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CYCLIZATIONS OF N-(1-CHLORO-2,2,2-TRIHALOETHYLIDENE)-O-METHYL-URETHANES WITH 5-AMINO-3-METHYL-ISOXAZOLE AND 3-AMINO-5-METHYLISOXAZOLE

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N-(1-Chloro-2,2,2-trihaloethylidene)-O-methylurethanes undergo cyclization with 5-amino-3-methylisoxazole and 3-amino-5-methylisoxazole to give respectively 6-trihalomethylisoxazolo[5,4-d]-pyrimidin-4(5H)-ones and 2-trihalomethyl-4H-isoxazolo[2,3-a]-1,3,5-triazin-4-ones.

Keywords: 5- and 3-aminoisoxazoles, N-(isoxazolyl)-N'-carbomethoxyamidines, 6-trihalomethyl-isoxazolo[5,4-*d*]pyrimidin-4(5H)-ones, 2-trihalomethyl-4H-isoxazolo[2,3-*a*]-1,3,5-triazin-4-ones, N-(1-chloro-2,2,2-trihaloethylidene)-O-methylurethanes, cyclization.

We have previously reported [1, 2] that the N-(1-chloro-2,2,2-trihaloethylidene)-O-methylurethanes **1a,b** are convenient synthon units for the construction of trihalomethyl-substituted condensed pyrimidine systems. In particular, the reaction of the urethanes **1** with arylamines gives 2-trihalomethylquinazol-4-ones [1] and with 2-aminothiophenes the 2-trihalomethyl-3,4-dihydrothieno[2,3-*d*]pyrimidin-4-ones [2]. With the target of annelating an isoxazole ring we have continued our initial investigations and studied the reaction of the urethanes **1a,b** with 5-amino-3-methylisoxazole (**2a**) and 3-amino-5-methylisoxazole (**2b**).

We have found that compounds **1a,b**, under mild conditions (benzene, 20°C) and in the presence of triethylamine, selectively imidoylate the aminoisoxazole **2a** to give the N-(isoxazol-5-yl)-N'-carbomethoxytrihaloacetamidines **3a,b**. Their ^{1}H NMR spectra show singlets for the CH_3O groups (3.83 and 3.73 ppm respectively) and $C_{(4)}$–H protons of the isoxazole ring (6.13 and 6.03 ppm respectively). Compounds **3a,b** are of low thermal stability and when refluxed in toluene for 3 h undergo cyclization to the trihalomethyl isoxazolo[5,4-*d*]pyrimidin-4(5H)-ones **4a,b**, evidently due to an intramolecular interaction of the carbomethoxy group of the urethane fragment and the π-electron excessive $C_{(4)}$ center of the isoxazole nucleus.

The IR spectra of compounds **4a,b** show absorption bands for the C=O group in the range 1700-1705 cm^{-1} and for N–H at 3170-3180 cm^{-1}. The ^{1}H NMR spectra show the N–H protons as broad singlets in the range 11-12 ppm. Comparison of this data with the spectroscopic data for 3,4-dihydrothieno[2,3-*d*]-pyrimidin-4-ones [2] allows us to assign the compounds **4a,b** a 4,5-dihydro structure. The method of synthesis proposed by us differs basically from those reported in the literature [3-6], in which bifunctional 5-amino-4-formyl(carbamoyl, thiocarbamoyl) isoxazoles are used for the construction of the pyrimidine ring.

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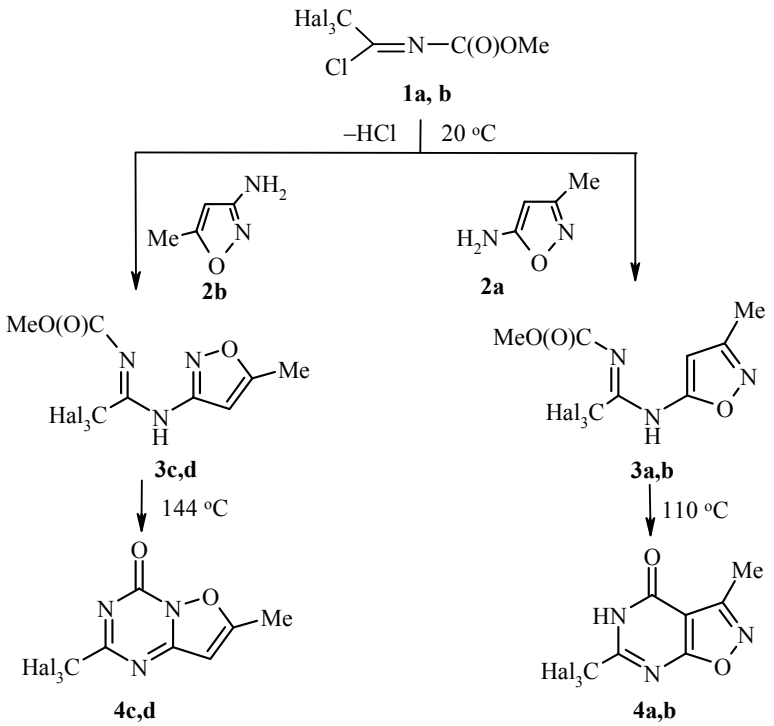

1 a Hal = F, **b** Hal = Cl; **3, 4 a, c** Hal = F; **b, d** Hal = Cl

The reaction of the N-ethylideneurethanes **1a,b** with 3-aminoisoxazole **2b** occurs at room temperature similarly to the reaction with amine **2a** and gives the amidines **3c,d** which tend to form cyclic products when heated in refluxing *o*-xylene. However, in contrast to amidines **3a,b**, the position of attack of the carbonyl group is not a carbon atom but the nitrogen atom of the isoxazole ring and this causes the formation of the

