α-acetylenic ketones or aldehydes, and (b) the condensation of nitrile oxides with triple bond compounds.[1] The former method often results in mixtures of isomeric products and the latter is limited by the availability of triple bond compounds. The corresponding double bond compounds are more available and react with nitrile oxides to give 2-isoxazolines. A simple and easy method for the oxidation of 2-isoxazolines to isoxazoles is, therefore, of interest.

The oxidation of 2-isoxazolines to isoxazoles is more difficult than the oxidation of pyrazolines to pyrazoles. Only 3,5-diaryl-2-isoxazolines are easily oxidized to isoxazoles by chromic trioxide in acetic acid solution, while both 3-aryl-5-alkyl- and 3-alkyl-5-aryl-2-isoxazolines under similar conditions are not affected or yield products of degradation.[2] Bromine,[3] which readily transforms pyrazolines to pyrazoles, as well as selenium dioxide[4] do not affect 2-isoxazolines, and potassium permanganate has been successful only in a very few cases;[5,6] usually it does not affect the isoxazoline ring and has been used, therefore, to oxidize double or triple bonds in side chains.[7] Chromic trioxide or manganese dioxide in acetone have been reported to oxidize stereoselectively *cis* 3,4,5-triphenyl- and 3,5-diaryl-4-carbethoxy (or 4-nitro)-2-isoxazolines.[4]

It has now been found that N-bromosuccinimide is a suitable reagent for bromination of 2-isoxazolines and subsequent dehydrobromination to isoxazoles. Usually the intermediate bromoderivative has not been isolated, and the reaction mixture was treated directly with weak bases (very often K acetate, more seldom triethylamine or KOH). The reaction is applicable to monoaryl- or 3,5-diaryl-2-isoxazolines as well as monoalkyl- or 3,5-dialkyl-2-isoxazolines.

[1] For a review on isoxazole synthesis see A. Quilico, *The Chemistry of Heterocyclic Compounds, Five and Six-Membered Compounds with N and O* (Edited by A. Weissberger) p. 5. Interscience, New York (1962).
[2] K. v. Auwers and H. Müller, *J. Prakt. Chem.* **137**, 102 (1933); G. Stagno d'Alcontres, *Gazz. Chim. Ital.* **82**, 627 (1952).
[3] Ref. 1, p. 102.
[4] G. Stagno d'Alcontres and G. Lo Vecchio, *Gazz. Chim. Ital.* **90**, 347 (1960).
[5] W. R. Vaughan and J. L. Spencer, *J. Org. Chem.* **25**, 1160 (1960).
[6] P. Venturella, A. Bellino and S. Cusmano, *Ann. Chim., Rome* **51**, 1074 (1961).
[7] A. Quilico, P. Grünanger and R. Mazzini, *Gazz. Chim. Ital.* **82**, 349 (1952).

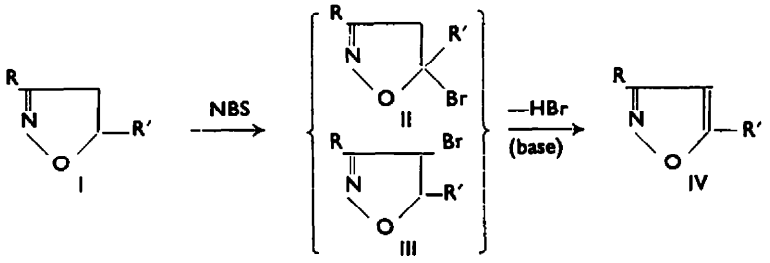
TABLE 1. ISOXAZOLES V (IV)

