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AN IMPROVED PROCEDURE FOR THE PREPARATION OF 2-ISOXAZOLINES

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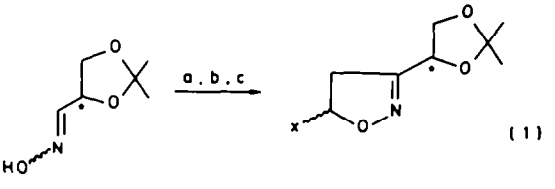
Abstract—Aldoximes were converted in high yields by N-Chlorosuccinimide into hydroxamic acid chlorides, and corresponding nitrile oxides generated by addition of triethylamine at 40–50° underwent 1,3-dipolar polar addition to alkenes, giving 2-isoxazolines. The whole procedure could be performed as a one-pot reaction. Oximes with other functions, sensitive to free chlorine could be converted selectively into hydroxamic acid chlorides by this procedure. Isopropylidene glyceraldoxime was added to acrolein diethylacetal thus affording an entrance to carbohydrate synthesis but the stereospecificity of the reaction is low. 2:3, 5:6-Di-O-isopropylidene-D-mannose oxime was converted to the N-hydroximinolactone by treatment with NCS and base.

2-Isoxazolines are obtained by 1,3-dipolar addition of nitrile oxides or nitronates to olefins.[1a-r] They prove to be of value as intermediates in organic synthesis.[2] The starting materials for this carbon–carbon coupling method are olefins, aldehydes, and aliphatic primary nitro compounds. These compounds are often relatively inexpensive and easily available chemicals which makes the method more attractive. The addition proceeds normally in good yields. Our laboratory has been engaged in a programme for developing novel routes to a number of heterocycles, cyclopentenoids, and polyols. It was found that the reduction of the 2-isoxazolines gave aldols in high yields and this method is therefore an alternative to the classical Claisen reaction.[1c,2c,f,i,m,n]

The most convenient procedure for the synthesis of the reactive nitrile oxides is dehydrohalogenation of hydroxamic acid chlorides which in turn are obtained by chlorination of the corresponding aldoximes with chlorine.[1a,3] The chlorination is preferably carried out in ether or chloroform at -30 to $-60°$. We have occasionally found that this procedure is rather capricious. The end point of the chlorination is sometimes difficult to determine (the introduction of chlorine is concluded when a transient greenish-blue colour appears). The high reactivity of chlorine towards other functional groups is another disadvantage. α-Oximinoacetone is chlorinated in the methyl group[4] and aromatic aldoximes containing electron donating groups, such as methyl or methoxy groups, are chlorinated in the nucleus.[1a,5] N-Bromosuccinimide has been used in a few cases[6] and recently water-insoluble oximes have been chlorinated with sodium hypochlorite in a two-phase system.[7]

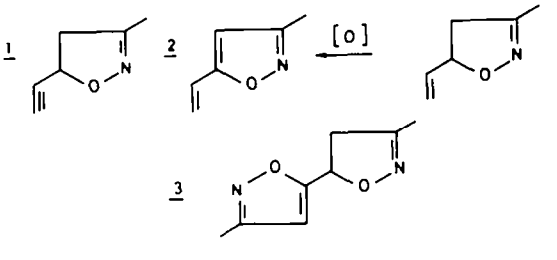
N-Chlorosuccinimide (NCS) provides a convenient method for chlorination of aromatic and aliphatic aldoximes in dimethylformamide.[8] We have found that NCS rapidly and selectively chlorinates aldoximes to hydroxamic acid chlorides at room temperature in dry chloroform with a trace of pyridine present. Subsequent addition of the olefin and triethylamine at 20–50° gave the 2-isoxazolines in good yields. The reactions were performed in the same flask. α-Oximinoacetone was not chlorinated in the methyl group, nor was chlorination observed in the aromatic ring of piperonal aldoxime. 2, 3-O-Isopropylidene-D-glyceraldoxime, obtained from D-mannitol, was chlorinated to the corresponding hydroxamic acid chloride and subsequently added to several olefins (eqn. 1). We thought that this reaction could serve in carbohydrate synthesis. However, the stereospecificity of the addition is poor.[9] The diastereomeric ratio is close to one according to the ^{13}C NMR spectra. Vinylene carbonate did not react with our nitrile oxides. The yields and the physical data of the 2-isoxazolines prepared are collected in Table 1. The mass spectra data were consistent with the structures given.



