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Dedicated to the memory of our teacher Professor Boris S. Drach

Synthesis and Transformations of 3-Aryl-5-dichloromethyl-1*H*-1,2,4-triazoles

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Abstract—A method of synthesis of 3-aryl-5-dichloromethyl-1*H*-1,2,4-triazoles was developed, some chemical transformations of the synthesized compounds were performed, and dichloromethyl fragment in these compounds was shown to exhibit the characteristics of aldehyde group.

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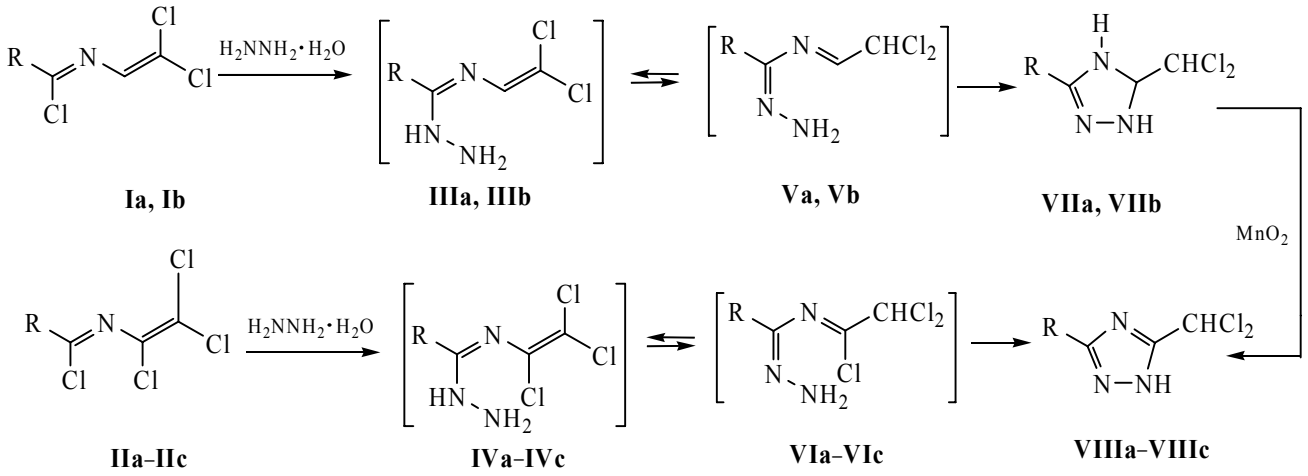
1,2,4-Triazoles and their derivatives possess a wide spectrum of biological activity [1–5]. Therefore, the synthesis of new representatives of this heterocyclic system is a promising area of research. Convenient starting reagents for obtaining such substances may be, as we show in this study, chlorine-containing 2-aza-1,3-dienes **I** and **II** (Scheme 1). Thus, treating the substrates **I** with hydrazine hydrate under common conditions led to formation of the substituted 1*H*-4,5-dihydro-1,2,4-triazoles (**VII**). An important role in this process plays a prototropic isomerism, which converts the non-reactive compounds **III** into more active tautomers **V,** which undergo cyclization. The C=N bond in the tautomer **V** undoubtedly is highly electrophilic, being activated owing to the presence of dichloromethyl residue.

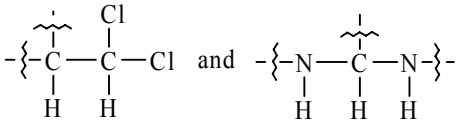
Triazoles **VII** are colorless crystalline substances sensitive to oxygen. Therefore, all the studies with these compounds should be performed using only freshly prepared samples. The structure of the compounds **VII** was confirmed reliably by spectral and chemical studies. Using ^{1}H NMR spectroscopy we proved that such cyclization products possess

Scheme 1.



R = Ph (**a**), 4-MeC_6H_4 (**b**), 4-ClC_6H_4 (**c**).

characteristic groups **A** and **B**, which are absent in the acyclic compounds **I**, **III,** and **V**.



