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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Synthesis of Esters and Amides of 5-Amino-1,2,4-triazole-3-carboxylic and 5-Amino-1,2,4-triazol-3-ylacetic Acids

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Abstract—Various synthetic routes to esters and amides of 5-amino-1,2,4-triazole-3-carboxylic and 5-amino-1,2,4-triazol-3-ylacetic acids were examined.

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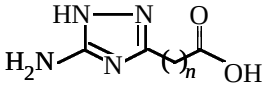
5-Amino-1,2,4-triazole-3-carboxylic (**I**) and 5-amino-1,2,4-triazol-3-ylacetic (**II**) acids and their esters and amides are valuable chemicals for the synthesis of drugs, herbicides [1–5], dyes [6–8], and high-energy-capacity compounds [9].

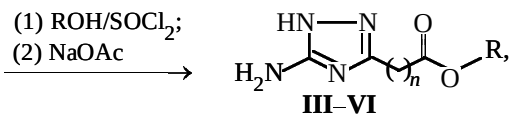
The goal of this study was the development of improved procedures for preparing esters and amides of acid **I** and **II**.

The above esters are most frequently prepared by esterification of acids **I** and **II** with alcohols in the presence of dry HCl [2, 4, 10, 11]. The reaction is reversible; therefore, its products are formed in moderate yields, and a large excess of anhydrous alcohol is required; to be reused, the alcohol should be dehydrated. The recently suggested [1] procedure for esterification of acid **I** with methanol in the presence of $SOCl_2$ (total yield of ester **III** 67%) eliminates this drawback; however, the reaction takes much time (24 h) and is performed at low temperature.

We found that methyl and ethyl esters **III**–**VI** can be prepared in good yields by esterification of acids **I** and **II** with alcohols in the presence of $SOCl_2$ with refluxing [reaction (1), see table]; in so doing, the synthesis time is as short as 4 h, and the spent alcohol can be repeatedly reused without preliminary dehydraion.



I, **II**

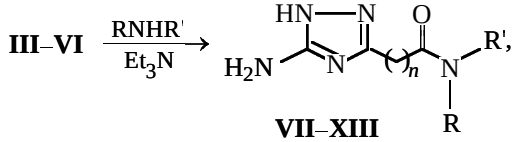


III–**VI** (1)

where n = 0 (**I**, **III**, **V**), 1 (**II**, **IV**, **VI**); R = Me (**III**, **IV**), Et (**V**, **VI**).

One of the simplest routes to amides of acids **I** and **II** might be the reaction of chlorides of these acids with amines. However, we failed to prepare the required acid chlorides. Refluxing of acids **I** and **II** with $SOCl_2$ or their heating with PCl_5 yielded an unseparable mixture of products, apparently because of side reactions such as self-acylation of amino group and nitrogen atoms of the triazole ring with the COCl group. Attempts to prepare the desired amides by the reaction of acids **I** and **II** with thionyl chloride and amines in pyridine at 0–100°C also failed.

The synthesis of amide of acid **I** by heating of ester **III** with aqueous ammonia was reported in [12]. However, we failed to prepare other amides by this procedure. The reactions of **III**–**VI** with amines in THF, performed by the procedure suggested previously [5] for preparing amides of 5-amino-4-alkyl-1,2,4-triazole-3-carboxylic acids, were very slow, probably because of the low solubility of the esters in THF. The best results were obtained when esters **III**–**VI** were heated with aliphatic amines in the presence of triethylamine at 85–90°C [reaction (2), see table]:



(2)

where n = 0 (**VII**, **IX**, **XI**, **XIII**), 1 (**VIII**, **X**, **XII**); NRR' = morpholine (**VII**, **VIII**), pyrrolidine (**IX**, **X**); R = Bn, R' = H (**XI**, **XII**; R = *i*-Pr, R' = H (**XIII**).

