Synthesis of Nitrooxazoles

W. James Hammar (1) and Mark A. Rustad*

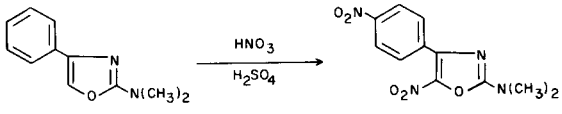
Riker Laboratories, Inc., 3M Company, St. Paul, Minnesota 55101

Received February 2, 1981

A reaction sequence involving halogenation and replacement of the halo substituent by a nitro group using dinitrogen tetraoxide has led to a general, convenient route to 5-nitrooxazoles. Reaction schemes employing both bromine and iodine as the halo substituent have been investigated; however, the method using iodine preceded by a mercuration step affords a better overall yield in the range of 20-50%. Both 2- and 4-nitrooxazoles can be prepared by this latter sequence, though in lower overall yields (4-12%).

J. Heterocyclic Chem., **18**, 885 (1981).

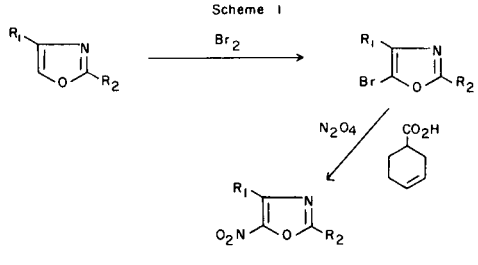
The oxazole ring is resistant to the usual strong acid nitration conditions. Oxazoles bearing phenyl substituents nitrate under a variety of conditions; however, the nitro group appears in the *para* position of the phenyl ring (2a-d). Activated aminooxazoles do undergo nitration on the oxazole ring (3) but the presence of phenyl substituents leads to dinitro derivatives. The alternative to direct nitration is a substitution reaction involving



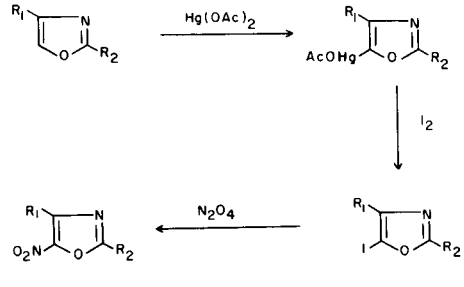
displacement of a labile substituent with nitrite. 4-Nitroisoxazoles have been prepared by a substitution process on 4-haloisoxazoles (4). 3-Nitroimidazo[1,2-*a*]benzimidazoles were prepared (5) by refluxing the 3-bromo derivative in dimethylformamide containing potassium nitrite. By a presumed radical pathway dinitrogen tetraoxide has been shown to effect the conversion of β-bromostyrene to β-nitrostyrene (6). Much earlier Stoermer reported the bromine in 2-bromobenzofurans can be replaced by a nitro group using dinitrogen trioxide (7). This heterogenous reaction is aided by periodically blowing the bromine vapor away. Later Stoermer (8) was able to accomplish this conversion in acetic acid solution at an elevated temperature to boil away the bromine. Recently Scherrer (9) in our laboratory has greatly expanded the generality of this benzofuran nitration procedure by using an olefinic bromine scavenger. This present paper reports the successful extension of this reaction sequence to the preparation of a wide variety of unknown nitrooxazoles. In addition a more convenient sequence involving a mercuration step has evolved which makes the overall conversion more versatile.

The oxazoles were prepared in standard fashion in fair yield (see Table I) by reaction of a α-bromoketone with the appropriate amide. Preparation of the nitrooxazole was conducted either via the bromo- or iodooxazole. Scheme I involves direct bromination of the oxazole followed by replacement of the bromine with dinitrogen tetraoxide. Direct reaction with dinitrogen tetraoxide fails. This work follows the initial discovery by Scherrer referred to above. In addition Scherrer found that with a 2-iodo substituted benzofuran the exchange reaction with dinitrogen tetraoxide is more facile and a scavenger is unnecessary (10). An iodo substituent is readily introduced into the oxazole ring by a mercuration/iodination sequence (11). Reaction of this iodooxazole with dinitrogen tetraoxide provides a superior route to 5-nitrooxazoles (Scheme II) with potential application to the synthesis of 2- and 4-nitrooxazoles. Yields in the best cases (not optimized) are above 50% overall from the oxazole (Table II). Scheme II does not work with ortho substituted 4-aryloxazoles which fail to mercurate in the 5-position presumably due to steric effects. In this very specific case one must rely on Scheme I to prepare the nitrooxazoles. Table II illustrates the 5-nitrooxazoles prepared using Scheme I and/or Scheme II. The latter scheme usually affords a slightly higher yield and appears to be independent of substituents since both aliphatic and aromatic oxazoles are converted quite readily to their corresponding nitrooxazoles. Scheme II is used to prepare 2- and 4-nitrooxazoles in poor yield (Table III); however, this represents the first synthesis of these classes of nitro heterocycles.