A **B**

In addition, the structure of the cyclization products **VII** was proved by their oxidation with manganese dioxide to the corresponding aromatic compounds **VIII** (Table 1), which we used further as the key compounds in the synthesis of various derivatives of 1,2,4-triazole according to Schemes 2 and 3. It should be noted that compounds **VIII** were obtained in turn by an independent method from the substituted 1,3,4,4-tetrachloro-2-aza-1,3-dienes: **II** → **IV** → **VI** → **VIII** (Scheme 1). The important substances in this chain of transformations are the intermediates **IV** and their prototropic tautomers **VI** containing reactive imidoyl chloride group, which actually undergoes cyclization to form 3-aryl-5-dichloromethyl-1*H*-1,2,4-triazoles **VIII**.

Both chlorine atom in compounds **VIII** are rather labile, but we failed to get the products of replacing them with secondary amines like N-substituted 1,2,4-triazoles [6] for the synthesis of aldehydes **X** (Scheme 2). If compounds **IX** were formed, they underwent dimerization to substituted 5*H*,10*H*-bis[1,2,4]triazolo-[1,5-*a*:1',5'-*d*]pyrazines, in line with the published data on the N-unsubstituted 1,2,4-triazoloaldehydes [7].

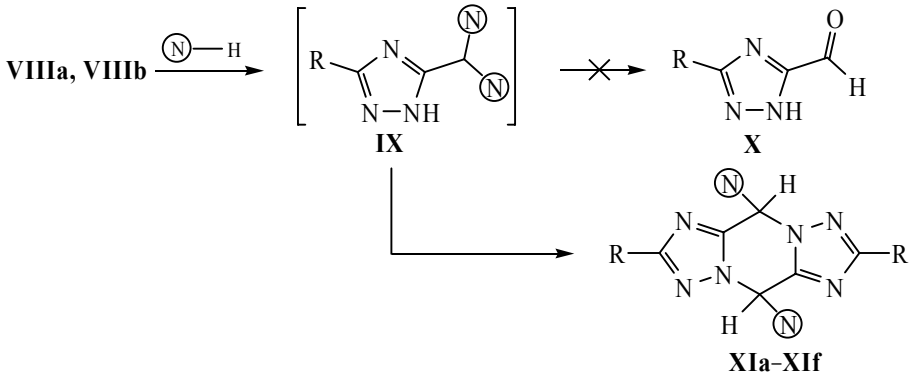
Compounds **XI** are stable white crystalline substances with high melting points, poorly soluble in organic solvents. Their structure was confirmed by comparing the ^{1}H NMR spectra of compounds **VIII** and **XI**. Thus, compounds **VIII** are characterized by the proton signals at 7.34–7.47 and 14.58–14.76 ppm ($CHCl_2$ and NH, respectively). These signals disappear at the formation of adducts **XI**, but the signals of protons appear attached to the aromatic nuclei and in

Table 1. Yields, melting points, and the data of elemental analysis of the synthesized compounds

