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Synthesis of 3-Alkyl-6-aryl(arylamino)-7*H*-[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazines

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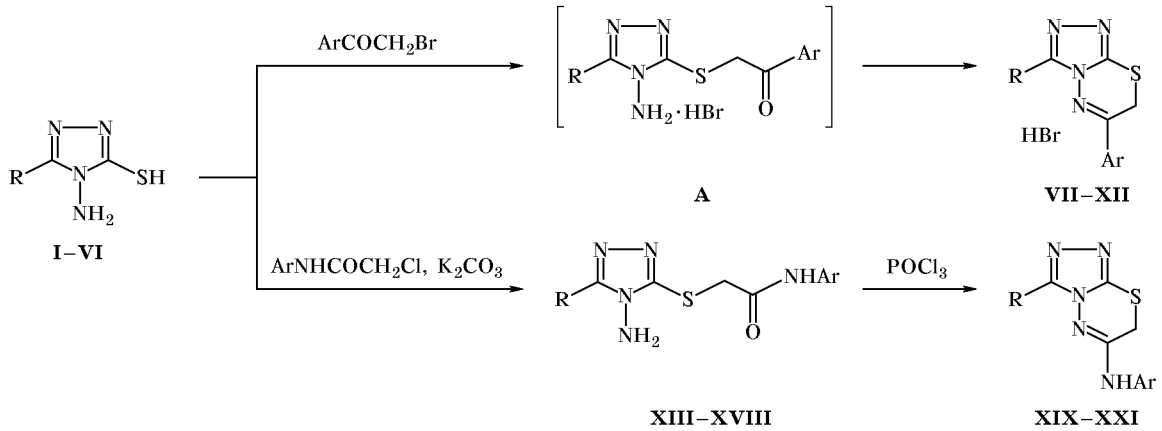
Abstract—Starting from 5-alkyl-4-amino-4*H*-1,2,4-triazole-3-thiols and substituted chloroacetanilides, the corresponding (5-alkyl-4-amino-4*H*-1,2,4-triazol-3-ylsulfanyl)acetanilides were synthesized. The products underwent intramolecular cyclization in boiling phosphoryl chloride to afford 3-alkyl-6-arylamino-7*H*-[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazines. 3-Alkyl-6-aryl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine hydrobromides were obtained by reaction of 5-alkyl-4-amino-4*H*-1,2,4-triazole-3-thiols with substituted phenacyl bromides.

Fused 1,2,4-triazole derivatives exhibit a wide spectrum of biological activity. In particular, they possess antibacterial [1, 2], antiviral, antiphlogistic, and other useful properties [3]. There are limited published data on reactions of 5-alkyl-4-amino-4*H*-1,2,4-triazole-3-thiols with alkylating agents. Specifically, the reactions with methyl iodide [1], chloroacetonitrile [2, 4], chloroacetic acid [5], and substituted phenacyl bromide [5–8] have been reported. Interest in heterocyclic *N*-arylamidines is explained by the fact that they are starting compounds in the synthesis of analgetics of a new generation [9]. We made an attempt to build up an *N*-arylamidine structure having a [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine skeleton. The presence of an aniline moiety in position *6* of the [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine system should considerably extend the synthetic potential of such compounds.

We have synthesized 7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazine derivatives from 5-alkyl-4-amino-

Scheme 1.



I, **VII**, **XIII**, **XIX**, R = H; **II**, **VIII**, **XIV**, **XX**, R = Me; **III**, **IX**, **XV**, R = Et; **IV**, **X**, **XVI**, R = Pr; **V**, **XI**, **XVII**, R = Bu; **VI**, **XII**, **XVIII**, **XXI**, R = CF_3; Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 2,3-$Me_2C_4H_3$ (**c**), 2-$MeOC_6H_4$ (**d**), 4-$MeOC_6H_4$ (**e**), 2-$MeOC_6H_4$ (**f**), 4-$EtOC_6H_4$ (**g**), 4-$PhOC_6H_4$ (**h**), 3,4-$MeO_2C_6H_3$ (**i**), 3,4-$(CH_2O)_2C_6H_3$ (**j**), 4-FC_6H_4 (**k**), 4-ClC_6H_4 (**l**), 4-BrC_6H_4 (**m**), 3,4-$Cl_2C_6H_4$ (**n**), 4-$NO_2C_6H_4$ (**o**), 3-$CF_3C_6H_4$ (**p**).

