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Synthesis and Properties of 3-Alkyl(aryl)-5-chloromethylisoxazoles

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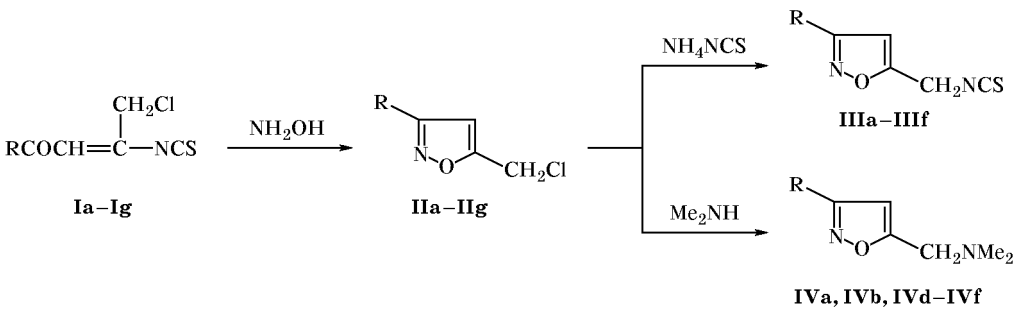
Abstract—3-Chloro-2-isothiocyanato-1-propenyl alkyl(aryl) ketones react with hydroxylamine hydrochloride to give 3-alkyl(aryl)-5-chloromethylisoxazole. Treatment of the latter with dimethylamine and ammonium thiocyanate leads to formation of previously unknown 3-alkyl(aryl)-5-dimethylamino(or isothiocyanato)-methylisoxazoles.

β-Chlorovinyl ketones are known to react with hydroxylamine hydrochloride to give mixtures of isomeric 3- and 5-alkylisoxazoles [1]. An analogous reaction with β-dialkylaminovinyl ketone as carbonyl component yields only 3-alkylisoxazoles [2, 3]. We previously found that reactions of alkyl(aryl) 2,3-dichloro-1-propenyl ketones with hydroxylamine hydrochloride in methanol lead to formation of 3-alkyl-(aryl)-5-chloromethylisoxazoles [4]. However, further studies showed that these products are mixtures of isomeric 3-alkyl-5-chloromethyl- and 5-alkyl-3-chloromethylisoxazoles which have similar boiling points and are therefore difficult to separate. The reaction of methyl 2,3-dichloro-1-propenyl ketone with hydroxylamine hydrochloride was examined by ^{1}H NMR spectroscopy. It was found that the product is a 2:3 mixture of 5-chloromethyl-3-methyl- and 3-chloromethyl-5-methylisoxazoles. As shown in [1], the formation of two isomers is the result of simultaneous attack by hydroxylamine on the carbonyl group and C^2 of the propenyl radical. Unlike alkyl 2,3-dichloro-1-propenyl ketones, aryl 2,3-dichloro-1-propenyl ketones react with hydroxylamine to give only one isomer, 3-aryl-5-chloromethylisoxazole. This may be due to electron-acceptor character of the aryl radical which enhances electrophilicity of the carbonyl group.

In the present work we tried to avoid formation of isomeric mixtures in the above processes. For this purpose, we studied reactions of alkyl(aryl) 3-chloro-2-isothiocyanato-1-propenyl ketones **I** with hydroxylamine hydrochloride. The reactions of ketones **I** with equimolar amounts of hydroxylamine hydrochloride and potassium hydroxide gave 70–83% of 3-alkyl-(aryl)-5-chloromethylisoxazoles **II** as the only products (Scheme 1). The formation of a single isomer of **II** is explained by the presence of only one center in molecule **I**, activated to nucleophilic attack.

Scheme 1.



Ia–Ig **IIa–IIg** **IIIa–IIIf** **IVa, IVb, IVd–IVf**

I–**IV**, R = Me (**a**), Et (**b**), Pr (**c**), *i*-Pr (**d**), Ph (**e**), 4-$CH_3C_6H_4$ (**f**), 4-ClC_6H_4 (**g**).