Comp. no.	Yield, %	mp, °C (solvent)	Found, %		Formula	Calculated, %	
			Cl(S)	N		Cl(S)	N
VIIa	91	107–113 decomp.[a]	30.96	18.07	$C_9H_9Cl_2N_3$	30.82	18.26
VIIb	95	99–102 decomp.[a]	28.87	17.20	$C_{10}H_{11}Cl_2N_3$	29.04	17.21
VIIIa	93[b]	136–138 decomp. (toluene)	30.99	18.21	$C_9H_7Cl_2N_3$	31.09	18.42
VIIIb	85[b]	165–167 (propan-2-ol)	29.15	17.01	$C_{10}H_9Cl_2N_3$	29.29	17.36
VIIIc	84[b]	177–179 (toluene)	40.38	16.03	$C_9H_6Cl_3N_3$	40.51	16.01
XIa	70	238–240[c] (DMF–MeCN, 9:1)	–	22.56	$C_{26}H_{28}N_8O_2$	—	23.13
XIb	67	218–220 (DMF–MeCN, 9:1)	–	24.52	$C_{26}H_{28}N_8$	—	24.76
XIc	64	212–214 (MeCN)	–	24.51	$C_{26}H_{32}N_8$	—	24.54
XId	71	215–217 (DMF–MeCN, 9:1)	–	23.15	$C_{28}H_{32}N_8$	—	23.31
XIe	65	242–245[c] (DMF–MeCN, 9:1)	–	21.97	$C_{30}H_{36}N_8$	—	22.03
XIf	89	239–241 (DMF–MeCN, 9:1)	12.98	19.81	$C_{26}H_{26}CI_2N_8O_2$	12.81	20.25
XIIa	75	174–176 (DMF–MeCN, 1:9)	–	21.16	$C_{16}H_{14}N_4$	—	21.36
XIIb	78	170–172 (DMF–MeCN, 1:9)	–	20.06	$C_{17}H_{16}N_4$	—	20.27
XIIIa	53	180–182 (EtOH–H_2O, 1:2)	–	31.45	$C_{12}H_7N_5$	—	31.66
XIIIb	78	172–174 (EtOH–H_2O, 1:2)	13.97	26.99	$C_{12}H_6ClN_5$	13.87	27.39
XIVa	53	204–205 (EtOH)	–	19.37	$C_{15}H_{14}N_4O_2$	—	19.85
XIVb	72	210–212(EtOH)	12.42	19.25	$C_{13}H_9ClN_4O_2$	12.28	19.41
XVa	70	235–237 (EtOH–H_2O, 1:1)	(20.63)	17.32	$C_{13}H_{10}N_4OS_2$	(21.21)	18.53
XVb	90	225–227 (EtOH–H_2O, 1:1)	(19.81)	17.50	$C_{14}H_{12}N_4OS_2$	(20.27)	17.71
XVc	61	224–226 (EtOH–H_2O, 1:1)	10.44 (19.06)	16.58	$C_{13}H_9ClN_4OS_2$	10.53 (19.04)	16.63
XVd	65	220–222 (EtOH–H_2O, 1:1)	10.09 (18.24)	15.90	$C_{14}H_{11}ClN_4OS_2$	10.10 (18.28)	15.97

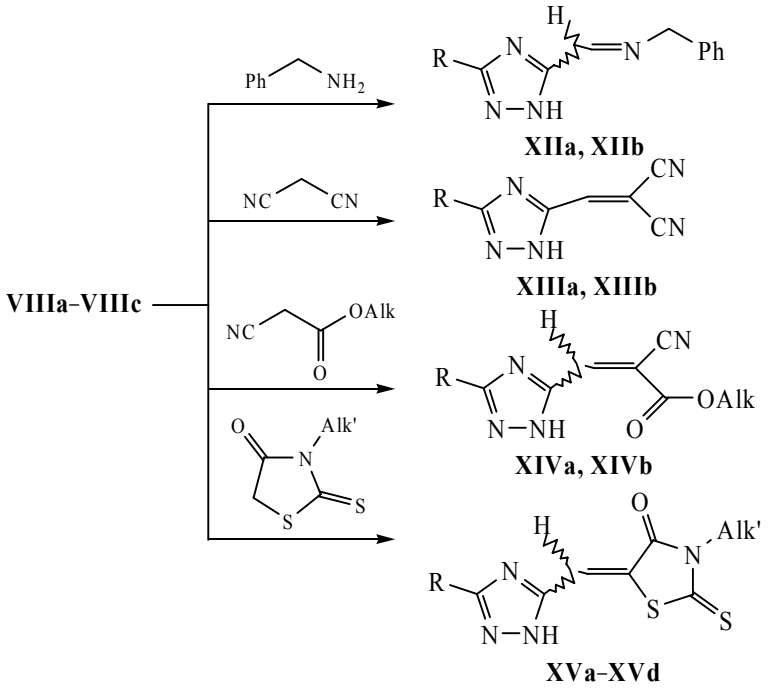
[a] After washing with water. [b] Yield by method *a*. [c] Corresponds to the published data [7].

Scheme 2.



R = Ph, Ⓝ = O(CH$_2$)$_4$N (**a**), (CH$_2$)$_4$N (**b**), Et$_2$N (**c**); R = 4-MeC$_6$H$_4$, Ⓝ = (CH$_2$)$_4$N (**d**), (CH$_2$)$_5$N (**e**); R = 4-ClC$_6$H$_4$, Ⓝ = O(CH$_2$)$_4$N (**f**).

