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NITRO GROUP SUBSTITUTION IN NITROCHLOROFUROXAN USING N- AND O-TRIMETHYLSILYL DERIVATIVES

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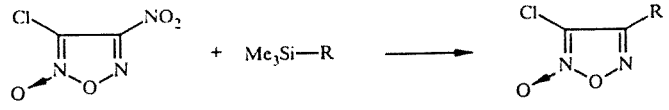
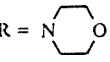
A method is proposed for replacing the nitro group in 4-nitro-3-chlorofuroxan using trimethylsilyl derivatives of secondary amines and amidoximes.

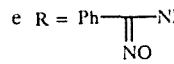
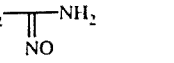
It is well-known that the nitro group in nitrofuroxans is substituted on treatment with various nucleophilic reagents [1-3] and this is one of the most commonly used methods for synthesizing functionalized furoxans. However, besides substitution, some nitro- and halofuroxans undergo furoxan ring opening in the presence of nucleophiles [4, 5]. Nitrochlorofuroxan (I) is a typical example of such substrates [5]. Our research has shown that substitution products cannot be obtained by reacting it with nucleophilic reagents, specifically amines and amidoximes. At the same time trimethylsilyl derivatives are known to be more active than the corresponding amines [6], so we decided to use them to replace the nitro group in furoxan I. Reactions involving the substitution of nitro or other groups in the presence of N- and O-trimethylsilyl derivatives have not previously been performed in heterocyclic series.

We found that compounds which were virtually impossible to synthesize by other means, namely the corresponding 3-chlorofuroxans (IIIa-f), could be obtained by reacting compound I with secondary amine N-trimethylsilyl derivatives (IIa-d) or with amidoxime O-trimethylsilyl derivatives (IIe-f).



I II a-f III a-f

II, III a $R = NMe_2$; b $R = NEt_2$; c R =  ; d R = 

e R =  ; f R = 

The position of the substituents in the furoxan ring was verified using ^{13}C NMR spectroscopy and the signals were assigned in accordance with the data in a previous work [7].

Trimethylsilyl derivatives of alcohols and primary aliphatic and aromatic amines, and trimethylsilyl cyanide did not afford substitution products when reacted with furoxan I.

Nitrochlorofuroxan is known to exist as a 70:30 mixture of two isomers, 4-nitro-3-chlorofuroxan (I) and 3-nitro-4-chlorofuroxan [7]. We found that only the former isomer participated in the substitution reaction, while the latter remained unchanged or decomposed when the conditions became more rigorous. This may be due to the fact that the chlorine atom at position 4 is more difficult to substitute than the nitro group.

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TABLE 1. Nitrochlorofuroxan Reaction with Secondary Amine N-Trimethylsilyl Derivatives and Amidoxime O-Trimethylsilyl Derivatives

Reaction conditions				Elutriator	Reaction product	Yield, %
solvent	T, °C	quantity of II, mmoles	duration, h			
CH_2Cl_2	18	7,2	2	$CHCl_3$—CCl_4, 1 : 1	IIIa	65
CH_3CN	18	7,2	2,5	$CHCl_3$—CCl_4, 2 : 1	IIIb	40
CH_3CN	18	5,4	1	CCl_4	IIIc	39
CH_3CN	18	5,4	1	$CHCl_3$—CCl_4, 2 : 1	IIId	30
CH_3CN	81	8,8	3	$CHCl_3$— acetone, 20 : 1	IIIe	39
CH_3CN	81	8,8	3	$CHCl_3$— acetone, 20 : 1	IIIf	35

The method outlined is clearly applicable to other heterocyclic compounds that are liable to undergo unwanted reactions in the presence of nucleophiles.

EXPERIMENTAL

IR spectra were obtained on a Specord M-80 in KBr tablets and in thin films. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument (300 and 75.5 MHz respectively) in $CDCl_3$ and $(CD_3)_2SO$ (in the case of IIIf), internal standard TMS. Mass spectra were obtained on a Varian CH-6 with 70 eV ionizing voltage. Melting points were determined using a Boetius-type platform with a heating rate of 4°C per minute at fusion point. Silica gel L 100/160 μ was used for column chromatography. Reaction course and purity of synthesized compounds were monitored using TLC on Silufol UV-254 plates with UV light detection at 254 nm, the spots being developed by spraying with 1% alcoholic diphenylamine solution, then heating.

Elemental analysis data for the synthesized compounds with respect to C, H, N and Cl was in line with calculated values.