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Table 1. TLC data and UV, IR, and ^{1}H NMR spectra of isoxazoles **IIa**–**IIg**, **IIIa**, **IIIb**, **IIId**, **IIIf**, **IVa**, **IVb**, and **IVe**

Comp. no.	R_f[a]	UV spectrum (MeOH) λ_{max}, nm (ε)	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm
IIa	0.67	222 (4550)	3148 (=C−H), 1614 (C=C, C=N), 720 (C−Cl)	2.11 s (3H, CH_3), 450 s (2H, CH_2), 6.09 s (1H, =CH)
IIb	0.66	224 (4560)	3144 (=C−H), 1608 (C=C, C=N), 753 (C−Cl)	1.19 t and 2.55 q (5H, CH_3CH_2), 3.45 s (2H, CH_2), 5.95 s (1H, =CH)
IIc	0.64	223 (4170)	3140 (=C−H), 1610 (C=C, C=N), 754 (C−Cl)	–
IId	0.57	220 (4480)	3142 (=C−H), 1625 (C=C, C=N), 750 (C−Cl)	1.25 d and 3.20 m [7H, $CH(CH_3)_2$], 4.54 s (2H, CH_2), 5.97 s (1H, =CH)
IIe	0.68	240 (9530)	3150 (=C−H), 1605 (C=C, C=N), 756 (C−Cl)	4.56 s (2H, CH_2), 6.5 s (1H, =CH), 7.35 m and 7.70 m (5H, H_{arom})
IIf	0.54	235 (9200)	3157 (=C−H), 1648 (C=C, C=N), 775 (C−Cl)	–
IIg	0.50	250 (1170)	3156 (=C−H), 1620 (C=C, C=N), 756 (C−Cl)	–
IIIa	0.60	–	3136 (=C−H), 2160 (NCS), 1605 (C=C, C=N)	1.95 s (3H, CH_3), 4.57 s (2H, CH_2), 6.30 s (1H, =CH)
IIIb	0.57	245 (1098)	3145 (=C−H), 2150 (NCS), 1618 (C=C, C=N)	–
IIId	0.50	225 (4760)	3150 (=C−H), 2160 (NCS), 1620 (C=C, C=N)	1.25 d and 3.30 m [7H, $CH(CH_3)_2$], 3.60 s (2H, CH_2), 6.10 s (1H, =CH)
IIIf	0.51	224 (9630)	3140 (=C−H), 2160 (NCS), 1640 (C=C, C=N)	2.35 s (3H, CH_3), 4.08 s (2H, CH_2), 6.50 s (1H, =CH), 7.18 m and 7.60 m (5H, H_{arom})
IVa	0.63	221 (4420)	3130 (=C−H), 1605 (C=C, C=N)	1.19 s (3H, CH_3), 2.96 s (6H, NCH_3), 3.55 s (2H, CH_2N), 5.96 s (1H, =CH)
IVb	0.61	230 (4520)	3145 (=C−H), 1640 (C=C, C=N)	1.15 t and 2.55 q (5H, CH_3CH_2), 2.15 s (6H, NCH_3), 3.45 s (2H, NCH_2), 5.95 s (1H, =CH)
IVe	0.54	250 (7500)	3138 (=C−H), 1603 (C=C, C=N)	2.18 s (6H, NCH_3), 3.60 s (2H, CH_2), 6.20 s (1H, =CH), 7.00 m and 7.35 m (5H, H_{arom})

[a] Eluent methanol–chloroform.

Therefore, hydroxylamine reacts only at the carbonyl carbon atom with subsequent cyclization.

The chlorine atom in chloromethylisoxazoles **II** is very labile, and it can readily be replaced by various nucleophiles. By reaction of compounds **II** with 2 equiv of ammonium thiocyanate we obtained 3-alkyl(aryl)-5-isothiocyanatomethylisoxazoles **III** in 70–89% yield. Treatment of isoxazoles **II** with 3 equiv of dimethylamine resulted in formation of 65–90% of 3-alkyl(aryl)-5-dimethylaminomethyl-isoxazoles **IV** (Scheme 1).