Scheme 3.



XII: R = Ph (**a**), 4-MeC$_6$H$_4$ (**b**); **XIII**: R = Ph (**a**), 4-ClC$_6$H$_4$ (**b**); **XIV**: R = 4-MeC$_6$H$_4$, Alk = Et (**a**); R = 4-ClC$_6$H$_4$, Alk = Me (**b**); **XV**: R = Ph, Alk' = Me (**a**), Et (**b**); R = 4-ClC$_6$H$_4$, Alk' = Me (**c**), Et (**d**).

the aliphatic fragments with the expected ratio of integral intensities. It should be noted that compounds **XI** were isolated as mixtures of two diastereomers (the signals of protons in the piperazine fragment appear as two separate singlets of different intensities) (Table 2).

Compounds **VIII** can be regarded as precursors of aldehydes, and their high reactivity makes it possible to use them in the synthesis of a variety of substances with a set of useful properties. Thus, Scheme 3 shows the condensation of triazoles **VIII** with benzylamine, malonodinitrile, alkyl cyanoacetates and *N*-alkylrhodanines.

The structure of compounds **XII** – **XV** was proved by elemental analysis (Table 1) and spectral studies

Table 2. Spectral characteristics of the synthesized compounds[a]

Comp. no.	IR spectra, ν, cm^{-1} (KBr)	^1H NMR spectra, δ, ppm (DMSO-d_6)
VIIa	–	5.32 m (1H, CH), 5.73 d (1H, $CHCl_2$, $^3J_{HH}$ 4.8 Hz), 6.75 d (1H, NH, $^3J_{HH}$ 6.3 Hz), 7.36–7.69 m ($5H_{arom}$, NH)
VIIb	–	2.38 s (3H, CH_3), 5.19 br.m (2H, CH, NH), 5.36 d (1H, NH, $^3J_{HH}$ 6.9 Hz), 5.51 d (1H, $CHCl_2$, $^3J_{HH}$ 6.6 Hz), 7.19–7.56 m ($4H_{arom}$)
VIIIa	2800–3200 (NH as.)	7.36 s (1H, $CHCl_2$), 7.49–8.04 m ($5H_{arom}$), 14.65 br.s (1H, NH)
VIIIb	2870–3150 (NH as.)	2.39 s (3H, CH_3), 7.34 s (1H, $CHCl_2$), 7.31–7.92m ($4H_{arom}$), 14.58 br.s (1H, NH)
VIIIc	2920–3190 (NH as.)	7.47 s (1H, $CHCl_2$), 7.58–8.04 m ($4H_{arom}$), 14.76 br.s (1H, NH)
XIa	3000–3500 (no bands)	2.63–3.59 m [16H, $2O(CH_2)_4N$], 6.50 s, 6.78 s (2H, 2CH, 1:4)[a], 7.45–8.15 m ($10H_{arom}$)
XIb	3000–3500 (no bands)	1.75–3.09 m [16H, $2(CH_2)_4N$], 6.85 s, 7.11 s (2H, 2CH, 3:2), 7.33–8.10 m ($10H_{arom}$)
XIc	3000–3500 (no bands)	0.99–2.94 m [22H, 2OH, $2(C_2H_5)_2N$], 6.65 s, 6.95 s (2H, 2CH, 1:2), 7.36–8.12 m ($10H_{arom}$)
XId	3000–3500 (no bands)	1.75–3.06 m [16H, $2(CH_2)_4N$], 2.37 br.s (6H, $2CH_3$), 6.80 s, 7.06 s (2H, 2CH, 9:8), 7.26–7.99 m ($8H_{arom}$)
XIe	3000–3500 (no bands)	1.36–2.89 m [22H, 2OH, $2(CH_2)_5N$], 2.37 br.s (6H, $2CH_3$), 6.46 s, 6.72 s (2H, 2CH, 1:1), 7.31–7.99 m ($8H_{arom}$)
XIf	3000–3500 (no bands)	2.61–3.57 m [16H, $2O(CH_2)_4N$], 6.60 s, 6.87 s (2H, 2CH, 8:9), 7.59–8.13 m ($8H_{arom}$)
XIIb	1677 (C=N), 3050–3290 (NH as.)	2.36 s (3H, CH_3), 4.85 s (2H, CH_2), 7.30–7.95 m ($9H_{arom}$), 8.52 s (1H, CH), 14.46 br.s (1H, NH)
XIIIa	2229 (C≡N), 2248 (C≡N), 3110–3230 (NH as.)	7.59–8.06 m ($5H_{arom}$), 8.50 s (1H, CH), 15.48 br.s (1H, NH)
XIIIb	2235 (C≡N), 2242(C≡N), 3060–3250 (NH as.)	–
XIVa	1726 (C=O), 2243 (C≡N), 3080–3210 (NH as.)	1.36 t (3H, CH_3), 2.40 s (3H, CH_3), 4.33 q (2H, CH_2), 7.34–7.95 m ($4H_{arom}$), 8.09 s (1H, CH), 15.17 br.s (1H, NH)
XIVb	1737 (C=O), 2246 (C≡N), 3050–3190 (NH as.)	3.90 s (3H, CH_3), 7.58–8.07 m ($4H_{arom}$), 15.39 br.s (1H, NH)
XVa	1683 (C=O)[b], 3170–3230 (NH as.)	3.39 s (3H, CH_3), 7.51–8.07 m (6H, $5H_{arom}$, CH), 15.09 br.s (1H, NH)
XVb	1716 (C=O)[b], 3075–3230 (NH as.)	1.22t (3H, CH_3), 4.06 q (2H, CH_2), 7.51–8.07 m (6H, $5H_{arom}$, CH), 15.10 br.s (1H, NH)
XVc	1710 (C=O)[b], 3090–3210 (NH as.)	3.43 s (3H, CH_3), 7.52–8.06 m (5H, $4H_{arom}$, CH), 15.12 br.s (1H, NH)
XVd	1715 (C=O)[b], 3060–3190 (NH as.)	1.24 t (3H, CH_3), 4.08 q (2H, CH_2), 7.51–8.08 m (5H, $4H_{arom}$, CH), 15.13 br.s (1H, NH)