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	Yield, %
		Hal	N		
3a*	$C_8H_8F_3N_3O_3$	22.52 / 22.69	17.04 / 16.73		71
3b	$C_8H_8Cl_3N_3O_3$	35.59 / 35.39	14.17 / 13.98	135-136 (benzene)	78
3c	$C_8H_8F_3N_3O_3$	22.41 / 22.69	16.59 / 16.73	69-70 (benzene–hexane, 3:1)	94
3d	$C_8H_8Cl_3N_3O_3$	35.64 / 35.39	13.75 / 13.98	168-169 (2-propanol)	92
4a	$C_7H_4F_3N_3O_2$	25.80 / 26.01	19.05 / 19.18	191-192 (benzene)	69
4b	$C_7H_4Cl_3N_3O_2$	39.32 / 39.61	15.87 / 15.65	168-169 (benzene)	73
4c	$C_7H_4F_3N_3O_2$	26.33 / 26.01	19.43 / 19.18	140-141 (benzene)	46
4d	$C_7H_4Cl_3N_3O_2$	39.44 / 39.61	15.92 / 15.65	215-216 (benzene)	53

* Viscous oil, purified by reprecipitation from ether using hexane.

TABLE 2. Spectroscopic Characteristics of Compounds **3a-d, 4a-d**

Compound	IR spectrum, ν, cm^{-1}		^1H NMR spectrum, δ, ppm*	^{19}F NMR spectrum, δ, ppm
	NH	CO		
3a	3165	1775	2.33 (3H, s, CH_3); 3.83 (3H, s, OCH_3); 6.13 (1H, s, C(4)H); 8.60 (1H, s, NH)	69.7
3b	3150	1760	2.31 (3H, s, CH_3); 3.73 (3H, s, OCH_3); 6.03 (1H, s, C(4)H); 7.68 (1H, s, NH)	
3c	3180	1765	2.46 (3H, s, CH_3); 3.84 (3H, s, OCH_3); 6.17 (1H, s, C(4)H); 9.36 (1H, s, NH)	68.7
3d	3195	1755	2.43 (3H, s, CH_3); 3.68 (3H, s, OCH_3); 6.02 (1H, s, C(4)H), 8.38 (1H, s, NH)	
4a	3170	1700	2.53 (3H, s, CH_3); 11.33 (1H, s, NH)	69.2
4b	3180	1705	2.52 (3H, s, CH_3); 11.65 (1H, s, NH)	
4c		1755	2.70 (3H, s, CH_3); 7.18 (1H, s, C(8)H); [2.75 (3H, s, CH_3); 6.70 (1H, s, C(8)H)]	71.1
4d		1750	2.70 (3H, s, CH_3); 7.12 (1H, s, C(8)H); [2.73 (3H, s, CH_3); 6.62 (1H, s, C(8)H)]	

* The ^1H and ^{19}F NMR spectra were recorded in $CDCl_3$ (compounds **3a-d**) and DMSO-d_6 (compounds **4a-d**). For compounds **4c,d** the values obtained in $CDCl_3$ are given in square brackets.

2-trihalomethyl-4H-isoxazolo[2,3-*c*]-1,3,5-triazin-4-ones **4c,d**. The signals for the $C_{(8)}$ protons appear in the ^1H NMR spectra in $CDCl_3$ solution at 6.70 (**4c**) and 6.62 ppm (**4d**) and in DMSO-d_6 solution at 7.18 (**4c**) and 7.12 ppm (**4d**) and do not disappear upon addition of water, thus confirming the presence of the triazine structure.

Compounds **4c,d** are members of the little studied condensed isoxazolo[2,3-*a*]-1,3,5-triazine system. There is evidence in the literature [7] for the synthesis of just isoxazolo[2,3-*a*]-1,3,5-triazine-2,4-diones in low yield by treating 3-aminoisoxazole with phenyl- or phenoxycarbonylisocyanates.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument (in CH_2Cl_2 solution for compound **3a** and as KBr tablets for compounds **3b-d** and **4a-d**). ^1H NMR and ^{19}F spectra were taken on a Varian Gemini spectrometer (300 and 282 MHz respectively) using TMS internal standard (^1H) or CCl_3F (^{19}F).

N-(3-Methyl-5-isoxazolyl)-N'-carbomethoxytrihaloacetamidines (3a,b) and **N-(5-Methyl-3-isoxazolyl)-N'-carbomethoxytrihaloacetamidines (3c,d)** (Tables 1 and 2). A solution of the aminoisoxazole **2a,b** (5 mmol) and triethylamine (0.5 g, 5 mmol) in benzene (15 ml) was added with stirring at room temperature to a solution of the N-ethylideneurethane **1a,b** (5 mmol) in benzene (15 ml). After stirring for 3 h, dioxane (10 ml) was added to the reaction mixture, the precipitated triethylamine hydrochloride was filtered off, and the solvent evaporated. The product was purified by crystallization or reprecipitation.

6-Trihalomethyl-3-methylisoxazolo[5,4-*d*]pyrimidin-4(5H)-ones (4a,b) and **2-Trihalomethyl-7-methyl-4H-isoxazolo[2,3-*a*]-1,3,5-triazin-4-ones (4c,d)** (Tables 1 and 2). A solution of compound **3a,b** (3 mmol) in toluene (15 ml) or of the amidine **3c,d** (3 mmol) in *o*-xylene (15 ml) was heated at reflux for 3 h. Solvent was then evaporated and the residue was purified by crystallization.

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