Russian Journal of Organic Chemistry, Vol. 38, No. 8, 2002, pp. 1178–1182. From Zhurnal Organicheskoi Khimii, Vol. 38, No. 8, 2002, pp. 1230–1234.

C- and N-Amidotrichloroethylation of Azoles*

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Received February 8, 2002

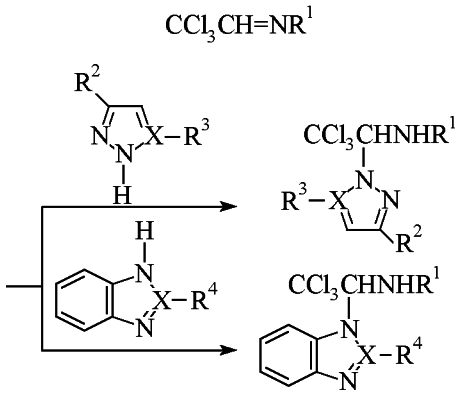
Abstract—1*H*-Pyrazoles, triazoles, and imidazoles in reaction with ethoxycarbonylimine and arylsulfonylimines of chloral yield addition products, corresponding 1-(1-amidotrichloroethyl)azoles. Derivatives of 1-alkylpyrazoles and pyrazolones react with chloral 4-chlorophenylsulfonylimine to furnish products of C-amidotrichloroethylation into position 4 of the azole ring.

In the framework of systematic research on amidoalkylating efficiency of acyl- and sulfonylimines of polyhaloaldehydes we succeeded formerly in performing amidoalkylation on a series of O-, S-, and N-containing heterocycles [1–5]. Among the latter several pyrroles [4], and also indole and its C- and N-methyl-substituted derivatives were used for amidoalkylation [5]. In these cases the reaction occurred without catalyst, did not require heating, and resulted in products of C-trichloroamidoalkylation of pyrroles in the position *2*, and indoles in the position *3*.

In the series of di- and triazoles up till now the amidoalkylation was not studied save the example described [6] of reaction between 1-alkyl(aryl)-3-alkyl(phenyl)pyrazol-5-ones and ethoxycarbonyl-, acetyl-, and benzoylimines of chloral that resulted in amidotrichoroethylation in the position *4* of the pyrazolone ring.

In extension of systematic investigation on reactivity, in particular in the amidoalkylation reaction, of acyl- and arylsulfonylimines of polyhaloaldehydes prepared from *N*,*N*-dichloroamides and polyhaloethenes [7] we studied chloral trichloroethylidenearenesulfonamides and ethoxycarbonylimine in reactions with a series of azoles: benzimidazole, 2-methylbenzimidazole, triazole, benzotriazole, 3,5-dimethylpyrazole, and also with N-methyl-substituted pyrazole and 1-heptyl-3-methylpyrazol-5-one.

It was established that reaction of chloral arylsulfonylimines with benzimidazole, 2-methylbenzimidazole, triazole, benzotriazole, and 3,5-dimethylpyrazole provided in high yield the products **I, III–VI** of azole nucleophilic addition at the activated C=N bond (Table 1). A similar product was also obtained in reaction of chloral ethoxycarbonylimine with triazole **II**.



I, R^1 = $SO_2C_6H_4Cl$, R^2 = H, XR^3 = N; **II**, R^1 = $OCOC_2H_5$, R^2 = H, XR^3 = N; **III**, R^1 = $SO_2C_6H_4Cl$, R^2 = CH_3, XR^3 = C–CH_3; **IV**, R^1 = $SO_2C_6H_4Cl$, XR^4 = CH, **V**, R^1 = $SO_2C_6H_4Cl$, XR^4 = C—CH_3; **VI**, R^1 = C_6H_4Cl, XR^4 = N; **VII**, R^1 = $SO_2C_6H_5$, XR^4 = N.

The structure of compounds synthesized was established from the IR and ^{1}H NMR spectra (Table 2), and the composition was confirmed by elemental analysis (Table 1).

In the IR spectra of nucleophilic addition products **I–VII** are present strong absorption bands of sulfonyl group, of alkyl and aryl CH bonds, and of NH group (Table 2). The ^{1}H NMR spectra of compounds from triazole series **I, II, VI, VII** contain doublet signals from protons of CH and NH groups with coupling constants of 9–10 Hz (Table 2). At the same time in the spectra of pyrazole and imidazole derivatives

* The study was carried out underfinancial support of the Committee of the Russian Academy of Sciences for support of young scientists (grant no. 158/1999).

