SYNTHESIS OF 1,2,4-OXADIAZOLE DERIVATIVES CONTAINING CHLORINE ATOMS IN THE SIDE CHAIN

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1,3-Dipolar cycloaddition of the N-oxides of acetonitrile, propionitrile, and p-nitrobenzonitrile to nitriles of polychloroalkanoic and polychloroalkenoic acids gives 1,2,4-oxadiazoles containing polychloroalkyl and alkenyl substituents at the 5-position.

1,2,4-Oxadiazole derivatives containing halogen atoms have for a long time stimulated the interest of research workers since they frequently exhibit high and specific biological activity. They are also of interest for the solution of certain problems in theoretical organic chemistry. One convenient and widely used method for obtaining 1,2,4-oxadiazole derivatives is the 1,3-dipolar cycloaddition of nitrile N-oxides to carbonitriles [1]. Despite the extensive use of nitriles as dipolarophiles in this reaction, nitriles of chloroalkanoic and chloroalkenoic acids have hardly received any study at all [2, 3].

In the present study we have for the first time investigated nitriles I-VI as dipolarophiles:

$R^2C(Cl)R^1CH_2CCl_2CN$ $R^2CH=CHCH_2CCl_2CN$

I-IV V, VI

I $R^1=H$, $R^2=CN$; II $R^1=H$, $R^2=Bu$; III $R^1=Me$, $R^2=CN$; IV $R^1=H$, $R^2=CH_2Cl$; V $R^2=CH_2Cl$; VI $R^2=CH(Cl)Me$

By selecting nitriles of chloroalkanoic and -alkenoic acids it was possible to evaluate the relative reactivity of the nitrile group in those nitriles with different numbers of chlorine atoms at the α-position as well as in nitriles also containing a C=C bond in the molecule.

The N-oxides of p-nitrobenzonitrile, propionitrile, and acetonitrile were used as 1,3-dipoles for reaction with nitriles of polychloroalkanoic acids I-IV and N-oxides of propionitrile and acetonitrile for reaction with nitriles V and VI.

p-Nitrobenzonitrile N-oxide was obtained by treatment of p-nitrophenylhydroximyl chlorides with triethylamine at a reduced temperature. The N-oxides of acetonitrile or propionitrile were obtained by treatment of nitroethane or 1-nitropropane with phenyl isocyanate in the presence of catalytic quantities of triethylamine.

In those cases where the reactions between acetonitrile and propionitrile N-oxides and nitriles I-VI were carried out according to the procedure in [4], in which the N-oxides were used *in situ* and the ratio of dipolarophile to 1,3-dipole was 1:1, it was not possible to obtain the required compounds from nitriles I, II, and IV. When nitriles III, V, and VI were used, the corresponding oxadiazoles were obtained in low yield. In these cases it is probable that the triethylamine used as a catalyst is partly or wholly consumed in a side reaction involving dehydrochlorination of the nitriles of the polychloro-substituted acids [5].

We used another method, which involved the initial preparation of N-oxides in the cold and then addition of the nitriles to a solution of the N-oxides. In these cases it was possible to obtain oxadiazoles in 30-57% yield, but oxadiazoles could not obtained from nitriles containing only a single chlorine atom at the α-position relative to a CN group. The initial nitriles and products from dimerization of the nitrile N-oxides — the corresponding furoxans – were isolated from the reaction

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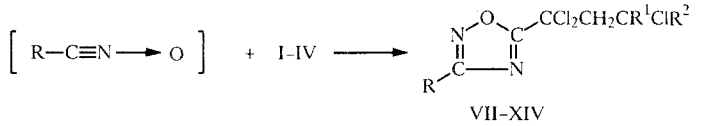
TABLE 1. Properties of 1,2,4-Oxadiazoles Synthesized