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Table 1. Yields, melting points, and elemental analyses of 3-alkyl-6-aryl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **VII**–**XII**, (5-alkyl-4-amino-4*H*-1,2,4-triazol-3-ylsulfanyl)acetanilides **XIII**–**XVIII**, and 6-arylamino-7*H*-[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazines **XIX**–**XXI**

Compound no.	Yield, %	mp, °C	Found, %		Formula	Calculated, %	
			N	S		N	S
VIIi	83	241	15.4	8.69	$C_{12}H_{12}N_4O_2S \cdot HBr$	15.7	8.96
VIIj	76	185	15.6	9.24	$C_{12}H_{10}N_4O_2S \cdot HBr$	15.8	9.00
VIIk	69	192	18.0	10.0	$C_{10}H_7FN_4S \cdot HBr$	17.8	10.2
VIIl	82	218	16.7	9.51	$C_{10}H_7ClN_4S \cdot HBr$	16.9	9.65
VIIo	73	>250	20.2	9.42	$C_{10}H_7N_5O_2S \cdot HBr$	20.5	9.35
VIIIa	86	217	18.3	10.5	$C_{11}H_{10}N_4S \cdot HBr$	18.0	10.3
VIIIb	78	211	17.4	9.98	$C_{12}H_{12}N_4S \cdot HBr$	17.2	9.84
VIIIg	73	131	15.7	8.85	$C_{13}H_{14}N_4OS \cdot HBr$	15.8	9.00
VIIIl	77	212	16.0	9.03	$C_{11}H_9ClN_4S \cdot HBr$	16.2	9.26
IXb	79	201	16.3	9.69	$C_{13}H_{14}N_4S \cdot HBr$	16.5	9.43
IXe	83	236	15.5	8.93	$C_{13}H_{14}rN_4OS \cdot HBr$	15.8	9.00
IXj	78	168	14.9	8.64	$C_{14}H_{15}BrN_4O_2S \cdot HBr$	14.6	8.35
IXk	69	189	16.7	9.65	$C_{12}H_{11}FN_4S \cdot HBr$	16.3	9.32
IXl	80	214	15.9	9.12	$C_{12}H_{11}ClN_4S \cdot HBr$	15.6	8.90
Xn	91	178	14.9	8.39	$C_{13}H_{13}ClN_4S \cdot HBr$	15.0	8.56
XIa	82	131	15.7	9.31	$C_{14}H_{16}N_4S \cdot HBr$	15.9	9.06
XIm	82	223	13.1	7.67	$C_{14}H_{15}BrN_4S \cdot HBr$	13.0	7.40
XIn	89	229	13.1	7.79	$C_{14}H_{14}Cl_2N_4S \cdot HBr$	13.3	7.58
XIIe	72	164	14.5	8.37	$C_{12}H_9F_3N_4OS \cdot HBr$	14.2	8.10
XIIi	74	198	13.0	7.34	$C_{13}H_{11}F_3N_4O_2S \cdot HBr$	13.2	7.52
XIIl	74	192	13.8	8.26	$C_{11}H_6ClF_3N_4S \cdot HBr$	14.0	8.01
XIIIp	72	146	21.8	10.3	$C_{11}H_{10}F_3N_5OS$	22.1	10.1
XIVc	84	173	24.2	10.6	$C_{13}H_{17}N_5OS$	24.0	11.0
XIVe	94	158	23.7	10.7	$C_{12}H_{15}N_5O_2S$	23.9	10.9
XIVg	83	226	23.0	10.3	$C_{13}H_{17}N_5O_2S$	22.8	10.1
XIVl	91	211	23.2	10.5	$C_{11}H_{12}ClN_5OS$	23.5	10.7
XVh	84	219	19.1	8.39	$C_{18}H_{19}N_5O_2S$	18.9	8.67
XVn	94	176	20.3	9.07	$C_{12}H_{13}Cl_2N_5OS$	20.2	9.25
XVIg	96	146	21.1	9.41	$C_{15}H_{21}N_5O_2S$	20.9	9.55
XVIp	82	149	19.6	9.16	$C_{14}H_{16}F_3N_5OS$	19.5	8.91
XVIIe	87	145	20.7	9.31	$C_{15}H_{21}N_5O_2S$	20.9	9.55
XVIIId	86	126	20.1	9.37	$C_{12}H_{12}F_3N_5O_2S$	20.2	9.22
XVIIIj	80	178	18.8	8.38	$C_{13}H_{12}F_3N_5O_3S$	18.7	8.53
XVIIIl	82	177	19.8	9.35	$C_{11}H_9ClF_3N_5OS$	19.9	9.10
XIXn	62	>250	23.4	10.4	$C_{10}H_7Cl_2N_5S$	23.3	10.7
XXc	83	>250	25.3	11.9	$C_{13}H_{15}N_5S$	25.5	11.7
XXg	93	>250	21.3	10.1	$C_{13}H_{15}N_5OS \cdot HCl$	21.5	9.83
XXl	74	>250	22.4	10.3	$C_{11}H_{10}ClN_5S \cdot HCl$	22.1	10.1
XXIl	77	>250	21.2	9.31	$C_{11}H_7ClF_3N_5S$	21.0	9.59