The structure of products **II**–**IV** was confirmed by the IR, ^{1}H NMR, and UV spectra and (in some cases) by independent synthesis. In the IR spectra of **II**–**IV** we observed absorption bands typical of isoxazole ring and substituents in position 5 (Table 1). The ^{1}H NMR spectra of **II**–**IV** contained singlets from the 4-H proton at δ 6.10–6.50 ppm, 5-CH_2 protons at δ 4.45–4.56 ppm, dimethylamino group, and protons of the alkyl or aryl substituent on C^3 (Table 1). The data of UV spectroscopy are consistent with the presence of heteroaromatic isoxazole ring (Table 1). 3-Alkyl-

Table 2. Yields, physical properties, and elemental analyses of compounds **IIa**–**IIg**, **IIIa**–**IIIf**, **IVa**, **IVb**, and **IVd**–**IVf**

Comp. no.	Yield, %	bp, °C (*p*, mm)	n_D^{20}	d_4^{20}	Found, %				Formula	Calculated, %			
					C	H	X[a]	N		C	H	X[a]	N
IIa	83	53–54 (1)	1.4836	1.2092	45.93	4.69	27.05	10.85	C_5H_6ClNO	45.63	4.56	26.99	10.65
IIb	82	59–60 (1)	1.4820	1.1660	49.97	5.98	24.89	9.82	C_6H_8ClNO	49.48	5.50	24.40	9.62
IIc	79	74–75 (2)	1.4808	1.1280	52.98	6.71	22.48	8.35	$C_7H_{10}ClNO$	52.66	6.27	22.25	8.78
IId	80	71–72 (2)	1.4800	1.1260	52.35	6.99	22.75	8.48	$C_7H_{10}ClNO$	52.66	6.27	22.25	8.78
IIe	70	129–130 (2)	1.5710	1.1230	62.90	4.75	18.55	7.82	$C_{10}H_8ClNO$	62.62	4.13	18.34	7.24
IIf	75	125–126 (2)	1.5780	1.1084	63.99	4.57	17.49	6.87	$C_{11}H_{10}ClNO$	63.62	4.82	17.00	6.75
IIg	70	148–149 (3)	1.5740	1.1290	52.78	3.27	31.47	6.48	$C_{10}H_7Cl_2NO$	52.63	3.07	31.14	6.15
IIIa	89	138–139 (3)	1.5340	1.2387	46.20	3.97	20.58	19.23	$C_6H_6N_2SO$	46.75	3.89	20.78	18.18
IIIb	84	145–146 (3)	1.5330	1.2218	50.17	4.91	19.40	16.23	$C_7H_8N_2SO$	50.00	4.76	19.04	16.67
IIIc	79	151–152 (3)	1.5270	1.2040	52.33	5.71	17.91	15.47	$C_8H_{10}N_2SO$	52.75	5.49	17.58	15.38
IIId	80	147–148 (3)	1.5250	1.1970	52.20	5.87	17.79	15.86	$C_8H_{10}N_2SO$	52.75	5.49	17.58	15.38
IIIe	70	168–170 (2)	1.5830	1.2280	60.57	3.89	14.25	12.65	$C_{11}H_{10}N_2SO$	61.11	3.71	14.82	12.96
IIIf	72	165–167 (2)	1.5860	1.2190	62.78	4.78	13.54	12.49	$C_{12}H_{10}N_2SO$	62.60	4.62	13.91	12.17
IVa	90	79–81 (4)	1.4660	0.9785	59.75	8.69	–	20.47	$C_7H_{12}N_2O$	60.00	8.57	–	20.00
IVb	88	90–92 (4)	1.4630	0.9537	62.40	9.15	–	18.40	$C_8H_{14}N_2O$	62.33	9.09	–	18.18
IVd	80	92–93 (3)	1.4610	0.9145	64.45	9.50	–	16.80	$C_9H_{16}N_2O$	64.28	9.52	–	16.66
IVe	70	129–130 (2)	1.5640	1.0834	71.41	6.83	–	13.78	$C_{12}H_{14}N_2O$	71.28	6.93	–	13.96
IVf	65	135–137 (3)	1.5630	1.0892	72.42	7.55	–	12.98	$C_{13}H_{16}N_2O$	72.22	7.40	–	12.96

[a] **IIa**–**IIg**, X = Cl; **IIIa**–**IIIf**, X = S.

