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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Synthesis of 1-Acyl- and 1-Arylsulfonyl Derivatives of 3,5-Diamino-1,2,4-triazole

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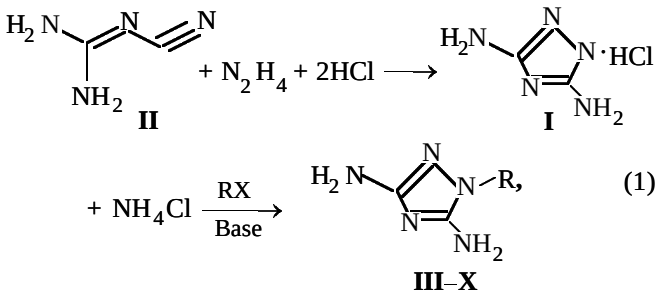
Abstract—Acylation of 3,5-diamino-1,2,4-triazole with anhydrides and chlorides of alkane- and arenecarboxylic acids and arenesulfonyl chlorides in aqueous solutions and under phase-transfer catalysis was studied.

Acyl, aroyl, and arenesulfonyl derivatives of 3,5-diamino-1,2,4-triazoles are used as intermediates for preparing nitro and azido derivatives of 1,2,4-triazoles [1–3], and also drugs and herbicides [4–7]. The most general route to acyl derivatives of 3,5-diamino-1,2,4-triazole is acylation of 3,5-diamino-1,2,4-triazole **I**, which can yield mono-, di-, and triacetyl derivatives depending on the reaction conditions [1, 4, 8–10]. However, triazole **I** is expensive, despite the fact that it is prepared from available substances: dicyanodiamide **II** and hydrazine [11]. The high cost of **I** is due to its difficult isolation from reaction mixtures. Our previous studies [12, 13] showed that some derivatives of **I** can be prepared from dicyanodiamide and hydrazine without isolation of **I**.

In this study we developed a procedure for preparing 1-acyl-, 1-aroyl-, and 1-arenesulfonyl-3,5-diamino-1,2,4-triazoles by acylation of products of the reaction of nitrile **II** with hydrazine without isolation of **I**:



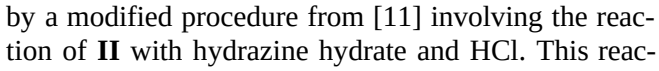
where R = Ac (**III**), EtCO (**IV**), PrCO (**V**), BuCO (**VI**), PhCO (**VII**), $PhSO_2$ (**VIII**), *p*-$MeC_6H_4SO_2$ (**IX**), *p*-$ClC_6H_4SO_2$ (**X**).

The reaction mixtures for acylation were prepared by a modified procedure from [11] involving the reaction of **II** with hydrazine hydrate and HCl. This reaction gave hydrochloride of **I** in 92–97% yield (determined according to [14]), with NH_4Cl as by-product.

Initially we studied acylation of the reaction mixtures with acetic anhydride, since 1-acetyl-3,5-diamino-1,2,4-triazole **III** is widely used as a reagent for preparing various 1,2,4-triazole derivatives, and, among the existing routes to **III**, the most convenient is acylation of **I** with acetic anhydride in aqueous solution [1].

Since triazole **I** occurs in the reaction mixture in the protonated form (pH 2–3), which does not react with acylating agents, the mixture should be preliminarily alkalized to convert the salt of **I** into the free base. However, for the acylation to be selective, ammonia should remain in the salt form. According to published data, for the equilibrium $\mathbf{I}\cdot H^+ \rightleftarrows \mathbf{I} + H^+$ $pK_a = 4.43$ [15], and for $NH_4^+ \rightleftarrows NH_3 + H^+$, $pK_a = 9.27$ [16]. Hence, pH 6.4–7.3 is an optimum at which the salt $\mathbf{I}\cdot H^+$ is virtually fully deprotonated but ammonia remains in the salt form. As bases in acylation with acetic anhydride, we used NaOH, Na_2CO_3, $NaHCO_3$, and sodium acetate.

