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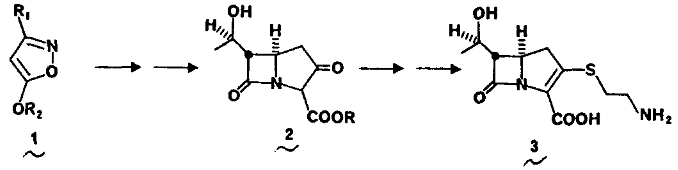
SYNTHESIS AND NUCLEOPHILIC SUBSTITUTIONS OF 3-ALKYL-5-CHLOROISOXAZOLES

R.V. Stevens† and K.F. Albizati[1]*
Department of Chemistry and Biochemistry
University of California at Los Angeles
Los Angeles, CA 90024

Summary. A 3-alkyl-5-chloroisoxazole synthesis is described based on the cycloaddition of nitrile oxides to 1,1-dichloroethylene, an inexpensive dipolarophile. Substitution of the chloride in these adducts by various nucleophiles is also described.

In connection with our studies on the synthesis of thienamycin (3) via nitrone-olefin cycloaddition,[2] we required a method for synthesizing 3-alkyl-5-alkoxy-isoxazoles (1). A number of methods were envisioned for converting (1) to (2) which would be more efficient than existing protocols.[3] We sought a route to synthesize a family of isoxazoles (1) which would allow easy variation of both R_1 and R_2.



A direct solution to this problem is the 1,3-dipolar cycloaddition of nitrile oxides to alkoxyacetylenes. A few isolated reports have described this approach.[4] However, the ability to vary R_2 of isoxazole (1) depends on the availability of a variety of alkynyl ethers. Unfortunately, synthetic methods allowing access to this relatively rare class of compounds are scarce and not flexible enough to allow wide structural variation.[5] Thus, we avoided this direct approach and developed a more versatile and economical two-step sequence.[6]

When various nitrile oxides were generated in 1,1-dichloroethylene (4) in the presence of excess triethylamine the 5-chloroisoxazoles[7] could be isolated as colorless oils or crystalline solids in the yields shown in Table I. Both nitro compounds and hydroxamoyl halides could serve as nitrile oxide precursors,[8] although the yields tended to be higher with the latter. The 5-chloroisoxazoles (6) are presumed to arise by dehydrochlorination of a 5,5-dichloro-Δ^2-isoxazoline intermediate (5) formed in the cycloaddition process. These isoxazolines were neither isolated nor detected. The alternative regioisomeric 4-chloroisoxazoles were never observed as reaction products.

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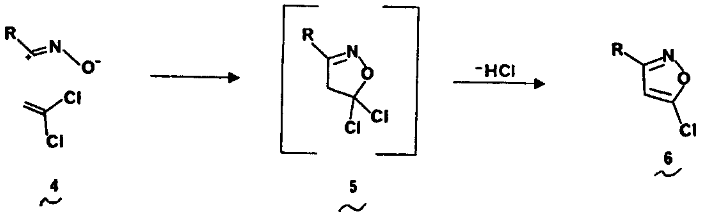
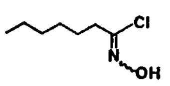
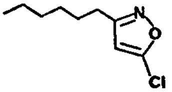
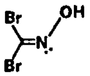
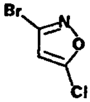
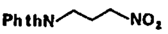
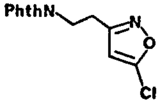
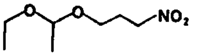
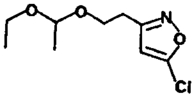
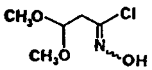
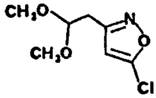
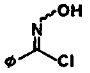
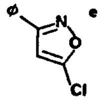
†Deceased March 9, 1984



Using nitro compounds as substrates, the general procedure consisted of slow addition[9] of a solution of the nitro compound in 1,1-dichloroethylene to two equivalents each of triethylamine and phenyl isocyanate in 1,1-dichloroethylene solution at 25°C. When the addition was complete,

Table 1. Preparation of 5-Chloroisoxazoles[a]

Nitrile oxide precursor	5-Chloroisoxazole	% Yield[b]
 [10a]		82
 [10b]		60
 [10c]	 [c,d]	30
 [10c]		36
 [10a,c]		73
 [10a]	 [e]	78

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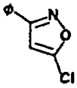
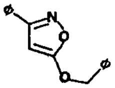
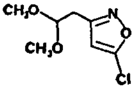
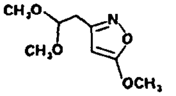
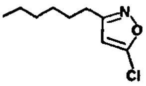
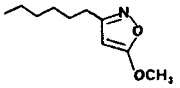
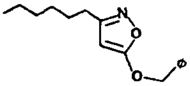
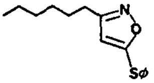
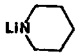
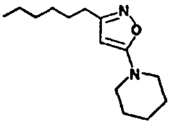
[a] All isoxazoles were fully characterized spectroscopically; [b] yields represent chromatographically pure products; [c] PhthN = phthalimide; [d] m.p. 127-129°C; [e] m.p. 49-51°C, lit.[6] 45-47°C.

the mixture was filtered and the filtrate concentrated in vacuo. The crude isoxazoles were purified by crystallization or silica gel chromatography. Using hydroxamoyl halides as substrates, a solution of 2.5 equivalents of triethylamine in 1,1-dichloroethylene was slowly added[9] to a solution of the hydroxamoyl halide in 1,1-dichloroethylene at 25°C. The reaction mixture was partitioned between ether and water to obtain a crude product which was purified by crystallization or silica gel chromatography.