With less nucleophilic anilines containing various

Synthesis conditions, yields, and properties of **III**–**XVIII**

Compound no.	Yield, % (method)	mp, °C*	^{1}H NMR spectrum, δ, ppm	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
III	69	217–218**	4.00 s (3H, OCH_3), 6.00 s (2H, NH_2), 12.35 s (1H, NH)	33.7	4.2	39.4	$C_4H_6N_4O_2$	33.8	4.3	39.4
IV	55	164–165	3.40 s (2H, CH_2), 3.62 s (3H, OCH_3), 5.65 s (2H, NH_2), 11.58 s (1H, NH)	38.2	5.16	35.8	$C_5H_8N_4O_2$	38.5	5.16	35.9
V	70	242–243**	1.35 t (3H, CH_3), 4.23 q (2H, OCH_2), 6.00 s (2H, NH_2), 12.38 s (1H, NH)	38.6	5.2	36.0	$C_5H_8N_4O_2$	38.5	5.2	35.9
VI	68	156–158**	1.25 t (3H, CH_3), 3.40 s (2H, CH_2), 4.20 q (2H, OCH_2), 5.60 s (2H, NH_2), 11.56 s (1H, NH)	42.2	6.1	40.1	$C_6H_{10}N_4O_2$	42.4	5.9	39.9
VII	74 (a)	222–224	3.55 m (8H, $4CH_2$), 5.62 s (2H, NH_2), 11.52 s (1H, NH)	43.0	5.6	35.4	$C_7H_{11}N_5O_2$	42.6	5.6	35.5
VIII	54 (a)	240–242	3.58 m (10H, $5CH_2$), 5.62 s (2H, NH_2), 11.58 s (1H, NH)	45.8	6.1	33.4	$C_8H_{13}N_5O_2$	45.5	6.2	33.2
IX	84 (a)	284–286	1.90 m (4H, $2CH_2$), 3.47 m (2H, NCH_2), 3.82 m (2H, NCH_2), 5.80 s (2H, NH_2), 12.05 s (1H, NH)	46.4	6.2	38.4	$C_7H_{11}N_5O$	46.4	6.1	38.7
X	54 (a)	266–268	1.80 m (4H, $2CH_2$), 3.22 t (2H, NCH_2), 3.38 s (2H, CH_2), 3.49 t (2H, NCH_2), 5.83 s (2H, NH_2), 11.67 s (1H, NH)	49.0	6.8	36.0	$C_8H_{13}N_5O$	49.2	6.7	35.9
XI	78 (a)	236–238	4.42 d (2H, NCH_2), 5.89 s (2H, NH_2), 7.21 m (5H, arom.), 8.27 s (1H, NH), 12.33 s (1H, NH)	55.4	5.2	32.0	$C_{10}H_{11}N_5O$	55.3	5.1	32.2
XII	76 (a)	172–175	3.31 s (2H, CH_2), 4.26 d (2H, NCH_2), 5.87 s (2H, NH_2), 7.23 m (5H, arom.), 8.43 s (1H, NH), 11.58 s (1H, NH)	56.9	5.7	30.6	$C_{11}H_{13}N_5O$	57.1	5.7	30.3
XIII	61 (a)	247–250	1.16 m (6H, $2CH_3$), 4.03 m (1H, NCH), 5.71 s (2H, NH_2), 7.33 m (1H, NH), 12.31 s (1H, NH)	42.4	6.4	41.7	$C_6H_{11}N_5O$	42.6	6.6	41.4
XIV	58 (b)	235–237	6.01 s (2H, NH_2), 7.01 m (1H, arom.), 7.24 m (2H, arom.), 7.77 m (2H, arom.), 9.60 s (1H, NH), 12.41 s (1H, NH)	53.0	4.6	34.4	$C_9H_9N_5O$	53.2	4.5	34.5
XV	46 (b)	209–210	3.45 s (2H, CH_2), 5.83 s (2H, NH_2), 7.01 m (1H, arom.), 7.26 m (2H, arom.), 7.56 m (2H, arom.) 10.23 s (1H, NH), 11.72 s (1H, NH)	55.5	5.2	32.2	$C_{10}H_{11}N_5O$	55.3	5.1	32.2
XVI	74 (b)	280–282	6.00 s (2H, NH_2), 7.24 m (2H, arom.), 7.82 m (2H, arom.), 9.84 s (1H, NH), 12.41 s (1H, NH)	45.8	3.2	29.4	$C_9H_8N_5ClO$	45.5	3.4	29.5
XVII	51 (b)	221–223	3.45 s (2H, CH_2), 5.84 s (2H, NH_2), 7.33 m (2H, arom.), 7.60 m (2H, arom.), 10.26 s (1H, NH), 11.74 s (1H, NH)	47.7	4.1	28.1	$C_{10}H_{10}N_5ClO$	47.7	4.0	27.8

Table (Contd.)

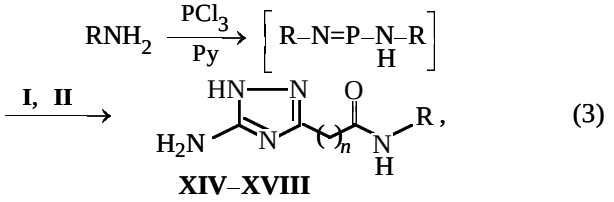
Compound no.	Yield, %	mp, °C*	^{1}H NMR spectrum, δ, ppm	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
XVIII	64 (b)	276–278	3.75 s (3H, OMe), 5.97 s (2H, NH_2), 6.81 m (2H, arom.), 7.66 m (2H, arom.), 9.48 s (1H, NH), 12.36 s (1H, NH)	51.2	4.7	29.7	$C_{10}H_{11}N_5O_2$	51.5	4.8	30.0

* Compounds **III** and **V** were recrystallized from H_2O; **IV**, **VI**–**X**, **XII**, **XIII**, and **XV**–**XVII**, from EtOH; and **XI**, **XIV**, and **XVIII**, from DMF.

** Published data, mp, °C: **III**, 220 [10]; **V**, 247 [11]; **VI**, 156–158 [3].

substituents in the benzene ring, the desired amides were not formed under the above conditions, and under more severe conditions (heating to 150°C without solvent or refluxing in DMF) an unseparable mixture of products was obtained.