Compound	R	R^1	R^2	Empirical formula	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm*	Yield, %
VII	CH_3	H	CN	$C_7H_6Cl_3N_3O$	2245 (C=N); 1590...1569 (C=N)	5,52 (1H, m, CH); 3,77 (2H, m, CH_2); 2,44 (3H, s, CH_3)	36
VIII	4-$NO_2C_6H_4$	H	CN	$C_{12}H_7Cl_3N_4O_3$	2245 (C=N); 1353, 865 (NO_2)	8,20 (4H, m, C_6H_4); 4,89 (1H, t, CHCl); 3,27 (2H, d, CH_2)	30
IX	CH_3	H	C_4H_9	$C_{10}H_{15}Cl_3N_2O$	1415 (=NO); 1590 (C=N)	4,35 (1H, m, CHCl); 3,40 (2H, m, CH_2Cl_2); 2,39 (3H, s, CH_3); 1,86 (2H, m, CH_2); 1,42 (4H, m, CH_2CH_2); 0,94 (3H, t, CH_3)	45
X	4-$NO_2C_6H_4$	H	C_4H_9	$C15H_{16}Cl_3N_3O_3$	1569 (C=N); 1356 (NO_2)	8,39 (4H, m, C_6H_4); 4,30 (1H, m, CHCl); 3,34 (2H, m, CH_2Cl_2); 1,86 (2H, m, CH_2); 1,41 (4H, m, CH_2CH_2); 0,93 (3H, t, CH_3)	31
XI	CH_3	CH3	CN	$C_8H_8Cl_3N_3O$	2245 (C=N); 1578 (C=N); 1590 (C=N); 1429 (=NO)	4,18 (2H, s, CH_2Cl); 2,50 (3H, s, CH_3Cl); 2,18 (3H, s, 3-CH_3)	30
XII	4-$NO_2C_6H_4$	CH_3	CN	$C13H_9Cl_3N_3O_3$	2214 (C=N); 1578 (C=N); 1349, 854 (NO_2)	8,32 (4H, m, C_6H_4); 3,71 (2H, d.d, CH_2); 2,13 (3H, s, CH_3)	20
XIII	CH_3	H	CH2Cl	$C_7H_8Cl_3N_2O$	1576 (C=N); 1390 (=NO)	4,45 (1H, m, CHCl); 3,76 (2H, d.d, CH_2Cl); 3,38 (2H, d.d, CHCl); 2,47 (3H, s, CH_3)	57
XIV	4-$NO_2C_6H_4$	H	CH_2Cl	$C_{12}H_{10}Cl_4N_3O_3$	1610, 1569 (C=N); 1353, 865 (NO_2)	8,33 (4H, m, C_6H_4); 4,52 (1H, m, CH); 3,24 (2H, m, CH_2); 3,40 (2H, m, CH_2Cl)	31
XV	CH_3	—	CH2Cl	$C_8H_9Cl_3N_2O$	1590 (C=N); 1650 (C=C)	5,87 (2H, m, CH=CH); 4,03 (2H, d, CH_2Cl); 3,43 (2H, d, CH_2); 2,33 (3H, s, CH_3)	43
XVI	CH_3	—	CHClCH3	$C_9H_{11}Cl_3N_2O$	1590 (C=N); 1650 (C=C)	5,87 (2H, m, CH=CH); 4,1 (2H, d, $CHCH_3$); 3,47 (2H, d, CH_2); 2,73 (2H, s, CH_2CH_3); 1,30 (3H, t, CH_3CH_2)	40
XVII	C_2H_5	—	CH_2Cl	$C_9H_{11}Cl_3N_2O$	1590 (C=N); 1650 (C=C)	5,80 (2H, m, CH=CH); 4,50 (2H, q, CH_2Cl); 3,37 (2H, d, CH_2); 2,73 (3H, s, CH_3); 1,57 (3H, d, CH_3Cl)	42
XVIII	C_2H_5	—	CHClCH3	$C_{10}H_{13}Cl_3N_2O$	1590 (C=N); 1650 (C=C)	5,80 (2H, m, CH=CH); 4,60 (2H, q, $CHCH_3$); 3,47 (2H, d, CH_2); 2,73 (2H, q, CH_2CH_3); 1,30 (3H, t, CH_3CH_2)	40
XIX	CH_3	—	CH2Cl	$C_8H_8Cl_2N_2O$	1650 (C=N); 1690 (C=C)	7,50 (1H, d, CH=CCl); 6,60 (2H, m, CH=CH); 4,30 (2H, d, CH_2); 2,30 (3H, s, CH_3)	80
XX	CH_3	—	CHClCH3	$C_9H_{10}Cl_2N_2O$	1650 (C=N); 1690 (C=C)	7,60 (1H, d, CH=CCl); 6,65 (2H, m, CH=CH); 4,33 (2H, d, CH_2); 2,73 (2H, q, CH_2CH_3); 1,30 (3H, t, CH_3CH_2)	79
XXI	C_2H_5	—	CH2Cl	$C_9H_{10}Cl_2N_2O$	1650 (C=N); 1690 (C=C)	7,40 (1H, d, CH=CCl); 6,53 (2H, m, CH=CH); 4,67 (1H, m, CHCl); 2,37 (3H, s, CH_3); 1,57 (3H, d, CH_3CH)	86
XXII	C_2H_5	—	CHClCH3	$C_{10}H_{12}Cl_2N_2O$	1650 (C=N); 1690 (C=C)	7,27 (1H, d, CH=CCl); 6,57 (2H, m, CH=CH); 4,77 (1H, m, CHCl); 2,80 (2H, q, CH_2CH_3); 1,33 (3H, t, CH_3CH_2); 1,60 (3H, d, CH_3)	83

