Tetrahedron Letters,Vol.23,No.44,pp 4563-4566,1982 0040-4039/82/444563-04$03.00/0
Printed in Great Britain

CYANOGEN CHLORIDE N-OXIDE CYCLOADDITIONS. A SIMPLE, SHORT ROUTE TO AT-125.

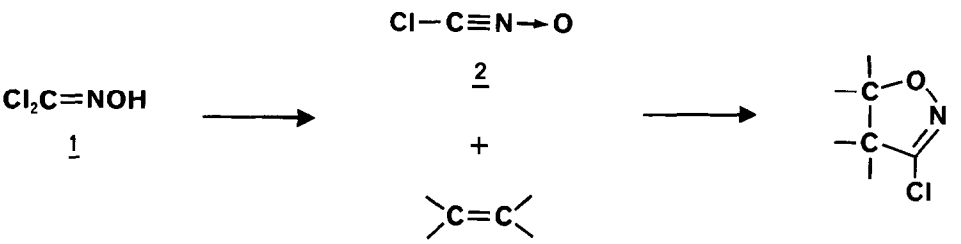
P. A. Wade*, M. K. Pillay and S. M. Singh

Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104, U.S.A.

Summary: Addition of $AgNO_3$ to dichloroformaldoxime in the presence of alkenes provides an efficient procedure for the preparation of 3-chloroisoxazolines including AT-125.

A conceptually obvious approach to the synthesis of 3-chloroisoxazolines involves cycloaddition of cyanogen chloride N-oxide(2) to alkenes (Scheme 1). Nature has decreed, however, a marked disinclination for nitrile oxide 2 to act in this desirable fashion. Thus, generation of 2 from dichloroformaldoxime(1) with aqueous sodium carbonate at room temperature results in only a 6% yield of cycloadduct with styrene and none at all with N-acetyl vinyl glycine[1]. Indeed, that nitrile oxide 2 can be generated and cycloadded in significant yield to an alkene has been demonstrated to our knowledge in only one case, the anion of a β,γ-unsaturated α-nitro ester[1].

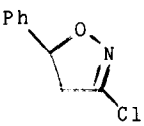
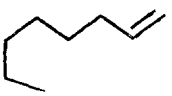
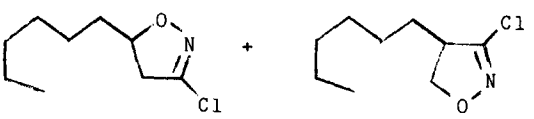
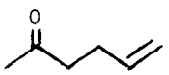
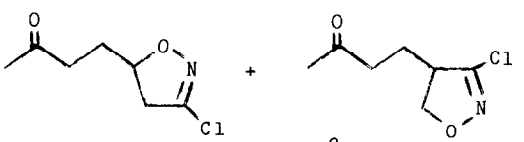
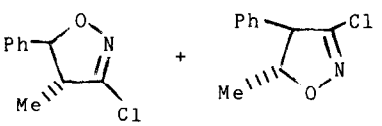
Scheme 1.



Our recent success[2] using silver nitrate rather than base to generate benzenesulfonylnitrile oxide prompted us to apply this methodology to dichloroformaldoxime. For successful reaction, silver nitrate would have to remove the first chlorine from the oxime but not the second. The ensuing nitrile oxide and any cycloadducts derived from it would have to react at a substantially slower rate with silver nitrate for this approach to succeed. Such is precisely the case.

Mono- and disubstituted alkenes afford 3-chloroisoxazoline cycloadducts (Table) in 40-73% yield using silver nitrate to generate nitrile oxide 2. The general procedure involves addition in small portions over 20 min of four equivalents of silver nitrate to a THF solution at 60-65°C containing five equivalents of dichloroformaldoxime and one of alkene[3]. Styrene reacted in a highly regioselective fashion under these conditions to give the product 3. Somewhat surprising was the observation that 1-octene and 5-hexene-2-one gave small but significant amounts of the 4-substituted products 5 and 7, respectively[4]. E-β-methylstyrene typically[5] gives a mixture of regioisomers in nitrile oxide cycloadditions as was the case here.

TABLE. CYANOGEN CHLORIDE N-OXIDE CYCLOADDUCTS

Alkene	Cycloadducts (Ratio[a])	% Yield[b]
	 3 (>98%)	73
	 4 (91:9) 5	71
	 6 (95:5) 7[c]	66
	 8 (66:34) 9	40[d]

[a] Based on nmr with confirmation by glc.