N.	R =	R′ =	M.p. (or b.p./mm)	Recrystallization solvent and shape of crystals[a]	Yield (%)	Ref[b]	Molecular formula	UV Spectra λ_{max} (mμ)	UV Spectra log ε
1	H	C_6H_5	(150°/50)	liquid: $n_D^{21} = 1{\cdot}5860$	81	8, 9	C_9H_7NO	265	4·20
2	C_6H_5	H	(70–75°/1)	liquid: $n_D^{24} = 1{\cdot}5632$	88	11, 12	C_9H_7NO	240	4·09
3	CH_3	n·C_8H_{17}	(101°/0·4)	liquid: $n_D^{20} = 1{\cdot}4570$	71	—	$C_{12}H_{21}NO$	< 220	
4	CH_3	C_6H_5	65°	methanol–water: leaflets		13, 14	$C_{10}H_9NO$	261·5	4·27
5	CH_3	$COOCH_3$	103–104°	methanol: leaflets	85	10	$C_6H_7NO_3$	226	3·98
6	C_6H_5	CH_3	42°	Petr. ether: leaflets	73	15	$C_{10}H_9NO$	240	4·15
7	C_6H_5	CH_2Cl	69·5°	pentane: soft white needles	28	16	$C_{10}H_8ClNO$	242	4·08
8	C_6H_5	CH_2Br	85–86°	methanol: leaflets	70	17	$C_{10}H_8BrNO$	227	4·20
9	C_6H_5	n·C_4H_9	(148°/0·6)	liquid: $n_D^{20} = 1{\cdot}5420$	92	—	$C_{13}H_{15}NO$	241	4·10
10	C_6H_5	n·C_8H_{17}	24–25°	pentane: white needles	95	—	$C_{17}H_{23}NO$	240	4·17
11	C_6H_5	C_6H_5	141°	ethanol: leaflets	90	18, 19	$C_{15}H_{11}NO$	245	4·25
								267	4·32
12	C_6H_5	p·ClC_6H_4	177°	benzene: needles	90	20	$C_{15}H_{10}ClNO$	248 (fl)	(4·26)
								273	4·44
13	C_6H_5	$CH{=}CHC_6H_5$	135°	methanol: prisms		21	$C_{17}H_{13}NO$	228	4·40
								235	4·36
								304	4·44
14	C_6H_5	α·naphthyl	76°	pentane–benzene: needles	96	—	$C_{19}H_{13}NO$	225	4·72
								301·5	4·10
15	C_6H_5	β·naphthyl	163°	ethanol: soft white needles	84	22	$C_{19}H_{13}NO$	236	4·54
								256	4·62
								298	4·33
16	C_6H_5	$COCH_3$	103–104°	methanol: leaflets	51	23, 24	$C_{11}H_9NO_2$	238	4·33
17	C_6H_5	$COOCH_3$	108°	methanol: needles	66	·	$C_{11}H_9NO_3$	227·5	4·24
18	C_6H_5	CN	88–89°	hexane: needles	80	—	$C_{10}H_6N_2O$	225	4·36

[a] Products are all colourless, unless otherwise stated.

[b] Only Refs, relating to the oldest known synthesis and to the method by which comparison samples have been prepared, are given. For additional literature see Ref. 1.

The isoxazoles prepared by this method have been listed in Table 1; yields are usually good and depend chiefly upon the purification of products. Bromination is particularly fast with 5-acyl-2-isoxazolines, whereas it is often incomplete with 5-alkyl substituted 2-isoxazolines.

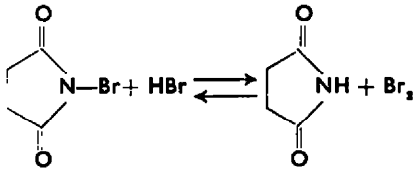


In 3,5-diphenyl-2-isoxazolines (I, R = R′ = C_6H_5) the bromine atom enters the position 5 and as soon as bromination is complete hydrogen bromide is eliminated from the product even if the reaction mixture is evaporated *in vacuo* at low temperature. Similarly, in the condensation of benzonitrile oxide with α-bromostyrene,[25] isolation of the 5-bromoderivative (II) is not possible. 3,5-Diphenyl-4-bromo-2-isoxazoline (III, R = R′ = C_6H_5), prepared by an independent route,[26] is perfectly stable under bromination conditions (boiling for 0·5 hour in CCl_4 solution in the presence of α,α′-azoisobutyronitrile). The mechanism suggested is, therefore, believed to be the most probable for all other 5-aryl-substituted 2-isoxazolines.