4*H*-1,2,4-triazole-3-thiols **I**–**VI** via the known reaction with substituted phenacyl bromides and by reaction with α-chloroacetanilides (Scheme 1). Initial 5-alkyl-4-amino-4*H*-1,2,4-triazole-3-thiols **I**–**VI** were prepared by heating of thiocarbonohydrazide with the corresponding carboxylic acids [10, 11]. The reaction of thiols **I**–**VI** with substituted α-chloroacetanilides smoothly afforded (5-alkyl-4-amino-4*H*-1,2,4-triazol-3-ylsulfanyl)acetanilides **XIII**–**XVIII**. Heating of the latter in boiling phosphoryl chloride resulted in intramolecular ring closure with formation of 3-alkyl-6-arylamino-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines

Table 2. ^{1}H NMR spectra of 3-alkyl-6-aryl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **VII**–**XII**, (5-alkyl-4-amino-4*H*-1,2,4-triazol-3-ylsulfanyl)acetanilides **XIII**–**XVIII**, and 6-arylamino-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **XIX**–**XXI**

Comp. no.	SCH_2, s	H_{arom}	NH_2, s	NH, br.s	Other protons
VIIi	4.16	7.11–7.57 m (3H)	–	–	3.84 s (6H, OCH_3), 9.12 s (1H, 3-CH)
VIIj	4.37	7.01–7.51 m (3H)	–	–	4.31 t (4H, OCH_2CH_2O), 9.11 s (1H, 3-CH)
VIIk	4.38	7.38 and 8.07 d.t (4H)	–	–	9.01 s (1H, 3-H)
VIIl	4.44	7.66 and 7.98 d.d (4H)	–	–	9.13 s (1H, 3-H)
VIIo	4.44	8.23 and 8.36 d.d (4H)	–	–	8.96 s (1H, 3-H)
VIIIa	4.47	7.67–8.07 m (5H)	–	–	2.60 s (3H, CH_3)
VIIIb	4.17	7.27 and 7.88 d.d (4H)	–	–	2.42 s (3H, CH_3), 2.52 s (3H, CH_3)
VIIIg	4.89	6.97 and 7.98 d.d (4H)	–	–	1.42 t (3H, CH_3), 2.45 s (3H, CH_3), 4.14 q (2H, OCH_2)
VIIIl	4.37	7.63 and 8.05 d.d (4H)	–	–	2.48 s (3H, CH_3)
IXb	4.38	7.37 and 7.94 d.d (4H)	–	–	1.36 t (3H, CH_3), 2.52 s (3H, CH_3), 2.97 q (2H, CH_2)
IXe	4.46	7.12 and 8.06 d.d (4H)	–	–	1.33 t (3H, CH_3), 2.97 q (2H, CH_2), 3.87 s (3H, OCH_3)
IXj	4.41	7.04–7.57 m (3H)	–	–	1.31 t (3H, CH_3), 2.96 q (2H, CH_2), 4.32 t (4H, OCH_2CH_2O)
IXk	4.42	7.43 and 8.08 d.t (4H)	–	–	1.32 t (3H, CH_3), 2.92 q (2H, CH_2)
IXl	4.49	7.65 and 8.07 d.d (4H)	–	–	1.31 t (3H, CH_3), 2.97 q (2H, CH_2)
Xl	4.36	7.48 and 8.04 d.d (4H)	–	–	1.06 t (3H, CH_3), 1.84 m (2H, CH_2), 2.91 t (2H, CH_2)
XIa	4.38	7.58–8.02 m (5H)	–	–	0.94 t (3H, CH_3), 1.43 m (2H, CH_2), 1.76 q (2H, CH_2), 2.94 t (2H, CH_2)
XIm	4.36	7.76 and 7.94 d.d (4H)	–	–	0.95 t (3H, CH_3), 1.42 m (2H, CH_2), 1.74 q (2H, CH_2), 2.89 t (2H, CH_2)
XIn	4.38	7.78–8.22 m (3H)	–	–	0.94 t (3H, CH_3), 1.43 m (2H, CH_2), 1.74 q (2H, CH_2), 2.91 t (2H, CH_2)
XIIe	4.48	7.11 and 7.98 d.d (4H)	–	–	3.88 s (3H, OCH_3)
XIIi	4.53	7.15–7.63 m (3H)	–	–	3.84 s (3H, OCH_3), 3.87 s (3H, OCH_3)
XIIl	4.41	7.50 and 8.04 d.d (4H)	–	–	–
XIIIp	4.13	7.40–8.07 m (4H)	6.12	10.7	8.46 s (1H, 3-H)
XIVc	3.94	6.92–7.31 m (3H)	5.71	9.66	2.11 s (3H, CH_3), 2.28 s (3H, CH_3), 2.34 s (3H, CH_3)
XIVe	4.02	6.86 and 7.48 d.d (4H)	5.90	10.2	2.28 s (3H, CH_3), 3.71 s (3H, OCH_3)
XIVg	4.02	6.84 and 7.43 d.d (4H)	5.89	10.2	1.30 t (3H, CH_3), 2.28 s (3H, CH_3),3.96 q (2H, OCH_2)
XIVl	4.02	7.31 and 7.58 d.d (4H)	5.83	10.4	2.31 s (3H, CH_3)
XVh	4.01	6.95–7.49 m (9H)	5.81	10.3	
XVn	4.02	7.48–7.93 m (3H)	5.81	10.6	1.24 t (3H, CH_3), 2.69 q (2H, CH_2)
XVIg	3.97	6.83 i 7.43 d.d (4H)	5.78	10.1	0.96 t (3H, CH_3), 1.33 t (3H, CH_3), 1.72 m (2H, CH_2), 2.66 t (2H, CH_2), 3.99 q (2H, OCH_2)
XVIp	4.07	7.40–8.05 m (4H)	5.88	10.7	0.92 t (3H, CH_3), 1.66 m (2H, CH_2), 2.64 t (2H, CH_2)
XVIIe	4.01	6.86 and 7.48 d.d (4H)	5.88	10.2	0.89 t (3H, CH_3), 1.35 m (2H, CH_2), 1.64 q (2H, CH_2), 2.65 t (2H, CH_2), 3.71 s (3H, OCH_3)
XVIIId	4.11	6.83–8.00 m (4H)	6.12	9.58	3.86 s (3H, OCH_3)
XVIIIj	4.05	6.69–7.15 m (3H)	6.02	9.86	4.20 s (4H, OCH_2CH_2O)
XVIIIl	4.12	7.22 and 7.57 d.d (4H)	6.10	10.3	–
XIXn	3.96	7.57–8.05 m (3H)	–	8.89	9.01 s (1H, 3-H)
XXc	3.92	7.05–7.27 m (3H)	–	8.93	2.14 s (3H, CH_3), 2.19 s (3H, CH_3),2.26 s (3H, CH_3)
XXg	4.00	6.95 i 7.63 d.d (4H)	–	9.87	1.31 t (3H, CH_3), 2.46 s (3H, CH_3), 3.98 q (2H, OCH_2)
XXl	3.88	7.27 and 7.71 d.d (4H)	–	9.75	2.46 s (3H, CH_3)
XXIl	3.96	7.28 and 7.68 d.d (4H)	–	9.78	–