At the equimolar ratio of **I** and base (pH 4.6–8.4), the major product of the reaction with acetic anhydride is **III**; its yield is virtually independent of particular base. Other acyl derivatives of **I** were not detected in the reaction mixtures. With sodium carbonate, hydrocarbonate, or acetate taken in excess, the reaction selectivity and yield of **III** remain unchanged. With excess NaOH (pH > 10), the yield of **III** decreases to 10–15%, because of the hydrolysis of ammonium chloride and competing reaction of the more nucleophilic ammonia with acetic anhydride:



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Free ammonia can also cause ammonolysis of the target product:

$$\mathbf{III} + NH_3 \longrightarrow \mathbf{I} + AcNH_2. \quad (3)$$

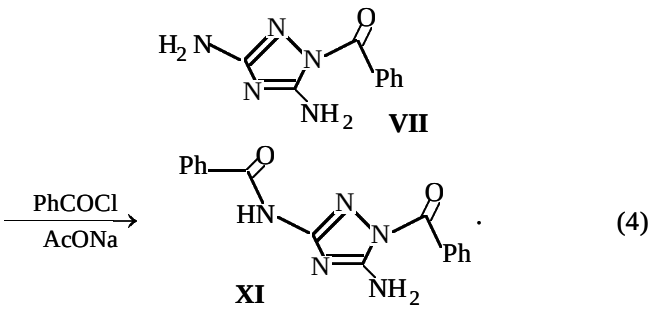
As the molar ratio $\mathbf{I} : Ac_2O$ is changed from 1 : 1 to 1 : (1.25–1.5), the yield of **III** increases from 62–71 to 78–80% (Table 1); larger excess of Ac_2O does not cause a further increase in the yield of **III**.

It is noteworthy that heating does not appreciably affect the selectivity of acylation with acetic anhydride and the yield of the target product (Table 2). In contrast to the majority of *N*-acyl azole derivatives, compound **III** shows enhanced resistance to hydrolysis, which may be due to the electron-donor effect of the 3,5-amino groups.

Thus, it is advisable to perform acylation with acetic anhydride at the molar ratio $\mathbf{I} : \text{base} : Ac_2O$ = 1 : (1–1.2) : 1.25. As in the range 0–50°C the acylation selectivity varies insignificantly, all the steps can be performed at the same temperature as one-pot synthesis. The use of NaOH is not appropriate, because excess NaOH can cause hydrolysis of NH_4Cl and decrease the reaction selectivity because of competing ammonolysis of the acylating agent.

Compounds **IV**–**VII** were prepared under similar conditions using appropriate anhydrides (Table 3). Compound **VII** is isolated from the reaction mixture together with benzoic acid. Benzoic acid can be readily removed by recrystallization from ethanol; yield of purified compound **VII** 35–40%.

With carboxylic acid chlorides and arenesulfonyl chlorides as acylating agents, it is necessary to introduce an additional amount of a base to bind the released HCl. Acylation with aliphatic acyl chlorides resulted only in their hydrolysis. Acylation with benzoyl chloride, which is more resistant to hydrolysis, at 20°C in the presence of sodium acetate gave a mixture of products consisting, according to liquid chromatography, of 14% **VII**, 42% 5-amino-3-benzamido-1-benzoyl-1,2,4-triazole **XI**, and 44% benzoic acid. Compound **XI** is apparently formed by acylation of **VII**:



(4)

Table 1. Yield of **III** at 20°C and pH 4.6–8.4

Molar ratio $\mathbf{I} : Ac_2O$	Yield, %	Molar ratio $\mathbf{I} : Ac_2O$	Yield, %
1 : 1.0	62	1 : 1.5	80
1 : 1.1	71	1 : 1.75	80
1 : 1.25	78	1 : 2.0	75

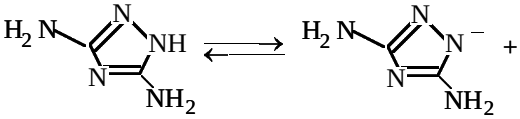
Table 2. Yield of **III** at the molar ratio $\mathbf{I} : Na_2CO_3 : Ac_2O$ = 1 : 1 : 1.25

T, °C	Yield, %	*T*, °C	Yield, %
0	79	50	77
30	78	70	72
40	77	90	68

Apparently, the rate of formation of **VII** is comparable with the rate of its subsequent acylation with benzoyl chloride into **XI**. We failed to prepare **VII** selectively even at a twofold excess of **I** relative to benzoyl chloride. This may be due to the fact that benzoyl chloride and compound **I** occur in different phases. Benzoyl chloride is poorly soluble in water, whereas triazole **I** is very well soluble; therefore, compound **VII** is mainly formed at the phase boundary. After being formed, compound **VII** dissolves in benzoyl chloride and undergoes further acylation.

The reaction with benzenesulfonyl chloride under the same conditions yielded compound **VIII** but was very slow; the yield of the target product did not exceed 35% in 72 h. Crystalline *p*-toluenesulfonyl chloride and *p*-chlorobenzenesulfonyl chloride under the same conditions gave **IX** and **X**; their yield in 3 days did not exceed 10%, and the major isolated compounds were unchanged arenesulfonyl chlorides.