(1)

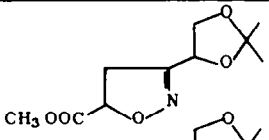
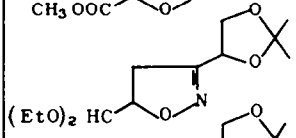
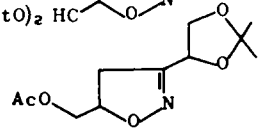
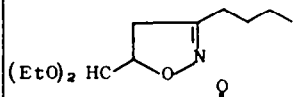
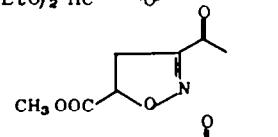
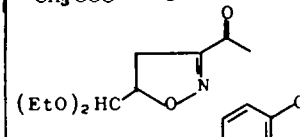
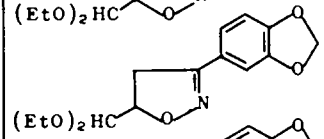
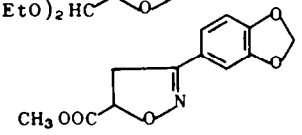
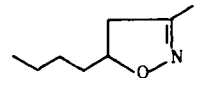
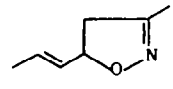
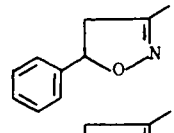
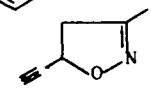
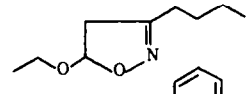
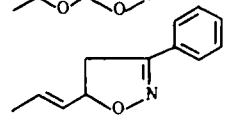
a. NCS b. CH_2CHX; X = $COOCH_3$, $CH(OEt)_2$, CH_2OAc; c. Et_3N

Vinylacetylene reacted preferentially at the double bond as was noted earlier.[10] 5-Vinylisoxazoles were recently prepared by oxidation of 5-vinylisoxazolines.[2f] Considerable amounts of **3** were also formed but **2** was not observed in the crude reaction mixture.

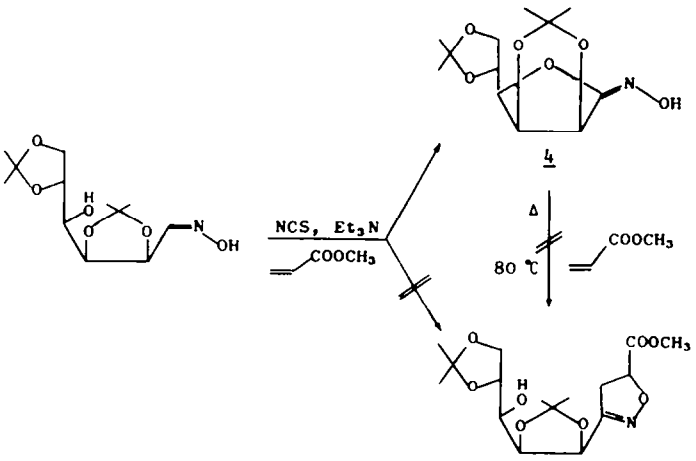


†Presented at the VIII International Symposium, Synthesis in Organic Chemistry, Cambridge, 19 July 1983.

Table 1. 2-Isoxazolines from olefins and oximes

2-Isoxazoline	Yield (%) [a]	^{1}H NMR, δ, multiplicity, Hz [b]
	80	1.39 (3H,s), 1.42 (3H,s), 3.30 (2H,d,J 9.4), 3.73 (3H,s), 3.8-4.3 (2H,m), 4.87 (1H,t,J 6), 4.99 (1H,t,J 8), in $CDCl_3$
	49	0.9-1.3 (6H,m), 1.35 (3H,s), 1.43 (3H,s), 3.03 (2H,d,J 9), 3.2-3.8 (4H,m), 3.8-5.0 (5H,m), in $CDCl_3$
	58 [b]	1.39 (3H,s), 1.45 (3H,s), 2.07 (3H,s), 2.86 (1H,dd,J 17 and 8), 3.12 (1H,ddd,J 17, 10, and 3), 3.7-4.4 (4H,m), 4.5-5.1 (1H,m) in $CDCl_3$
	54 [c]	0.92 (3H,br.t), 1.11 (3H,t,J 7), 1.18 (3H,t, J 7), 1.45 (4H,m), 2.25 (2H,t,J 7), 2.6-3.0 (2H,m), 3.2-3.9 (4H,m), 4.2-4.6 (2H,m)
	50 [d]	2.41 (3H,s), 3.26 (2H,d,J 9.3), 3.72 (3H,s), 5.0 (1H,t,J 9.3)
	33	1.17 (3H,t,J 7), 1.20 (3H,t,J 7), 2.40 (3H,s) 3.00 (2H,d,J 9), 3.3-3.8 (4H,m), 4.2-4.8 (2H, m)
	53	1.13 (3H,t,J 7), 1.20 (3H,t,J 7), 3.21 (2H,d, J 8), 3.3-3.9 (4H,m), 4.2-4.9 (2H,m), 5.9 (2 H,s), 6.6-7.2 (3H,m)
	60 [e,f]	3.52 (2H,d,J 9), 3.75 (3H,s), 5.05 (1H, t,J 9), 5.92 (2H,s), 6.6-7.3 (3H,m) in $CDCl_3$
	61	0.90 (3H,br.t), 1.0-1.8 (6H,m), 1.90 (3H,s), 2.43 (1H,dd,J 17 and 9), 2.83 (1H,dd,J 17 and 11), 4.0-4.7 (1H,m)
	72	1.68 (3H,d,J 5), 1.90 (3H,s), 2.54 (1H,dd,J 16 and 9), 2.91 (1H,dd,J 16 and 9), 4.5-5.1 (1H,m), 5.1-5.7 (2H,m)
	84	1.87 (3H,s), 2.68 (1H,dd,J 17 and 9), 3.16 (1H,dd,J 17 and 10), 5.27 (1H,dd,J 9 and 10), 7.11 (5H,s)
	14 [h]	1.95 (3H,s), 2.42 (1H,d,J 2), 2.89 (1H,dd,J 17 and 8), 3.12 (1H,dd,J 17 and 10), 4.92 (1 H, ddd,J 10, 8, and 2)
	56	0.93 (3H,br.t), 1.13 (3H,t,J 7), 1.3-1.9 (4H, m), 2.30 (2H,t,J 7), 2.5-2.9 (2H,m), 3.2-4.0 (2H,m), 5.26 (1H,dd,J 6 and 2)
	84	1.72 (3H, d, J 4), 2.6-3.6 (2H,m), 4.6-6.0 (3H,m), 7.0-7.8 (5H,m)