We managed to prepare the anilides by treatment of anilines with PCl_3 followed by the reaction of the resulting organophosphorus compound, without its isolation, with acids **I** and **II**. By this procedure we prepared compounds **XIV**–**XVIII** [reaction (3), see table]:



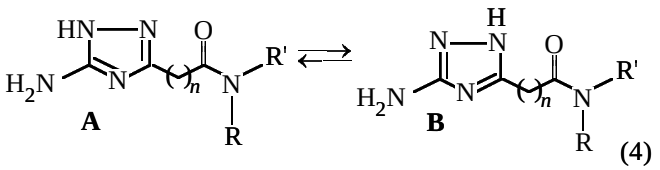
(3)

XIV–**XVIII**

where n = 0 (**XIV**, **XVI**, **XVIII**), 1 (**XV**, **XVII**); R = Ph (**XIV**, **XV**), *p*-ClC_6H_4 (**XVI**, **XVII**), *p*-$MeOC_6H_4$ (**XVIII**).

The compositions and structures of the compounds prepared were determined by elemental analysis, ^{1}H NMR spectroscopy, and mass spectrometry; their purity was confirmed by HPLC.

The compounds obtained exhibit prototropy and can exist in the form of tautomers **A** and **B** [equilibrium (4)]. According to ^{1}H NMR spectra, in DMSO tautomer **A** prevails [δ(NH_2) 5.6–6.0 ppm, see table]. Minor amounts of tautomer **B** were detected in the spectra of amides **VII**, **IX**, **X**, **XIV**, and **XVIII** (additional broadened singlet ot the amino group at 4.8–5.1 ppm). The chemical shifts of amino group protons in tautomers **A** and **B** are consistent with published data for other 3(5)-amino-1,2,4-triazoles [13].



(4)

The mass spectra of all the compounds prepared contain a strong peak of molecular ion.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Unity 300 spectrometer (300 MHz, DMSO-d_6, internal reference TMS). The mass spectra were taken on a Finnigan MAT-Incos 50 device with direct sample inlet (electron impact, 70 eV). The melting points were determined with a PTP device. The HPLC analysis was performed with a Milikhrom-5 chromatograph equipped with a UV detector and an 80 × 2-mm column packed with Separon C_{18}; the mobile phase was methanol (flow rate 80 μl min^{-1}). The detection was performed at λ 210 nm.

Acids **I** and **II** were predried in a vacuum at 105–110°C for 24 h.

Esters of 5-amino-1,2,4-triazole-3-carboxylic (III, V) and 5-amino-1,2,4-triazol-3-ylacetic (IV, VI) acids. A 0.047-mol portion of $SOCl_2$ was added dropwise with stirring to a mixture of 0.047 mol of acid **I** or **II** and 0.4 mol of anhydrous methanol or ethanol. The mixture was heated to boil and refluxed for 1 h, after which an additional 0.047 mol of $SOCl_2$ was added, and the refluxing was continued for 3 h more. Excess alcohol was distilled off in a water-jet-pump vacuum, and a saturated solution of sodium acetate was added with cooling to the residue to pH 5–6. The precipitate thus obtained was filtered off, washed with water, and recrystallized.

Amides of 5-amino-1,2,4-triazole-3-carboxylic (VII, IX, XI, XIII, XIV, XVI, XVIII) and 5-amino-1,2,4-triazol-3-ylacetic (VIII, X, XII, XV, XVII) acids. (a) A mixture of 0.1 mol of ester **III**–**VI**, 0.02 mol of triethylamine, and 0.012 mol of aliphatic amine was heated at 85–90°C for 3 h (synthesis of **XIII** was performed in a sealed ampule), after which triethylamine and excess aliphatic amine were distilled

off in a vacuum, 2–3 ml of water was added to the residue, and the precipitate was filtered off and recrystallized.

(b) A 0.006-mol portion of PCl_3 was added with stirring and cooling to a mixture of 0.012 mol of appropriate aniline and 4 ml of pyridine. The mixture was stirred for 10 min at room temperature, after which 0.01 mol of acid **I** or **II** was added, the mixture was stirred for an additional 10 min at room temperature, heated to 110–120°C, kept at this temperature for 45 min, and diluted with 10 ml of H_2O. The precipitate thus formed was filtered off and recrystallized.

CONCLUSIONS

(1) It is advisable to prepare methyl and ethyl esters of 5-amino-1,2,4-triazole-3-carboxylic and 5-amino-1,2,4-triazol-3-ylacetic acids by esterification of the corresponding acids with alcohols in the presence of $SOCl_2$ with refluxing (yield 55–70%).

(2) It is advisable to prepare amides of 5-amino-1,2,4-triazole-3-carboxylic and 5-amino-1,2,4-triazol-3-ylacetic acids by the reactions of aliphatic amines with methyl or ethyl esters of the corresponding acids at 85–90°C in the presence of triethylamine (yield 54–84%) or by successive treatment of aromatic amines with PCl_3 and the corresponding acids in pyridine (the second step, at 110–120°C); yield 46–74%.

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