Table 1. Yields, melting points, and elemental analyses of compounds **I**–**X**

Compd. no.	Yield, %	mp, °C	Found, %					Formula	Calculated, %				
			C	H	Cl	N	S		C	H	Cl	N	S
I	70	172–175	29.37	2.26	38.46	14.85	7.35	$C_{10}H_8Cl_4N_2O_2S$	30.7	2.07	36.36	14.36	8.22
II	80	135–137	28.74	3.43	37.58	17.73		$C_7H_9Cl_3N_4O_2$	29.24	3.15	36.99	19.49	
III	89	128–130	36.57	3.14	34.24	9.45	7.57	$C_{13}H_{13}Cl_4N_3O_2S$	37.43	3.14	34.69	10.07	7.69
IV	72	130–135	42.81	2.72	33.04	9.61	7.56	$C_{15}H_{11}Cl_4N_3O_2S$	41.03	2.52	32.45	9.57	7.30
V	87	84–85	42.93	2.70	32.12	9.67	7.52	$C_{16}H_{13}Cl_4N_3O_2S$	42.60	2.46	31.44	9.31	7.11
VI	70	189–190	37.84	2.24	33.24	12.74	6.78	$C_{14}H_{11}Cl_4N_4O_3S$	38.21	2.29	32.22	12.7	7.27
VII	71	164–166	41.25	2.89	28.22	13.49	8.23	$C_{14}H_{12}Cl_3N_4O_2S$	41.45	2.73	26.22	13.81	7.90
VIII	71	198–200	39.64	3.75	32.55	9.68	8.21	$C_{14}H_{15}Cl_4N_3O_2S$	39.16	3.52	33.33	9.79	7.45
IX	40	218–220	45.17	4.39	30.21	8.96	6.89	$C_{19}H_{24}Cl_4N_3O_3S$	44.63	4.54	29.29	8.68	6.61

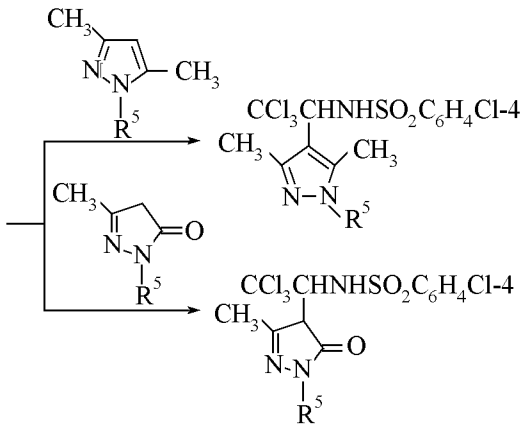
(compounds **III**–**V**) no splitting of CH and NH resonances is observed, and these proton signals appear as individual considerably broadened singlets (Table 2). The proton signals from the para-substituted aromatic rings are observed in the spectra of compounds **I, III**–**VI, VIII, IX** as two doublets corresponding to AA_1BB_1 spin system. In the spectra of compounds **VI** and **VII** the signals of the aromatic protons and those of the benzotriazole fragment are overlapped; the latter signals appear as three multiplets. In the spectrum of compound **IV** the protons of benzimidazole fragment give three groups of signals of equal intensity, and therewith in the spectrum are seen two doublets belonging to the protons of the *para*-substituted aromatic ring (Table 2).

It should be noted that compounds **I**–**VII** are easily hydrolyzed in the presence of water and at heating affording the initial azole and 1-hydroxy-2,2,2-trichloroethylamides that have been isolated and characterized before [8]. This instability of products **I**–**VII** against water was already observed at registering ^{1}H NMR spectra in DMSO at heating to 50°C. Here alongside the signals. e.g., of azole **I**, arose the proton peaks from 1-hydroxy-2,2,2-trichloroethylamide [8].

It was demonstrated that 1,3,5-trimethylpyrazole reacted with chloral 4-chlorophenylsulfonylimine at heating to 80°C for 20 h without catalyst or in the presence of boron trifluoride etherate yielding up to 70% of a product of C-amidoalkylation in the *4* position of the pyrazole ring (compound **VIII**) (Table 1).

Similarly occurred the reaction between trichloroethylidene(4-chlorobenzene)sulfonamide and 1-heptyl-3-methylpyrazol-5-one: The reaction gave rise to a product of 4-amidotrichloroethylation in the pyrazole ring **IX**. The use of boron trifluoride etherate here and in reaction of 1,3,5-trimethylpyrazole did not reduce the process time, but decreased the yield of the target products (compounds **VIII** and **IX**).

$CCl_3CH{=}NSO_2C_6H_4Cl\text{-}4$



R^5 = CH_3 (**VIII**), C_7H_{15} (**IX**).

Thus we demonstrated that arylsulfonyl- and ethoxycarbonylimines of chloral under mild conditions reacted with triazoles, imidazoles, and 1H-pyrazole affording in high yield products of nucleophilic addition to the C=N bond. It was also established that *N*-alkyl-substituted pyrazoles and pyrazolones in reaction with chloral 4-chlorophenylsulfonylimine furnished products of C-amidoalkylation in the *4* position of the heterocycle. These reactions require more stringent conditions than the previously studied C-amidoalkylation of pyrroles and indoles.