Scheme I

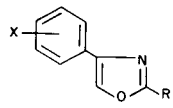


Scheme II



0022-152X/81/050885-04$02.25

Table I



4-Aryloxazoles

Compound No.	X	R	Yield	Recrystallization Solvent	Mp	Empirical Formula		Analysis Calcd.	(Found)
							C	62.0	(61.7)
1	*p*-Cl	CH_3	47%	hexane	87-89°	$C_{10}H_8ClNO$	H	4.2	(4.1)
							N	7.2	(7.3)
							C	62.0	(61.9)
2	*o*-Cl	CH_3	16%	(distilled)	bp 110-123/ 0.5 mm	$C_{10}H_8ClNO$	H	4.2	(4.1)
							N	7.2	(7.1)
							C	63.6	(63.6)
3	*p*-Cl	C_2H_5	40%	hexane	60-61°	$C_{11}H_{10}ClNO$	H	4.8	(4.9)
							N	6.8	(6.8)
							C	70.4	(70.3)
4	*p*-Cl	C_6H_5	62%	chloroform/hexane	126-128°	$C_{15}H_{10}ClNO$	H	3.9	(3.7)
							N	5.5	(5.5)
							C	67.8	(67.8)
5	*p*-F	CH_3	28%	hexane	52-54°	$C_{10}H_8FNO$	H	4.5	(4.4)
							N	7.9	(7.9)
							C	50.4	(50.3)
6	*o*-Br	CH_3	34%	(distilled)	bp 121-4/ 2.3 mm	$C_{10}H_8BrNO$	H	3.4	(3.4)
							N	5.9	(5.8)
							C	76.3	(76.6)
7	*p*-CH_3	CH_3	36%	hexane	47-48°	$C_{11}H_{11}NO$	H	6.4	(6.4)
							N	8.1	(8.1)
							C	69.8	(70.1)
8	*p*-OCH_3	CH_3	50%	ether/hexane	98-100°	$C_{11}H_{11}NO_2$	H	5.9	(5.8)
							N	7.4	(7.3)
							C	58.5	(58.9)
9	*p*-NO_2	CH_3	28%	ethanol	155-156°	$C_{10}H_8N_2O_3$	H	4.4	(3.8)
							N	13.6	(13.8)

EXPERIMENTAL (15)

General Procedure for the Preparation of 4-Aryloxazoles.

A mixture of 0.2 mole of bromoketone and 0.5 mole of amide were heated at 120-140° for three hours. This mixture was poured onto ice and partitioned between ether and water. The organic layer was washed with dilute sodium hydroxide solution, dilute hydrochloric acid solution and saturated sodium chloride solution. The organic layer was dried over magnesium sulfate. The oxazole was purified by distillation or filtration through silica gel eluting with carbon tetrachloride and recrystallizing the solid from an appropriate solvent. The details of the unknown oxazoles are recorded in Table I.

General Procedure for the Synthesis of Nitrooxazoles.

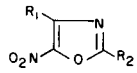
Scheme I.

The oxazole was dissolved in carbon tetrachloride (10 cc/g of solid) and one equivalent of bromine was added dropwise with stirring. After 0.5 hour at ambient temperature the carbon tetrachloride layer was decanted away and the solid was partitioned between ether and saturated sodium bicarbonate solution. The organic layer was washed with aqueous sodium bisulfite solution then saturated sodium chloride solution. The organic layer was dried over magnesium sulfate. The isolated bromooxazole was dissolved in dichloromethane (10 cc/g of bromooxazole) and two equivalents of 3-cyclohexene carboxylic acid was added. At ambient temperatures two equivalents of nitrogen tetroxide dissolved in dichloromethane (10 cc/g of nitrogen tetroxide) was added slowly. The reaction was stirred overnight at room temperature. The organic solution was washed sequentially with aqueous sodium bisulfite solution, 5% sodium hydroxide solution and saturated sodium chloride solution. The organic layer was dried over magnesium sulfate. The details of the compounds are recorded in Table II.