[a] Here and further for the compound **XI** the ratio of diasteremers is shown in parentheses. [b] Band with shoulder.

(Table 2). In the IR spectra of these substances broad bands of NH stretching vibrations (3050–3230 cm^{-1}) are present, in the spectra of compounds **XIII** and **XIV** there is a band of stretching vibrations of cyano groups (at 2229–2248 cm^{-1}, in the spectra of compounds **XIII** as two bands), as well as the absorption band of ester group (1726–1737 cm^{-1}) for compounds **XIV** and the carbonyl group of rhodanine fragment (1710–1716 cm^{-1}) for compounds **XV**. In the ^1H NMR spectra of these compounds there are the signals of NH (14.46–15.48 ppm) and of aromatic and aliphatic protons with the expected ratio of integrated intensities.

Thus, we have investigated the reaction of chlorine-containing 2-aza-1,3-dienes **I** and **II** with hydrazine-hydrate. This reaction results in the formation of substituted 1,2,4-triazoles with dichloromethyl group, and we used the latter for further functionalization with the aim of the synthesis of biologically active substances.

EXPERIMENTAL

The IR spectra were recorded on a Vertex 70 spectrometer from tablets with KBr. The ^{1}H NMR spectra were taken on a Varian VXR-300 instrument from solutions in DMSO-d_6 with TMS as internal reference.

3-Aryl-5-dichloromethyl-4,5-dihydro-1*H*-1,2,4-triazoles (VIIa, VIIb). To a solution of 0.06 mol of hydrazine-hydrate in 10 ml of anhydrous dioxane over 0.5 h was added dropwise with stirring a solution of 0.01 mol of a compound **Ia** or **Ib** in 20 ml of dioxane. The mixture was stirred for 12 h at 20–25°C, the hydrazine hydrochloride was filtered off, and dioxane was removed in a vacuum at 40°C. The residue was treated with water, the precipitate formed was filtered off, washed with water, and dried in a vacuum (1 mm Hg) at 40°C for 1 h. The compounds **VIIa** and **VIIb** obtained were analyzed without further purification.