[a] Purified by prep.TLC; liquids. [b] $[\alpha]_D^{25}$ -3.7,$CHCl_3$. [c] b.p. 92-95 °C/0.2 mmHg. [d] b.p. 81 °C/0.15 mmHg. [e] m.p. 109 °C (methanol). [f] Analysis: Found C 57.35, H 4.41, N 5.72. Calc. C 57.83, H 4.45, N 5.62 %). [g] in CCl_4 unless otherwise stated. [h] 18 % of 3 is also obtained.



Scheme 1.

It was tried to use the sterically crowded 2:3, 5:6-di-O-isopropylidene-D-mannose oxime for inducing asymmetry in the isoxazoline moiety. The *N*-hydroximinolactone was the only product isolated from the reaction. Nor gave reflux of **4** with excess of methyl acrylate or styrene the desired isoxazoline (Scheme 1).

EXPERIMENTAL

α-Oximinoacetone was prepared according to Ref. 11.

2,3-O-Isopropylidene-D-glyceraldoxime. The distilled 2,3-O-isopropylidene-D-glyceraldehyde[12] contained *ca.* 10% acetic acid (^{1}H NMR). It was immediately added to an aqueous soln of hydroxylamine hydrochloride (1.2 eq) and sodium bicarbonate (1.5 eq), and stirred overnight. The soln was filtered and extracted with methylene chloride which was dried over sodium sulfate and evaporated. The crude oily oxime was sufficiently pure for further reactions. B.p. 80°/0.5 mmHg, the yield was 83%. $[\alpha]_D^{29}$ + 69.8°. ^{1}H NMR (CCl_4): δ 1.39 (3H,s), 1.42 (3H,s), 3.5–5.2 (3H, m), 6.84 and 7.29 (Σ 1H, d, *J* 4.4 and 6.8 H), 8.9 (1H, br.s.).

The other *oximes* were prepared according to standard procedures.

The olefins were commercial products.

General procedure for preparing 2-isoxazolines. Chlorsuccinimid (NCS, 20 mmole) was stirred in a flask containing dry chloroform (18 ml) and 0.1 ml pyridine. The oxime (20 mmole) was added at 25° in one portion. The chlorination was usually over in *ca* 10 min as observed by the disappearance of the suspended NCS. For larger batches it is advisable to cool the solution with tap water and add the oxime in portions. The olefin (25 mmole) was added and the temperature raised to 40–50°. Triethylamine (21 mmole in 3 ml of $CHCl_3$) was added drop by drop over *ca* 30 min. After a further 20 min at the same temperature the soln was washed with water (2 × 15 ml) dried, and evaporated *in vacuo*. The isoxazoline were purified by crystallization, distillation or by preparative TLC (SiO_2, CH_2Cl_2/CH_3CN, 0–10%).

If the olefin is sensitive to acids, e.g. ethyl vinyl ether, the hydroxamic acid chloride was instead added to a mixture of the olefin and triethylamine. For reactive olefins, such as acrylates or styrene, the 1,3-dipolar addition can with advantage be performed at room temp. Benzaldoxime was chlorinated rather slowly at 25° by NCS. The entire reaction was therefore performed at 40–50°. In order to avoid losses because of volatility the reactions with ethyl vinylether and vinylacetylene were performed at 20°.

1 and **3** (liquids) were separated by prep TLC (SiO_2, CH_2Cl_2, CH_3CN, 4%). The yield of **3** was 18%. ^{1}H NMR (CCl_4): δ 1.95 (3H, s), 2.19 (3H,s), 3.00 (1H, dd, J 17 and 8 Hz), 3.27 (1H, dd, J 17 and 10 Hz), 5.4 (1H, dd, J 8 and 10 Hz), 5.98 (1H, s).

The hydroximinolactone **4** was isolated in a yield of 70–80% by treatment of 2:3, 5:6-di-O-isopropylidene-D-mannose oxime with an equimolar amount of NCS in dry chloroform in the presence of one equivalent of pyridine, m.p. 170–173° (lit[12] 174–174.5°).

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