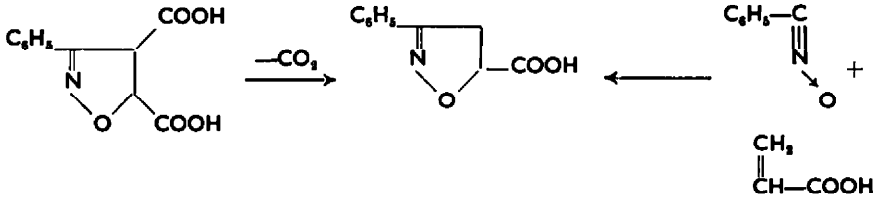
As with 5-alkyl-substituted 2-isoxazolines it has been impossible to isolate the extremely unstable intermediate bromoderivatives, bromination may proceed, at least in part, through the 4-bromoderivative (III).[27]

[8] L. Claisen and R. Stock, *Ber. Dtsch. Chem. Ges.* **24**, 130 (1891).
[9] Identical with sample obtained from 5-phenyl-2-isoxazoline by chromic trioxide oxidation: P. Grünanger, unpublished results. Ring opening with MeONa gives ω-cyanacetophenone.
[10] L. Claisen, *Ber. Dtsch. Chem. Ges.* **42**, 59 (1909).
[11] G. Stagno d'Alcontres and P. Grünanger, *Gazz. Chim. Ital.* **80**, 741 (1950).
[12] R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.* 2215 (1962).
[13] L. Claisen and O. Lowman, *Ber. Dtsch. Chem. Ges.* **21**, 1149 (1889); M. Ceresole, *Ibid.* **17**, 812 (1884).
[14] Identical with the product obtained from acetonitrile oxide and phenylacetylene: see Ref. 36.
[15] Identical with the product obtained from benzonitrile oxide and 2-bromopropene.
[16] G. Stagno d'Alcontres and G. Cuzzocrea, *Atti Soc. Peloritana Sci.* **3**, 179 (1956/57).
[17] G. Stagno d'Alcontres and G. Lo Vecchio, *Gazz. Chim. Ital.* **90**, 1239 (1960).
[18] C. Goldschmidt, *Ber. Dtsch. Chem. Ges.* **28**, 2540 (1895).
[19] A. Claus, *J. Prakt. Chem.* [2] **54**, 405 (1896); see also Ref. 26.
[20] P. Grünanger and P. Vita Finzi, *Gazz. Chim. Ital.* **89**, 1771 (1959).
[21] R. Ciusa and A. Terni, *Atti Accad. Naz. Lincei* [5] **20**, II, 25 (1911).
[22] A. Banchetti, *Gazz. Chim. Ital.* **70**, 761 (1940); R. B. Shenoi, R. C. Shah and T. S. Wheeler, *J. Chem. Soc.* 247 (1940).
[23] L. Panizzi, *Gazz. Chim. Ital.* **73**, 99 (1943).
[24] P. Grünanger and S. Mangiapan, *Gazz. Chim. Ital.* **88**, 149 (1958).
[25] P. Grünanger, *Gazz. Chim. Ital.* **84**, 359 (1954).
[26] G. Stagno d'Alcontres and P. Grünanger, *Gazz. Chim. Ital.* **80**, 831 (1950).
[27] Experiments now in progress with the cooperation of A. Perotti and the aid of NMR spectroscopy should indicate that in these cases the bromine atom goes in both the 4- and 5-positions, and that the dehydrobromination rate is much faster for II than for III.

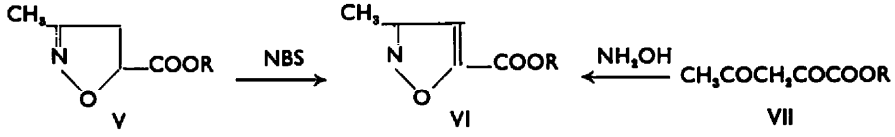
The elimination of hydrogen bromide during bromination is shown by the bromine development, which has been noted in nearly all cases, except when the bromoderivative has been actually isolated (see the 2-isoxazolines derived from acenaphtylene[28]). The bromine comes clearly from the following equilibrium:



The formation of 3-phenylisoxazole-5-carboxylic acid (IV, R = C_6H_5; R′ = COOH) of known and unequivocal structure[29] from methyl 3-phenyl-2-isoxazoline-5-carboxylate (I, R = C_6H_5, R′ = $COOCH_3$) represents the first experimental evidence of 4-decarboxylation of 3-phenyl-2-isoxazoline-4,5-dicarboxylic acid and related derivatives, obtained by different routes:[30]



The condensation product of nitroethane with methyl acrylate has the structure of methyl 3-methyl-2-isoxazoline-5-carboxylate (V, R = CH_3) and is not the 4-carboxylate reported by Bachman and Strom.[31] In fact, the 2-isoxazoline derivative is easily converted to methyl 3-methylisoxazole-5-carboxylate (VI, R = CH_3), identical with the product obtained by the procedure of Claisen[10] from the β-dicarbonyl compound (VII) through the free acid (VI, R = H). It is, therefore, reasonable to conclude that the 3-ethyl- and 3-propyl-derivatives prepared by Bachman and Strom also have the methyl 3-alkyl-2-isoxazoline-5-carboxylate structure.



EXPERIMENTAL

All m.ps are uncorrected. UV spectra were determined in 95% EtOH by means of a Perkin–Elmer Model 137 UV spectrophotometer. Microanalyses were performed by Dr. Lucia Maggi Dacrema.

2-Isoxazolines. The 2-isoxazolines were prepared by condensation of nitrile oxides and ethylenic compounds, except 5-phenyl-2-isoxazoline, prepared in low yield from fulminic acid and styrene

[28] G. Bianchi, P. Grünanger and A. Perotti, *Tetrahedron Letters* 2157 (1964).

[29] J. Schottle, *Ber. Dtsch. Chem. Ges.* **45**, 2340 (1912); Ref. 23; A. Quilico and G. Speroni, *Gazz. Chim. Ital.* **76**, 148 (1946); E. Mugnaini e P. Grünanger, *Rend. Accad. Naz. Lincei* [7] **14**, 95, 275 (1953); A. Quilico and P. Grünanger, *Ist. Lomb. Sci. Lett.* **88**, 990 (1955).

[30] A. Quilico, G. Stagno d'Alcontres and P. Grünanger, *Nature Lond.* **166**, 226 (1950); Ref. 6, 11; A. Quilico and P. Grünanger, *Gazz. Chim. Ital.* **85**, 1250, 1449 (1955); P. Grünanger and P. Vita Finzi, *Rend. Accad. Naz. Lincei* **26**, 386 (1959).

[31] G. B. Bachman and L. E. Strom, *J. Org. Chem.* **28**, 1150 (1963).

following the procedure already known,[32] and 3-phenyl-2-isoxazoline, obtained by alkaline degradation of Mannich base methiodide as described.[33] The physical properties of previously unknown 2-isoxazolines are reported in Table 2: acetonitrile oxide has been prepared *in situ* from nitroethane and phenylisocyanate,[34] benzonitrile oxide from benzohydroxamyl chloride and 14% NaOH.[35] All 3-phenyl-2-isoxazolines present the typical absorption band at 261–264 mμ, except 3-phenyl-5-cyano-2-isoxazoline (λ_{max} = 257 mμ; log ε 4·14).

Reaction of 2-isoxazolines with N-*bromosuccinimide.* To a solution of 2-isoxazoline (0·05 mole) in 200 ml CCl_4, N-bromosuccinimide (0·05 mole) and a trace of α,α'-azoisobutyronitrile were added and the mixture refluxed for 0·5–1 hr. The bright red colour first developed disappeared toward the end of the reaction, and evolution of hydrogen bromide was noticed.