We suggested that the selectivity of acylation with carboxylic acid chlorides and arenesulfonyl chlorides could be increased by converting triazole **I** into the anion and performing the reaction with phase-transfer catalysis. The anion should be considerably more nucleophilic and reactive as compared to the neutral molecule. For equilibrium (5), pK_a = 12.12 in water at 20°C [17]. Hence, at pH > 14.12, compound **I** in water occurs in the anionic form:



(5)

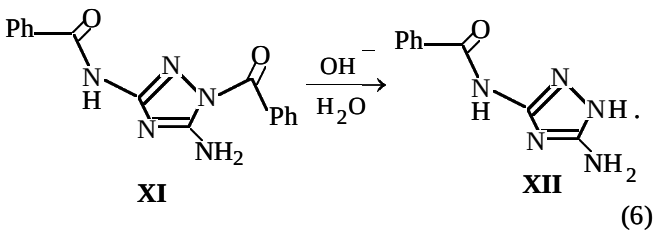
To provide the required basicity, no less than 3 mol of NaOH per mole of **II** should be added to the reac-

Table 3. Synthesis conditions, yields, and properties of acylation products **III**–**XII** (molar ratio **I** : acylating agent = 1 : 1)

Compound	Acylating agent	Base	Molar ratio **I** : base	*T*, °C	τ, h	Yield, % (synthesis procedure)	mp,[1] °C	Found, % / Calculated, %			Formula
								C	H	N	
III	AcCl	NaOH	1 : 1.2[2]	5	0.5	28 (*b*)	228 (dec.)[3]	34.00 / 34.04	5.07 / 5.00	49.59 / 49.62	$C_4H_7N_5O$
IV	$(EtCO)_2O$	NaOAc	1 : 1.25	20	1.0	75 (*a*)	166–167	38.75 / 38.65	5.83 / 5.85	45.18 / 45.34	$C_5H_9N_5O$
V	$(PrCO)_2O$	NaOAc	1 : 1.25	20	1.0	70 (*a*)	112–113	42.80 / 42.60	6.52 / 6.55	41.41 / 41.39	$C_6H_{11}N_5O$
	PrCOCl	NaOH	1 : 1.2[2]	5	0.5	29 (*b*)					
VI	$(BuCO)_2O$	NaOAc	1 : 1.25	20	1.0	75 (*a*)	123–124	45.93 / 45.89	7.20 / 7.15	38.25 / 38.22	$C_7H_{13}N_5O$
VII	$(PhCO)_2O$	NaOAc	1 : 1.25	45	1.0	47 (*a*)[4]	154–156	53.26 / 53.32	4.39 / 4.46	34.50 / 34.40	$C_9H_9N_5O$
	PhCOCl	NaOAc	1 : 2.25	20	2.0	8 (*a*)[4]					
	PhCOCl	NaOH	1 : 1.0[2]	5	0.5	58 (*b*)					
	PhCOCl	NaOH	1 : 1.2[2]	5	0.5	52 (*b*)					
VIII	$PhSO_2Cl$	NaOAc	1 : 2.25	20	72	35 (*a*)	222–224[5]	40.84 / 40.16	3.80 / 3.79	29.20 / 29.27	$C_8H_9N_5O_2S$
	$PhSO_2Cl$	NaOH	1 : 1.2[2]	5	0.5	70 (*b*)					
IX	*p*-$MeC_6H_4SO_2Cl$	NaOAc	1 : 2.25	20	72	10 (*a*)	216–217	43.00 / 42.68	4.38 / 4.38	27.20 / 27.65	$C_9H_{11}N_5O_2S$
	p-$MeC_6H_4SO_2Cl$	NaOH	1 : 1.2[2]	5	0.5	60 (*b*)					
X	*p*-$ClC_6H_4SO_2Cl$	NaOAc	1 : 2.25	20	72	9 (*a*)	213–215	35.21 / 35.11	2.89 / 2.95	25.66 / 25.59	$C_8H_8ClN_5O_2S$
	p-$ClC_6H_4SO_2Cl$	NaOH	1 : 1.2[2]	5	0.5	50 (*b*)					
XI	PhCOCl	NaOAc	1 : 2.25	20	72	41 (*a*)[4]	198 (dec.)	65.66 / 62.53	4.18 / 4.26	23.00 / 22.79	$C_{16}H_{13}IN_5O_2$
	PhCOCl	NaOH	1 : 1.0[2]	5	0.5	15 (*b*)[4]					
XII	PhCOCl	NaOH	1 : 1.2[2]	5	0.5	12 (*b*)	310–312	46.00 / 45.89	7.24 / 7.15	37.60 / 38.22	$C_9H_9N_5O$