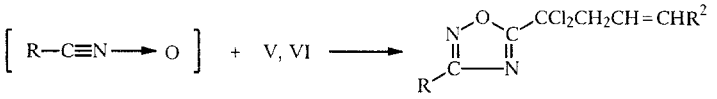
*Values of δ in ppm were measured from the centers of multiplets; PMR spectra were recorded in $CDCl_3$ and DMSO-d_6 solution.

mixtures. It was also not possible to obtain the required 1,2,4-oxadiazole derivatives when the reaction between α-monochloro-substituted nitriles and N-oxides was carried out in the presence of boron trifluoride etherate, which is usually employed for activation of the nitrile group [6]. At the same time nitriles containing two chlorine atoms at the α-position relative to the nitrile group readily underwent a reaction with N-oxides to form the corresponding oxadiazoles in 30-57% yield. As confirmaton of this, dinitriles I and III, which contain two chlorine atoms at the α-position relative to one CN group and a single chlorine atom at the α-position relative to the other, selectively react at that CN group which has two chlorine atoms at the α-position. Thus, it is possible to conduct the reaction selectively, with the oxadiazoles retaining one CN group from the initial dinitrile molecule (see Table 1)



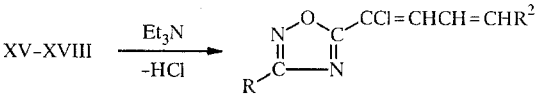
VII-XIV

The activated nitrile group proved more reactive towards 1,3-dipolar cycloaddition with the carbonitrile N-oxides than the carbon–carbon double bond. When alkenoic acid nitriles V and VI were reacted with N-oxides, no products derived from cycloaddition to the C=C double bond could be detected and only the corresponding 1,2,4-oxadiazole derivatives were isolated:



XV-XVIII

Heterocyclic analogs of chloro-substituted sorbic acid XIX-XXII were obtained as a result of dehydrochlorination of 1,2,4-oxadiazole derivatives XV-XVIII.



XIX-XXII

EXPERIMENTAL

PMR spectra were recorded on a Bruker WM-250 instrument and IR spectra were recorded on a Perkin–Elmer 983-G instrument. The course of the reaction and purity of the compounds obtained were monitored by means of TLC on Silufol plates in the solvent system benzene–hexane (iodine vapor used for development).