When the 5-chloroisoxazoles were treated with 3-5 equivalents of a nucleophile in dry THF, the chloride displacement products were produced in good yield (Table II).[11] Carbon nucleophiles were not extensively investigated, although 2-lithio-1,3-dithiane and the sodium salt of

Table II. Nucleophilic Substitution of 5-Chloroisoxazoles [a]

Substrate	Nucleophile[c], Conditions	Product	% Yield [b]
	$NaOCH_2\phi$ 3h/60 °C		85
	$NaOCH_3$ 6h/65 °C		70
	$NaOCH_3$ 18h/65 °C		99
"	$NaOCH_2\phi$ 5h/60 °C		72
"	ϕSLi 10h/60 °C		48
"	 2h/25 °C		53

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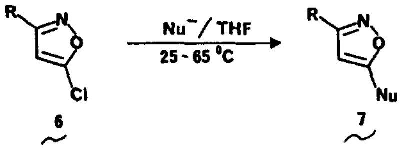
[a] All isoxazoles were fully characterized spectroscopically; [b] Yields represent chromatographically pure products; [c] The alkoxides were generated from the alcohol and sodium metal, thiophenol and piperidine were deprotonated with n-BuLi at 0°C.



dimethyl malonate failed to provide any products of displacement. The isoxazoles were isolated by ether extraction with final purification by crystallization or silica gel chromatography. No products of isoxazole cleavage were observed. The products presumably arise via an addition-elimination mechanism although free-radical substitution via an $S_{RN}1$ process is an intriguing possibility.

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Notes

1. Current address, the Scripps Institution of Oceanography, La Jolla, California.
2. Stevens, R.V.; Albizati, K.F. J. Chem Soc., Chem. Commun., 1982, 104.
3. Much of the work in this area has been compiled in a recent review. See Kametani, T. Heterocycles, 1982, 17, 463.
4. a) Grunanger, P.; Langella, M.R. Gazz., 1959, 89, 1784; b) Grunanger, P. Rend. Accad. Naz. Lincei., 1958, 24, 163; c) Kozikowski, A.P.; Goldstein, S. J. Org. Chem., 1983, 48, 1139.
5. Most methods for preparing this class of compounds utilize strongly basic reagents. See Rutledge, T.F. "Acetylenic Compounds"; Reinhold Books, New York, 1968, pp. 35-44. Also see Tanaka, K.; Shirashi, S.; Nakai, T.; Ishikawa, N. Tetrahedron Lett., 1978, 3103 for a reasonably general solution to this problem.
6. A brief study by Micetich has demonstrated that the relatively stable arylnitrile oxides will undergo cycloaddition with 1,1-dichloroethylene. See Micetich, R.G. Org. Prep. Proc. Intl., 1970, 2, 225 and Micetich, R.G.; Chin, C.G. Can. J. Chem., 1970, 48, 1371.
7. Partial NMR data for 5-chloroisoxazoles: ^{1}H NMR ($CDCl_3$) ~δ 6.5-6.0 (isoxazole C-4 H); ^{13}C NMR ($CDCl_3$) ~δ 165 (isoxazole C-3), ~δ 100 (isoxazole C-4), ~δ 155 (isoxazole C-5).
8. Grunanger, P.; Grundmann, C. "The Nitrile Oxides"; Springer-Verlag, Berlin, 1971.
9. For the additions, a constant-addition funnel was utilized. The addition rates were approximately 1-5 mmol of nitrile oxide precursor in 5-25 mL of 1,1-dichloroethylene per hour.
10. a) These intermediates were produced from the oximes by treatment with N-chlorosuccinimide in DMF; see Stevens, R.V. Tetrahedron, 1976, 32, 1599 and Liu, K.-C.; Shelton, B.R.; Howe, R.K. J. Org. Chem., 1980, 45, 3916; b) procedure from A.A. Hagedorn, private communication; c) the synthesis of this substance is described in the Ph.D. Dissertation of K. Albizati, University of California at Los Angeles, 1983.
11. Similar displacements of 5-chloroisoxazoles has been accomplished with substrates bearing an electron-withdrawing group at C-4 and on 3-phenyl-5-chloroisoxazole. See Postovskii, I.Y.; Sokolov, S.V. Zhur. Obshchei Khim, 1959, 29, 3446; Speroni, G.; Giachetti, E. Gazz. Chim. Ital., 1953, 83, 192 and ref. 6.

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