[1] Compounds **III**–**VII** and **XI** were crystallized from ethanol; **VIII**–**X** and **XII**, from ethanol–DMF. [2] Additional 2 mol of NaOH was introduced per mole of **II**. [3] mp 228–230°C [9]. [4] According to liquid chromatography. [5] mp 225°C [18].

tion mixture [see scheme (1)]. Since NH_4Cl is fully hydrolyzed under these conditions, the released ammonia was removed by boiling the reaction mixture. The subsequent acylation with acetyl and butyryl chlorides in a CH_2Cl_2–water mixture in the presence of benzyltriethylammonium chloride yielded only 1-acyl derivatives **III** and **V**, and the reaction with benzoyl chloride, along with the major product **VII**, yielded also **XI** or 5-amino-3-benzamido-1,2,4-triazole **XII** depending on the molar ratio **I** : NaOH (Table 3, method *b*). Compound **XII** is apparently formed by hydrolysis of **XI**:



XI **XII** (6)

In particular, at an equimolar ratio of triazole **I** to NaOH, compound **XI** was isolated in 15% yield

(Table 3), and compound **XII** was not detected. At a 20% excess of alkali, compound **XI** was absent in the reaction products, and compound **XII** was isolated from the aqueous phase in 12% yield. Hence, compound **VII** formed under the conditions of phase-transfer catalysis is subsequently "slowly" acylated to dibenzoyl derivative **XI**, which is hydrolyzed to product **XII** with excess alkali. Probably, the hydrolysis of **XI** is promoted by an acidic proton of the benzoylamino group, responsible for the dissociation of **XI** in an alkali solution with the dissolution of **XI** in the aqueous phase and its subsequent hydrolysis.

The low yields of the acetyl (**III**) and butyryl (**V**) derivatives and the lack of acylamino derivatives in the reaction products may be due to the high rate of hydrolysis of aliphatic acyl chlorides.

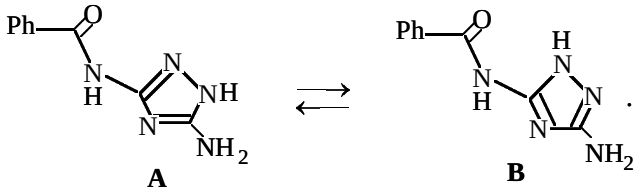
Acylation of **I** under the phase-transfer conditions is also an efficient route to 1-arenesulfonyl-3,5-diamino-1,2,4-triazoles. Under these conditions, from appropriate arenesulfonyl chlorides, we prepared compounds **VIII**–**X** in 50–70% yields (Table 3). The main substance content in the crude products was no less than 90% according to the ^{1}H NMR data.

The composition and structure of the compounds synthesized were confirmed by elemental analysis (Table 3) and by IR, UV, and ^{1}H NMR spectroscopy.

In the IR spectra of acyl derivatives **III**–**VII** and **XI**, the stretching vibration bands of the carbonyl group bonded to the nitrogen atom of the triazole ring are manifested at 1680–1710 cm^{-1}, whereas the vibration frequencies of the "amide" carbonyl group in **XI** and **XII** are lower: 1650–1660 cm^{-1}. The spectra of arenesulfonyl chlorides **VIII**–**X** contain a strong absorption band at 1150–1160 cm^{-1}, which was assigned to the symmetric vibrations of the SO_2 group.

The UV spectra of **III**–**VII** are similar to the spectra of 5-amino-1-acyl-1,2,4-triazoles reported in [9] and exhibit two maxima at 217–230 and 273–290 nm. The spectra of 1-arenesulfonyl-3,5-diamino-1,2,4-triazoles **VIII**–**X** are also characterized by two maxima in the ranges 220–234 and 261–269 mn. The UV spectrum of 5-amino-3-benzamido-1,2,4-triazole **XII** differs from that of isomeric 1-benzoyl-3,5-diamino-1,2,4-triazole **VII** by the absence of the long-wave maximum at about 290 nm and the presence of a shoulder at about 253 nm; this is consistent with the data for 3-R-5-acylamino-1,2,4-triazoles [9].