Table 2. IR and ^{1}H NMR spectra of compounds **I**–**IX**

Compd.	IR spectrum, ν, cm^{-1}				^{1}H NMR spectra, δ, ppm (*J*, Hz)						
	SO_2 (C=O)	CH alc	CH arom	NH	CH_3	N–CH_3	CH-CCl_3	H asol	C_6H_4X	NH	Solvent
I	1170 1340	2720 2860	3090 3130	3230			5.21 e (9.2)	8.46	7.57 e, 7.91 e (AA_1BB_1)	8.99 e	$(CD_3)_2CO$
II	1710	2780 2920 2970	3130	3170			6.89 e (9.6)	8.35	1.20 t, 4.12 q[a]	9.29 e (9.6)	DMSO-d_6,
III	1160 1340	2920 2950 2970	3070 3090	3310	2.24		5.61	5.82	7.53 e, 7.29 e (AA_1BB_1)	6.64	$CDCl_3$
IV	1170 1350	2720 2850 2970	3060 3100	3260			5.04	7.58 (2H) 7.45 (1H)	7.82 e, 7.64 e (AA_1BB_1) 7.20 (2H)	8.25	DMSO-d_6
V	1190 1320	2610 2750		3310		2.64	5.05	6.94 7.20	7.83 e, 7.65 e (AA_1BB_1)	7.91	DMSO-d_6
VI	1190 1360	2720	3060 3080	3330			5.20 e (9.2)	7.92	7.67 e, 7.44 e (AA_1BB_1)	9.04 e (9.2)	DMSO-d_6
VII	1180 1350	2620 3850	3070 3100	3250			5.22 e (9.2)	7.44	7.92, 7.60 m[b]	8.92 e (9.2)	DMSO-d_6
VIII	1150 1320	2930	3050 3080	3270 2.08	2.24	3.58	5.58		7.35 e, 7.56 e (AA_1BB_1)	5.73	$CDCl_3$
IX	1180 1330	2860 2920 2950	3060 3090	3260	2.10	3.50 t[c]	5.35 e (8.8)	5.00 (8.8)	7.84 e, 7.47 e (AA_1BB_1		$CDCl_3$
IX	1180 1330	2860 2920 2950	3060 3090	3260	2.03	3.43 T[d]	4.80		7.70 e, 7.48 e (AA_1BB_1)		DMSO-d_6

[a] The spectrum of the ethyl group from the ethoxycarbonyl fragment og compound **II** is reported.

[b] The spectrum of C_6H_5 group of compound **VII** is given.

[c] The chemical shift of N–CH_2 group from the fragment N–$CH_2(CH_2)_5CH_3$ is reported; the order signals of the fragment are sa follows ($CDCl_3$, δ, ppm): 1.6 m (CH_2); 1.24 m $(CH_2)_4$; 1.93 m (CH_3).

[d] The chemical shift of N–CH_2 group from the fragment N–$CH_2(CH_2)_5CH_3$ is reported in the spectrum recorded in DMSO-d_6. The order signals (δ, ppm) are 0.56 m (CH_3), 1.27 m $(CH_2)_5$.

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometers Bruker DPX-400 (400 Mhz) and Jeol FX-90 Q (90 MHz) in organic solutions of 5–10% concentration, internal reference HMDS.

IR spectra were recorded on spectrophotometer Specord 75IR from KBr pellets.

Imidazoles and triazoles used in the work were purified by recrystallization. 1,3,5-Trimethylpyrazole was obtained from 3,5-dimethylpyrazole and methyl iodide. 1-Heptyl-3-methylpyrazol-5-one was prepared from methyl acetoacetate and heptylhydrazine [9]. The imines used were obtained from acids dichloroamides and trichloroethylene [10, 11].

***N*-[1-(1,2,4-Triazol-2-yl)-2,2,2-trichloroethyl]-4-chlorobenzenesulfonamide (I).** A mixture of 2.60 g (0.01 mol) of N,N-dichloro(4-chlorobenzene)sulfonamide and 13.1 g (0.1 mol) of trichloroethylene was boiled at 85–90°C under continuous bubbling of argon. The reaction was carried out for 8–9 h till the end of chlorine liberation (test with iodo-starch paper). Then trichloroethylene was distilled off in a vacuum, the residue was dissolved in 10 ml of anhydrous chloroform, and 0.69 g (0.01 mol) of 1,2,4-triazole was added. The mixture was stirred at room temperature for 3–4 h. The formed colorless precipitate was filtered off, washed with anhydrous chloroform, and dried. We obtained 2.71 g of compound **I**.