TABLE 2. HITHERTO UNDESCRIBED 2-ISOXAZOLINES (I)

R =	R' =	M.p.	B.p./mm	Molecular formula	Anal. N% found	calcd.	UV Spectra λ_{max} (mμ)	log ε
H	C_6H_5		107–108°/0·4	C_9H_9NO	9·18	9·52	<220	
CH_3	n·C_8H_{17}		115°/0·6	$C_{12}H_{23}NO$	7·34	7·10	<220	
C_6H_5	n·C_4H_9	41°		$C_{13}H_{17}NO$	7·02	6·89	264	4·11
C_6H_5	n·C_8H_{17}	60°		$C_{17}H_{25}NO$	5·46	5·40	265	4·12
C_6H_5	α·naphthyl	62°		$C_{19}H_{15}NO$	5·09	5·13	223	4·91
							271	4·21
							281	4·17
C_6H_5	β·naphthyl	128°		$C_{19}H_{15}NO$	5·14	5·13	266	4·33

When the reaction was complete, the mixture was cooled, and 39·6 g fused K acetate and 13·2 ml glacial acetic acid added and the mixture refluxed for 1 hr, cooled and poured in ice-cold water, containing 30 g NaOH. The organic layer was separated, the aqueous layer extracted twice with ether and the extracts combined with the organic layer. After drying, the solvents were removed and the residue crystallized from a suitable solvent or distilled under red. press.

In some cases where the residue gave a positive Br_2 test, the product was heated with excess triethylamine. A second route is also possible: instead of treating with K acetate and acetic acid, the reaction mixture was filtered, and the residue after evaporation of the filtrate was treated with excess triethylamine for 8–10 hr, or with methanolic KOH. The isoxazole was then isolated in the usual manner.

Isoxazoles. Some isoxazoles Nos. 4, 11 from α-diketones, Nos. 4, 5, 6, 8, 16 from nitrile oxides, Nos. 1, 2, 12 from 2-isoxazolines (Table 1) were identified by direct comparison with samples prepared by known methods. Other isoxazoles (Nos. 7, 13, 15) have physical properties as given in the literature. The structure of isoxazoles prepared for the first time have been proved either by direct comparison with samples prepared by another route or by conversion to compounds of known structure:

3-*Methyl-5-n-octylisoxazole* (compound N. 3 Table 1). This is identical with the product obtained from nitroethane, phenyl isocyanate and 1-decyne,[36] (Found: N, 6·85. Calc. for $C_{19}H_{31}NO$: N, 7·17%).

3-*Phenyl-5-n-butylisoxazole* (No 9). This was synthetized from benzonitrile oxide and 1-hexyne in ether. (Found: N, 6·83. Calc. for $C_{13}H_{15}NO$: N, 6·96%.)

3-*Phenyl-5-n-octylisoxazole* (No. 10). This was synthetized from benzonitrile oxide and 1-decyne in ether as a colourless liquid which solidified on cooling. (Found: N, 5·73. Calc. for $C_{17}H_{23}NO$: N, 5·44%.)

[32] G. Stagno d'Alcontres and F. Mollica, *Rend. Accad. Naz. Lincei* **10**, 52 (1951); G. Stagno d' Alcontres and G. Fenech, *Gazz. Chim. Ital.* **82**, 175 (1952).
[33] Zu-Yoong Kyi and W. Wilson, *J. Chem. Soc.* 798 (1953).
[34] T. Mukaiyama and T. Hoshino, *J. Amer. Chem. Soc.* **82**, 5339 (1960).
[35] A. Quilico and G. Speroni, *Gazz. Chim. Ital.* **76**, 148 (1946).
[36] P. Vita Finzi and P. Grünanger, unpublished results.

3-Phenyl-5-α-naphthylisoxazole (No. 14). (Found: N, 5·19. Calc. for $C_{19}H_{13}NO$: N, 5·16%.)

Methyl 3-phenylisoxazole-5-carboxylate (No. 17). (Found: C, 64·84; H, 4·70; N, 7·12. Calc. for $C_{11}H_9NO_3$: C, 65·02; H, 4·46; N, 6·89%.)

The compound was hydrolysed with cold methanolic KOH and after acidification the m.p. of the known 3-phenylisoxazole-5-carboxylic acid, m.p. 178°, was not depressed on admixture with an authentic sample.[20]

3-Phenyl-5-cyanoisoxazole (No. 18). (Found: N, 16·70. Calc. for $C_{10}H_6N_2O$: N, 16·46%.) Basic hydrolysis yielded 3-phenylisoxazole-5-carboxylic acid.

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