The NMR spectra of 1-acyl- and 1-arenesulfonyl-3,5-diamino-1,2,4-triazoles **III**–**X** contain two singlets from protons of amino groups. The 3-NH_2 protons give a signal at 5.36–5.65 ppm, and the 5-NH_2 protons, a signal at 7.32–7.55 ppm for acyl derivatives **III**–**VII** and at 6.90–6.97 ppm for arenesulfonyl derivatives **VIII**–**X**. The spectrum of **XI** does not contain the 3-NH_2 signal but contains a singlet of the amide proton at 10.67 ppm; the 5-NH_2 signal is shifted downfield relative to **VII** owing to the electron-withdrawing effect of the additional benzoyl group. According to the NMR spectrum, compound **XII** in DMSO occurs in the form of tautomers **A** (major) and **B**:



A **B**

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Unity-300 spectrometer (300 MHz) in DMSO-d_6, internal reference TMS. The IR spectra were recorded on a Specord IR-75 spectrometer from mulls in mineral oil. The UV spectra (aqueous solutions) were taken on an SF-26 spectrophotometer. High-performance liquid chromatography was performed on a Milikhrom chromatograph equipped with a UV detector and a 60 × 3-mm column (sorbent Silasorb C_{18}, 5 μm, mobile phase methanol, elution rate 5 μl min^{-1}, detection at 230 nm).

1-Acyl- and 1-arenesulfonyl-3,5-diamino-1,2,4-triazoles III–X and 5-amino-3-benzamido-1-benzoyl-1,2,4-triazole XI. (*a*) To 0.0333 mol of hydrazine hydrate (55% solution), we added dropwise with stirring at a temperature not exceeding 50°C 0.0666 mol of HCl (30% solution) and 0.0333 mol of **II** over a period of 10–15 min; the mixture was heated for 1 h at 50°C. Then the required amount of a base was added, and the acylating agent was added dropwise with stirring at the required temperature (Tables 1–3). The mixture was stirred for a period indicated in Table 3; the precipitate was filtered off, washed with water, dried, and analyzed by ^{1}H NMR and HPLC. The precipitates of **III**–**VI**, according to ^{1}H NMR, contained no less than 90% main substance, and compound **VII**, according to HPLC, contained ~50% benzoic acid. Compounds **III**–**VII** were purified by recrystallization from ethanol. To separate mixtures from acylation with benzoyl chloride, the precipitate was dissolved in 60 ml of boiling ethanol, and the solution was cooled. The precipitate of **XI** was filtered off, recrystallized, and analyzed. The mother liquor after the separation of **XI** was evaporated to a volume

of 15 ml and cooled; the precipitate of **VII** was recrystallized and analyzed. Compounds **VIII**–**X** were washed with chloroform to separate unchanged arenesulfonyl chloride, recrystallized, and analyzed.

(*b*) To the solution from the reaction of hydrazine hydrate, HCl, and compound **II** by method *a*, we added the required amount of NaOH (Table 3) and boiled until the evolution of NH_3 was complete (30–40 min); water was added to compensate for the evaporation. The mixture was diluted with distilled water to a volume of 12.5 ml and cooled; 0.003 mol of benzyltriethylammonium chloride and a solution of the acylating agent in 6 ml of CH_2Cl_2 were added. The mixture was stirred for 20 min; the precipitate of the target product was filtered off, washed successively with water and methylene chloride, dried, and analyzed. Compounds **III**–**XI** were purified similarly to method *a*.

5-Amino-3-benzamido-1,2,4-triazole XII. (*a*) The reaction mixture after the separation of compound **VII** prepared by method *b* at the molar ratio **I** : NaOH = 1 : 1.2 was neutralized with 10% HCl to pH 7–8. The precipiptate thus formed was filtered off, washed with 5 ml of boiling ethanol to separate benzoic acid, and crystallized from DMF–ethanol.

Compound **XII** was also prepared in 86% yield by independent synthesis: hydrolysis of 0.001 ml of **XI** in 10 ml of 1 M NaOH at 5°C for 2 h.

CONCLUSIONS

(1) One-pot procedures were developed for acylation and arenesulfonylation of 3,5-diamino-1,2,4-triazole in reaction mixtures from the reaction of dicyanodiamide with hydrazine.

(2) It is advisable to prepare 1-acyl-3,5-diamino-1,2,4-triazoles by acylation of 3,5-diamino-1,2,4-triazole with carboxylic acid anhydrides in aqueous solution (70–80% yields), and 1-arenesulfonyl-3,5-diamino-1,2,4-triazoles, by acylation of 3,5-diamino-1,2,4-triazole with arenesulfonyl chlorides under conditions of phase-transfer catalysis (50–70% yields).

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