3-Aryl-5-dichloromethyl-1*H*-1,2,4-triazoles (VIIIa–VIIIc). *a*. To a solution of 0.01 mol of a compound **IIa–IIc** in 20 ml of anhydrous THF at 5°C was added 0.033 mol of hydrazine hydrate, the mixture was stirred at 20–25°C for 12 h, the precipitate was filtered off, the solvent was removed in a vacuum. To the residue was added 100 ml of water, the precipitate formed was filtered off. The obtained compounds **VIIIa–VIIIc** were purified by recrystallization.

b. To a solution of 0.005 mol of freshly prepared sample of compound **VIIa** or **VIIb** in 50 ml of dioxane was added 0.05 mol of manganese dioxide. The mixture was refluxed for 2 h, the precipitate was filtered off and washed with hot dioxane. The solvent was removed in a vacuum, and the residue was treated with water (100 ml). The precipitate was filtered off, and the formed compound **VIIIa** or **VIIIb**, respectively, was purified by recrystallization from 2-propanol. Yield 59–66%. Mixed samples of compound **VIIIa** or **VIIIb** obtained by the methods *a* and *b* showed no depression of the melting points, the respective IR and ^{1}H NMR spectra were identical.

2,7-Diaryl-5,10-di(morpholino, piperidino, pyrrolidino, diethylamino)-5*H*,10*H*-bis[1,2,4]-triazolo-[1,5-*a*:1',5'-*d*]pyrazines (XIa–XId). To a suspension of 0.025 mol of a compound **VIIIa–VIIIc** in 15 ml of anhydrous THF was added 0.1 mol of either morpholine, or piperidine, or pyrrolidine, or diethylamine, and the mixture was stirred at 20–25°C for 24 h. The resulting precipitate was filtered off, washed with water and compounds **XIa–XId** were purified by recrystallization.

***N*-[(3-Aryl-1*H*-1,2,4-triazol-5-yl)methyliden]benzylamine (XIIa, XIIb)**. To a suspension of 0.025 mol of a compound **VIIIa** or **VIIIb** in 15 ml of anhydrous THF was added 0.075 mol of benzylamine, the mixture was stirred at 20–25°C for 24 h. The resulting precipitate was filtered off, washed with water, and obtained compound **XIIa** or **XIIb** was purified by recrystallization.

2-[(3-Aryl-1*H*-1,2,4-triazol-5-yl)methyl]malonic nitrile (XIIIa, XIIIb). To a solution of 0.003 mol of a compound **VIIIb** or **VIIIc** in 25 ml of ethanol was added 0.003 mol of malonodinitrile, 1.4 ml of acetic acid, and 0.2 ml of piperidine, and the mixture was refluxed for 24 h. The solvent was removed in a vacuum, the residue was treated with water, the precipitate formed was filtered off, washed with water, and obtained compound **XIIIa** or **XIIIb** was purified by recrystallization.

Methyl and ethyl 3-(3-aryl-1*H*-1,2,4-triazol-5-yl)-2-cyanoacrylates (XIVa, XIVb). To a solution of 0.002 mol of a compound **VIIIb** or **VIIIc** in 30 ml of ethanol was added 0.002 mol of methyl or ethyl cyanoacetate, 1 ml of acetic acid, and 0.1 ml of piperidine, and the mixture was refluxed for 72 h. The solvent was removed in a vacuum, the residue was treated with water, the precipitate formed was filtered off, washed with water, and obtained compound **XIVa** or **XIVb** was purified by recrystallization.

3-Alkyl-5-[(3-aryl-1*H*-1,2,4-triazol-5-yl)methyl]-2-thioxo-1,3-tiazolidin-4-ones (XVa–XVc). To a solution of 0.0022 mol of a compound **VIIIa–VIIIc** in 20 ml of ethanol was added 0.0022 mol of *N*-alkylrhodanine in 10 ml of ethanol, 1 ml of acetic acid and 0.1 ml of piperidine, and the mixture was refluxed for 72 h. The solvent was removed in a vacuum, the residue was treated with water, the precipitate formed was filtered off, washed with water, and obtained compound **XVa–XVc** was purified by recrystallization.

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