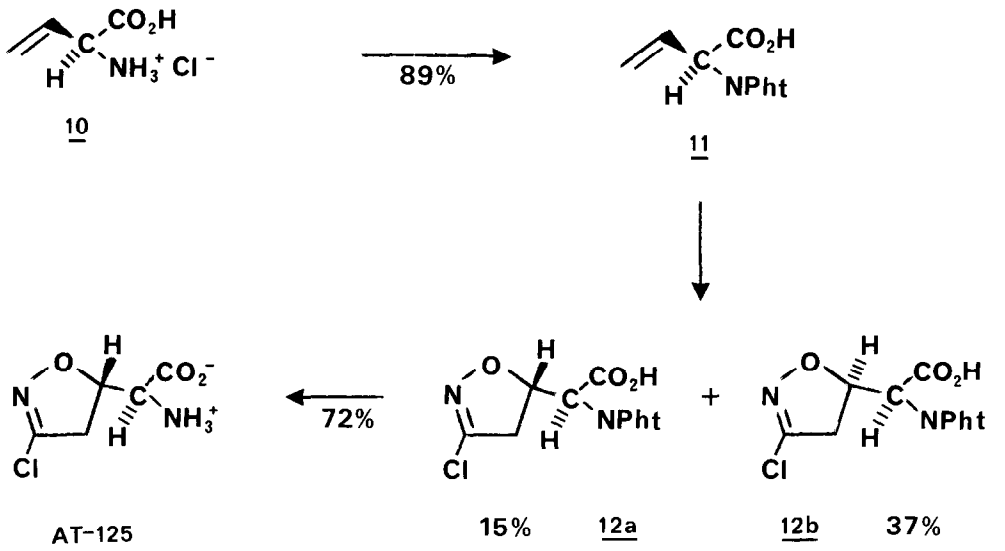
[b] For pure isolated products. Structures were identified by nmr, ir, ms, and elemental analysis. Yields are based on starting alkene.

[c] Separated by preparative glc.

[d] Substantial amounts of unreacted alkene remained.

We have applied this successful 1,3-dipolar cycloaddition to the preparation of the antimetabolite AT-125 (acivicin)[6] (Scheme 2). Starting material for our synthesis was the readily available hydrochloride salt 10 of (S)-vinyl glycine[7]. First, the nitrogen of vinyl glycine was protected by phthalylation[8] giving the organic soluble imide 11 in 89% yield. The imide was subjected to cycloaddition (8 equivalents of $AgNO_3$ and 10 of dichloroformaldoxime) affording two products, 12a and 12b, in 52% combined yield[9]. Both products had the desired regiochemistry although reaction stereoselectivity favored the undesired cycloadduct 12b[10] (71:29 ratio). Chromatographic separation[11] and deprotection of cycloadduct 12a according to the procedure of Kelly and Wierenga[6a] afforded AT-125, identical with an authentic sample of the natural product[12].

Scheme 2.



Advantages of this approach to AT-125 are the short number of steps, the avoidance of enantiomer resolution and the relative ease of separating the diastereomeric cycloadducts. The approach is adaptable to other nitrile oxides and, accordingly, the 3-phenylsulfonyl analog of AT-125 has been synthesized[13]. One clear disadvantage of the route is the unfavorable diastereomer ratio obtained. We are investigating other amine protecting groups as well as acid protecting groups in the hope of improving this situation.

Acknowledgment. This investigation was supported by PHS grant number CA-26943, awarded by the National Cancer Institute, DHHS.

References and Notes

(1) Baldwin, J. E.; Hoskins, C.; Kruse, L. J. Chem. Soc., Chem. Commun. 1976, 795.

(2) Wade, P. A.; Pillay, M. K. J. Org. Chem. 1981, 46, 5425.

(3) Work-up consisted of dilution with CH_2Cl_2, filtration, cautious washing of the filtrate with several portions of 5% aqueous sodium hydroxide to destroy side products, water washing, drying over Na_2SO_4, and concentration. The crude products were conveniently purified by chromatography (silica gel, CH_2Cl_2 elution) and distillation at reduced pressure.

(4) Most nitrile oxides give no detectable amounts of 4-substituted cycloadducts with simple terminal alkenes. Perhaps there is an attractive interaction between the chlorine of nitrile oxide 2 and appropriate allylic hydrogens favoring the formation of the observed minor isomers.

(5) For example, benzonitrile oxide also gives a 66:34 ratio favoring the 5-phenyl isomer: Bianchi, G.; DeMichelli, C.; Gandolfi, R. J. Chem. Soc., Perkin 1, 1976, 1518.

(6) For other syntheses of AT-125, see: (a) Kelly, R. C.; Schletter, I.; Stein, S. J.; Wierenga, W. J. Am. Chem. Soc. 1979, 101, 1054. (b) Baldwin, J. E.; Kruse, L. I.; Cha, J. K. ibid, 1981, 103, 942. (c) Silverman, R. B.; Holladay, M. ibid 1981, 103, 7357. (d) See also: Hagedorn, A. A.; Miller, B. J.; Nagy, J. O. Tetrahedron Lett. 1980, 229.

(7) Afzali-Ardakani, A.; Rapoport, H. J. Org. Chem. 1980, 45, 4817.

(8) Following a standard procedure: Nefkens, G. H. L.; Tesser, G. I.; Nivard, R. J. F. Rec. Trav. Chim. Pays-Bas 1960, 79, 688.

(9) Also, an 18% recovery of imide 11 was obtained.

(10) A similar result has been noted for vinyl glycine itself. See reference 6d.

(11) MPLC using silica gel (Merck 60, 230-400 mesh) as column packing. With 87:13 benzene-acetic acid, 11 eluted first followed by 12b and then 12a.

(12) We thank Dr. R. C. Kelly (Upjohn) for a sample of the natural product.

(13) Currently under biological investigation at the National Cancer Institute.

(Received in USA 4 August 1982)