Scheme II.

An equimolar mixture of the oxazole and mercuric acetate was heated on a steam cone for 1-3 hours. Complete solution occurred followed by generation of a crystalline solid. The mixture was triturated with ether. The solid was washed with ether and air dried. This organomercurial was suspensed in carbon tetrachloride (2-4 cc/g of solid). A warm solution containing one equivalent of iodine in carbon tetrachloride was added dropwise as decolorization occurred. (In the preparation of 5-iodooxazoles this decolorization occurred in less than a minute. With 2- and 4-iodooxazoles decolorization took 1-2 hours.) The resulting mixture was filtered. The filtrate was washed with dilute sodium bisulfite solution and dried over magnesium sulfate. After removing the drying agent 3-4 equivalents of nitrogen tetroxide was added to the filtrate. (In the preparation of 5-nitrooxazoles the reaction was complete in 30-60 minutes. However, the reaction generally took longer, 5-24 hours, for 2-and 4-nitrooxazoles.) The reaction mixture was washed with dilute sodium bisulfite solution and dried over magnesium sulfate. The details of the compounds are recorded in Tables II and III.

Table II

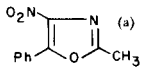
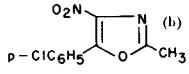
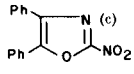


5-Nitrooxazoles

Compound No.	R_1	R_2	% Yield Scheme I	% Yield Scheme II	Recrystallization Solvent	Mp	Empirical Formula		Analysis Calcd.	(Found)
								C	56.8	(56.4)
10	C_6H_5	H	8	21	benzene/hexane	85-88°	$C_9H_6N_2O_3$	H	3.2	(3.1)
								N	14.7	(14.7)
								C	58.8	(59.1)
11	C_6H_5	CH_3	20	32	hexane	84-85°	$C_{10}H_8N_2O_3$	H	3.9	(3.8)
								N	13.7	(13.5)
								C	50.3	(50.5)
12	*o*-ClC_6H_4	CH_3	17	nil	ethyl acetate/ petroleum ether	110-112°	$C_{10}H_7ClN_2O_3$	H	2.9	(2.9)
								N	11.7	(11.8)
								C	50.3	(49.8)
13	*p*-ClC_6H_4	CH_3	30	40	ethyl acetate/ hexane	104-105°	$C_{10}H_7ClN_2O_3$	H	2.9	(3.0)
								N	11.7	(11.7)
								C	52.3	(52.1)
14	*p*-ClC_6H_4	C_2H_5	26		hexane	71-73°	$C_{11}H_9ClN_2O_3$	H	3.6	(3.6)
								N	11.1	(11.0)
								C	59.9	(59.6)
15	*p*-ClC_6H_4	C_6H_5	11		chloroform/ hexane	136-138°	$C_{15}H_9ClN_2O_3$	H	3.0	(2.9)
								N	9.3	(9.2)
								C	42.4	(42.5)
16	*o*-BrC_6H_4	CH_3	15	nil	ethyl acetate/ petroleum ether	109-112°	$C_{10}H_7BrN_2O_3$	H	2.5	(2.5)
								N	9.9	(10.1)
								C	42.4	(42.6)
17	*p*-BrC_6H_4	CH_3	36	41	ethanol	125-128°	$C_{10}H_7BrN_2O_3$	H	2.5	(2.6)
								N	9.9	(9.9)
								C	54.1	(53.9)
18	*p*FC_6H_4	CH_3	9	45	methanol	98-101°	$C_{10}H_7FN_2O_3$	H	3.2	(3.1)
								N	12.6	(12.6)
								C	60.5	(60.2)
19	*p*-$CH_3C_6H_4$	CH_3	24	48	methanol	85-96°	$C_{11}H_{10}N_2O_3$	H	4.6	(4.5)
								N	12.8	(12.9)
								C	56.4	(56.0)
20	*p*$CH_3OC_6H_4$	CH_3	9	40	methanol	114-117°	$C_{11}H_{10}N_2O_3$	H	4.3	(4.1)
								N	12.0	(11.9)
								C	47.8	(47.9)
21	*p*-$O_2NC_6H_4$	CH_3	2	43	methanol	117-121°	$C_{10}H_7N_3O_5$	H	3.1	(2.7)
								N	16.3	(16.1)
								C	52.2	(52.4)
22	*t*-Bu	CH_3	26			bp 80/2.5 mm	$C_8H_{12}N_2O_3$	H	6.6	(6.6)
								N	15.2	(15.1)
								C	54.5	(54.6)
23	CH_3	$-(CH_2)_4CH_3$		19	(a)		$C_9H_{14}N_2O_3$	H	7.1	(6.9)
								N	14.1	(13.9)
								C	58.8	(58.7)
24	CH_3	C_6H_5		52	ethyl acetate/ hexane	127-129°	$C_{10}H_8N_2O_3$	H	3.9	(3.8)
								N	13.7	(13.6)
								C	67.7	(67.7)
25	C_6H_5	C_6H_5	10	51	benzene/hexane	138-140°	$C_{15}H_{10}N_2O_3$	H	3.8	(3.7)
								N	10.5	(10.5)