***N*-[1-(1,2,4-Triazol-2-yl)-2,2,2-trichloroethyl]-ethoxycarbonylamine (II).** To 1.13 g (0.01 mol) of *N*-(2,2,2-trichloroethylidene)ethoxycarboxamide prepared from *N*,*N*-dichlorourethane and trichloroethylene [11] was added 10 ml of anhydrous carbon tetrachloride and 0.69 g (0.01 mol) of 1,2,4-triazole, and the mixture was stirred at room temperature for 5 h. We obtained 2.55 g of compound **II**.

***N*-[1-(3,5-Dimethylpyrazol-1-yl)-2,2,2-trichloroethyl]-4-chlorobenzenesulfonamide (III).** The preparation procedure was similar to the synthesis of compound **I**. From 2.60 g (0.01 mol) of *N*,*N*-dichloro-(4-chlorobenzene)sulfonamide, 13.1 g (0.1 mol) of trichloroethylene, and 0.96 g (0.01 mol) of 3,5-dimethylpyrazole (the second stage was carried out in anhydrous benzene) was obtained 3.67 g of compound **III**.

***N*-[1-(Benzimidazol-1-yl)-2,2,2-trichloroethyl]-4-chlorobenzenesulfonamide (IV)** was synthesized similarly to compound **I** from trichloroethylidene(4-chlorobenzene)sulfonamide prepared from 2.60 g (0.01 mol) of *N*,*N*-dichloro(4-chlorobenzene)sulfonamide, 13.1 g (0.1 mol) of anhydrous trichloroethylene, and 1.18 g (0.01 mol) of benzimidazole in anhydrous benzene. We obtained 3.20 g of compound **IV**.

***N*-[1-(2-Methylbenzimidazol-1-yl)-2,2,2-trichloroethyl]-4-chlorobenzenesulfonamide (V)** was synthesized similarly to compound **I** from trichloroethylidene(4-chlorobenzene)sulfonamide prepared from 2.60 g (0.01 mol) of *N*,*N*-dichloro(4-chlorobenzene)sulfonamide and 13.1 g (0.1 mol) of anhydrous trichloroethylene, and 1.32 g (0.01 mol) of methylbenzimidazole. We obtained 3.03 g (67%) of compound **V**.

***N*-[1-(Benzotriazol-1-yl)-2,2,2-trichloroethyl]-4-chlorobenzenesulfonamide (VI**) was synthesized similarly to compound **I** from trichloroethylidene(4-chlorobenzene)sulfonamide prepared from 2.60 g (0.01 mol) of *N*,*N*-dichloro(4-chlorobenzene)sulfonamide and 13.1 g (0.1 mol) of anhydrous trichloroethylene, and 1.20 g (0.01 mol) of benzotriazole in anhydrous benzene. We obtained 3.08 g of compound **VI**.

***N*-[1-(Benzotriazol-1-yl)-2,2,2-trichloroethyl]-4-benzenesulfonamide (VII)** was synthesized similarly to compound **I** from trichloroethylidenebenzenesulfonamide prepared from 2.14 g (0.01 mol) of *N*,*N*-benzenesulfonamide and 13.1 g (0.1 mol) of anhydrous trichloroethylene, and 1.20 g (0.01 mol) of benzotriazole in anhydrous benzene. We obtained 2.62 g of compound **VII**.

***N*-[1-(1,3,5-Trimethylpyrazol-4-yl)-2,2,2-trichloroethyl]-4-chlorobenzenesulfonamide (VIII).** To trichloroethylidene(4-chlorobenzene)sulfonamide prepared from 2.60 g (0.01 mol) of *N*,*N*-dichloro(4-chlorobenzene)sulfonamide and 13.1 g (0.1 mol) of trichloroethylene after excess trichloroethylene was distilled off in a vacuum was added 1.1 g (0.01 mol) of 1,3,5-trimethylpyrazole and 15 ml of anhydrous benzene. The mixture was heated to 80°C for 15–20 h, then it was cooled, and hexane or petroleum ether was added thereto. The separated precipitate was filtered off, dried, and recrystallized from ethanol. We obtained 3.07 g of compound **VIII**.

1-Heptyl-3-methyl-4-[(4-chlorobenzenesulfonamido)-2,2,2-trichloroethyl]pyrazol-5-one (IX) was obtained in a similar way as compound **VIII** from trichloroethylidene(4-chlorobenzene)sulfonamide prepared from 2.60 g (0.01 mol) of *N*,*N*-dichloro(4-chlorobenzene)sulfonamide and 13.1 g (0.1 mol) of trichloroethylene, and 1.96 g (0.01 mol) of 1-heptyl-3-methylpyrazol-5 one synthesized analogously to [9]. Yield 2.04 g.

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