(aryl)-5-isothiocyanato(dimethylamino)methylisoxazoles **III** and **IV** were also synthesized by reactions of, respectively, 2,3-bis(isothiocyanato)- and 3-dimethylamino-2-isothiocyanato-1-propenyl alkyl(aryl) ketones with hydroxylamine hydrochloride.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer from samples prepared as thin films. The ^{1}H NMR spectra were measured on a Tesla BS-487B instrument (80 MHz) from 5–10% solutions in CCl_4, $CDCl_3$, or CD_3OD using HMDS as internal reference. The UV spectra were recorded on a Specord UV-Vis spectrophotometer in methanol. The purity of the products was checked by TLC on Silufol UV-254 plates with methanol–chloroform as eluent. Initial alkyl(aryl) 3-chloro-2-isothiocyanato-1-propenyl ketones were synthesized by the procedure reported in [5]. The yields, physical properties, and elemental analyses of the products are given in Table 2.

3-Alkyl(aryl)-5-chloromethylisoxazoles IIa–IIg (*general procedure*). To a solution of 7 g (0.1 mol) of hydroxylamine hydrochloride in 25 ml of methanol we added dropwise (under vigorous stirring at 20–25°C) a solution of 5.6 g (0.1 mol) of potassium hydroxide in 70 ml of water and then 0.1 mol of ketone **I** in 25 ml of methanol. The mixture was heated for 5 h at 55–60°C, cooled, washed with 150 ml of a dilute aqueous solution of potassium carbonate, and extracted with benzene. The extract was dried over $CaCl_2$, the solvent was distilled off, and the residue was distilled under reduced pressure.

3-Alkyl(aryl)-5-isothiocyanatomethylisoxazoles IIIa–IIIf (*general procedure*). To a solution of 15.2 g (0.2 mol) of ammonium thiocyanate in 100 ml of water we added dropwise (under vigorous stirring at 20–25°C) 0.1 mol of 3-alkyl(aryl)-5-chloromethylisoxazole **IIa**–**IIf** dissolved in 25 ml of ethanol. The mixture was heated for 4 h under reflux and was then treated as described above.

3-Alkyl(aryl)-5-dimethylaminomethylisoxazoles IVa, IVb, and IVe (*general procedure*). A solution of 0.1 mol of 3-alkyl(aryl)-5-chloromethylisoxazole **II** in 25 ml of benzene was added dropwise under vigorous stirring at 20–25°C to a mixture of 60 ml (0.3 mol) of 33% aqueous dimethylamine and 100 ml of benzene. The mixture was heated for 5 h at 60–70°C, cooled, washed with 100 ml of a dilute aqueous

solution of potassium carbonate, and treated as described above.

Independent synthesis of 3-alkyl(aryl)-5-isothiocyanato(or dimethylamino)methylisoxazoles III and IV (Table 1). To a solution of 7 g (0.1 mol) of hydroxylamine hydrochloride in 25 ml of methanol we added dropwise under vigorous stirring a solution of 5.6 g (0.1 mol) of potassium carbonate in 70 ml of water and then 0.1 mol of appropriate alkyl(aryl) 2,3-bis(isothiocyanato)- or 3-dimethylamino-2-isothiocyanato-1-propenyl ketone. The mixture was heated for 5 h under reflux and was then treated as described above. Samples of isoxazole derivatives obtained by different methods were identical in ^{1}H NMR and IR spectral parameters, boiling points, and refractive indices.

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