The elemental analysis data for C, H, and N in the compounds synthesized corresponded to the calculated values.

Preparation of 1,2,4-Oxadiazole Derivatives VIII, X, XII, and XIV. To an ice-cooled solution (temperature in the reaction flask 3-5°C) of 1.67 g (0.01 mole) of p-nitrophenylhydroximyl chloride in 50 ml of absolute benzene was added dropwise a solution of 1.39 ml (0.01 mole) of triethylamine in 10 ml of benzene. The mixture was agitated for 30 min at 3-5°C. Without separating the precipitate of triethylamine hydrochloride which had formed, 0.01 mole of nitrile I-IV in 10 ml of benzene was added dropwise to the reaction mixture, which was then refluxed for 15-20 h with agitation. The precipitate was filtered off and washed with benzene on the filter. The filtrate was evaporated off at reduced pressure. The residue was chromatographed on a SiO_2 column (2.5 × 50 cm), eluting with hexane and then a 1:1 benzene–hexane mixture. The initial nitrile was obtained after removal of solvent from the hexane fraction, and 1,2,4-oxadiazole derivatives were obtained in 20-30% yield (see Table 1) after removal of solvent rom the subsequent fraction. The following were synthesized in this manner: 3-methyl-5-(1,1,3-trichloro-3-cyanopropyl)-1,2,4-oxadiazole (VII); 3-(4-nitrophenyl)-5-(1,1,3-trichloro-3-cyanopropyl)-1,2,4-oxadiazole (VIII); 3-methyl-5-(1,1,3-trichloroheptyl)-1,2,4-oxadiazole (IX); 3-(4-nitrophenyl)-5-(1,1,3-trichloroheptyl)-1,2,4-oxadiazole (X); 3-methyl-5-(1,1,3-trichloro-3-cyanobutyl)-1,2,4-oxadiazole (XI); 3-(4-nitrophenyl)-5-(1,1,1-trichloro-3-cyanobutyl)-1,2,4-oxadiazole (XII); 3-methyl-5-(1,1,3-4-tetrachlorobutyl)-1,2,4-oxadiazole (XIII); 3-(4-

nitrophenyl)-5-(1,1,3,4-tetrachlorobutyl)-1,2,4-oxadiazole (XIV); 3-methyl-5-(1,1,5-trichloropent-3-enyl)-1,2,4-oxadiazole (XV); 3-methyl-5-(1,1,5-trichloro-hex-3-enyl)-1,2,4-oxadiazole (XVI); 3-ethyl-5-(1,1,5-trichloropent-3-enyl)-1,2,4-oxadiazole (XVII); and 3-ethyl-5-(1,1,5-trichlorohex-3-enyl)-1,2,4-oxadiazole (XVIII).

Preparation of 1,2,4-Oxadiazole Derivatives XIX-XXII. To an agitated refluxing solution of 0.01 mole of oxadiazole derivative XV-XVII in 50 ml of absolute benzene was added dropwise a solution of 1.39 ml (0.01 mole) of triethylamine in 10 ml of benzene over a period of 2 h. The precipitate of triethylamine hydrochloride was filtered off and the filtrate was concentrated. The residue was passed through an SiO_2 chromatography column (1.5 × 40 cm, eluent hexane–benzene, 1:10) and 1,2,4-oxadiazole derivatives XIX-XXII were isolated in 79-86% yield. The following were synthesized in this manner: 3-methyl-5-(1,5-dichloropenta-1,3-dienyl)-1,2,4-oxadiazole (XIX); 3-methyl-5-(1,5-dichlorohexa-1,3-dienyl)-1,2,4-oxadiazole (XX); 3-ethyl-5-(1,5-dichloropenta-1,3-dienyl)-1,2,4-oxadiazole (XXI); and 3-ethyl-5-(1,5-dichlorohexa-1,3-dienyl)-1,2,4-oxadiazole (XXII).

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