Reaction between Nitrochlorofuroxan I and Secondary Amine N-trimethylsilyl Derivatives (General Method). A solution of trimethylsilyl derivative IIa-d in 10 ml of solvent was added dropwise to a solution of 0.6 g (3.6 mmoles) of compound I in 50 ml of the same solvent. The mixture was stirred at room temperature (solvent, quantity of nucleophiles IIa-d and reaction times are shown in Table 1), then the reaction mass was evaporated (apart from the synthesis of IIIa). When 50 ml of CH_2Cl_2 had been added to the residue, it was washed with water and dried over $MgSO_4$. After the solvent had been driven off, the residue was chromatographed on a column packed with silica gel. Elutriators and reaction product yields with respect to 4-nitro-4-chlorofuroxan used initially are given in Table 1.

4-Dimethylamino-3-chlorofuroxan (IIIa, $C_4H_6ClN_3O_2$), mp 46-48°C, decomposed on standing. IR spectrum: 2980, 2935 (C−H), 1620 cm^{-1} (C=N). M^+ 163, 165. PMR spectrum: 2.99 ppm (6H, s, 2Me). ^{13}C NMR spectrum: 104.99 ($C_{(3)}$), 156.62 ($C_{(4)}$), 38.60 ppm (Me).

4-Diethylamino-3-chlorofuroxan (IIIb, $C_6H_{10}ClN_3O_2$). Oil, decomposed on standing. IR spectrum: 2990, 2940 (C−H), 1610 cm^{-1} (C=N). M^+ 191, 193. PMR spectrum: 1.19 (6H, t, 2Me), 3.41 ppm (4H, q, $2CH_2$). ^{13}C NMR spectrum: 104.66 ($C_{(3)}$), 154.94 ($C_{(4)}$), 43.00 (CH_2), 13.24 ppm (Me).

4-Piperidino-3-chlorofuroxan (IIIc, $C_7H_{10}ClN_3O_3$), mp 48-50°C. IR spectrum: 2960, 2870 (C−H), 1625 cm^{-1} (C=N). M^+ 203, 205. PMR spectrum: 1.64 (6H, m, $3CH_2$−C), 3.33 ppm (4H, d, $2CH_2$−N). ^{13}C NMR spectrum: 105.63 ($C_{(3)}$), 156.92 ($C_{(4)}$), 47.74 (CH_2−N), 24.69 and 23.65 ppm (CH_2−C).

4-Morpholino-3-chlorofuroxan (IIId, $C_6H_8ClN_3O_3$), mp 112-114°C. IR spectrum: 2970, 2870 (C−H), 1620 cm^{-1} (C=N). M^+ 205, 207. PMR spectrum: 3.37 (4H, s, $2CH_2$−N), 3.78 ppm (4H, s, $2CH_2$−O). ^{13}C NMR spectrum: 105.17 ($C_{(3)}$), 156.61 ($C_{(4)}$), 65.81 (CH_2−O), 46.73 ppm (CH_2−N).

Reaction between Nitrochlorofuroxan I and Amidoxime O-Trimethylsilyl Derivatives* (General Method). When 1.35 ml (9.7 mmoles) of triethylamine and 1.23 ml (9.7 mmoles) of trimethylchlorosilane had been added to a solution of 8.8

*Obtained *in situ* using the method described in work [8].

mmoles of amidoxime IIe-f in 100 ml benzene, the reaction mixture was stirred for 1 h at room temperature. The resultant triethylamine salt was filtered off and the filtrate was evaporated down. Then 0.6 g (3.6 mmoles) of compound I was added to the resultant residue diluted with 50 ml of CH_3CN. After boiling for 3 h, the solvent was driven off, the residue was diluted with 50 ml CH_2Cl_2, washed with water and dried over $MgSO_4$. When the solvent had been evaporated off, the residue was chromatographed on a column packed with silica gel. Elutriators and reaction product yields are shown in Table 1.

Benzamidoxime O-3-Chlorofuroxanyl Ester (IIIe, $C_9H_7ClN_4O_3$), mp 148°C (decomp.). IR spectrum: 3500, 3375 (NH_2), 1635 cm^{-1} (C=N). M^+ 254, 256. PMR spectrum: 7.23 (2H, s, NH_2), 7.52 (3H, m, Ph), 7.70 ppm (2H, m, Ph). ^{13}C NMR spectrum: 104.90 ($C_{(3)}$), 161.54 ($C_{(4)}$), 158.95 Ph–C), 127.13, 128.74, 130.47 and 131.22 ppm (Ph).

Phenylacetamidoxime O-3-Chlorofuroxanyl Ester (IIIf, $C_{10}H_9ClN_4O_3$), mp 81-83°C. IR spectrum: 3450, 3360 (NH_2), 3040, 2940, 2870 (C–H), 1620 cm^{-1} (C=N). M^+ 268, 270. PMR spectrum: 3.60 (2H, s, CH_2), 5.00 (2H, s, NH_2), 7.33 ppm (5H, m, Ph). ^{13}C NMR spectrum: 104.60 ($C_{(3)}$), 161.10 ($C_{(4)}$), 158.49 (CH_2–C), 127.71, 128.75, 128.99 and 133.94 (Ph), 36.53 ppm (CH_2).

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