(a) Short path distillation, bp.

Table III

Compound No.		Yield	Recrystallization Solvent	Mp	Empirical Formula		Analysis Calcd.	(Found)
26		5%	methanol	109-110°	$C_{10}H_8N_2O_3$	C	58.8	(58.6)
						H	3.9	(4.0)
						N	13.7	(13.7)
27		4%	hexane	92-94°	$C_{10}H_7ClN_2O_3$	C	50.3	(50.5)
						H	3.0	(2.7)
						N	11.7	(12.0)
28		12%	methanol	105-107°	$C_{15}H_{10}N_2O_3$	C	67.7	(67.4)
						H	3.8	(3.6)
						N	10.5	(10.7)

(a) Starting oxazole lit. (12). (b) Starting oxazole lit. (13). (c) Starting oxazole lit. (14).

Acknowledgement.

The authors are grateful to Dr. R. A. Scherrer (Riker Laboratories, Inc.) for many helpful discussions.

REFERENCES AND NOTES

(1) Current address is Central Research Laboratories, 3M Company, St. Paul, Minnesota 55144.

(2a) R. H. Wiley, *Chem. Rev.*, **37**, 402 (1945); (b) T. van Es and O. G. Backeberg, *J. Chem. Soc.*, 1363 (1963); (c) E. Gustak, *Ark. Kemi*, **24**, 15 (1952); (d) T. P. Sycheva, t. Kh. Trupp and M. N. Shchukina, *J. Gen. Chem. USSR*, **32**, 1051 (1962).

(3) R. Gompper and O. Christmann, *Chem. Ber.*, **92**, 1944 (1959).

(4) S. D. Sokolov, T. N. Egorova and N. S. Kuryatov, *Khim. Geterotsikl. Soedin.*, 1329 (1973), *Chem. Abstr.*, **80**, 27150n (1974).

(5) V. A. Anisimova and A. M. Simonov, *ibid.*, **2**, 258 (1975); *Chem. Abstr.*, **82**, 170796z (1975).

(6) T. E. Stevens, *J. Org. Chem.*, **25**, 1658 (1960).

(7) R. Stoermer, *Ber.*, **35**, 1633 (1902).

(8) R. Stoermer, *ibid.*, **44**, 1853 (1911).

(9) R. A. Scherrer, S. R. Rohlfing, R. M. Stern, W. J. Hammar, C. M. Leir and R. M. Winandy, Second Chemical Congress of the North American Continent, Las Vegas, Nevada, 1980, Abstract #MEDI 23.

(10) R. A. Scherrer, private communication.

(11) O. P. Shvaika and G. P. Klimisha, *Khim. Geterotsikl. Soedin.*, **5**, 677 (1966); *Chem. Abstr.*, **66**, 46356m (1967).

(12) G. Ya. Kondrat'eva and C.-H. Huang, *J. Gen. Chem. USSR.*, **32**, 2315 (1962).

(13) H. A. Houwing, J. Wildeman and A. M. VanLeusen, *Tetrahedron Letters*, 143 (1976).

(14) H. Bredereck and R. Gommpper, *Chem. Ber.*, **87**, 700 (1954).

(15) Melting points are uncorrected. Varian T-60-A (nmr) and Perkin Elmer 137 (ir) instruments were used to record spectral data on the compounds.