XIX–**XXI**. The structure of compounds **VII**–**XIX** was confirmed by spectral data and elemental analyses. The ^{1}H NMR spectra of acetanilides **XIII**–**XVIII** contain a two-proton singlet from the SCH_2 group in the region δ 4.0–4.5 ppm and a two-proton singlet from the amino group in the region δ 5.8–6.3 ppm. The amide NH proton appears as a broadened singlet at δ 9.8–10.3 ppm. The chemical shifts of protons in the alkyl substituents on C^5 and substituents in the anilide moiety have their usual values. Unlike anilides **XIII**–**XVIII**, the ^{1}H NMR spectra of compounds **XIX**–**XXI** lack amino group signal, and signals from the amide and aromatic protons are slightly displaced downfield. The yields, melting points, and elemental analyses of compounds **VII**–**XXI** are given in Table 1, and Table 2 contains their ^{1}H NMR parameters.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker-300 spectrometer (300 MHz) using DMSO-d_6 as solvent and TMS as internal reference.

3-Alkyl-6-aryl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazine hydrobromides VII–**XII.** A mixture of 10 mmol of 5-alkyl-4-amino-4*H*-1,2,4-triazole-3-thiol **I**–**VI** and 10 mmol of the corresponding substituted phenacyl bromide in 20–30 ml of ethyl acetate was heated for 2–3 h under reflux. It was then cooled, and the colorless precipitate was filtered off and recrystallized from ethanol or ethanol–dimethylformamide.

(5-Alkyl-4-amino-4*H*-1,2,4-triazol-3-ylsulfanyl)-acetanilides XIII–**XVIII.** A solution of 10 mmol of 2-chloroacetanilide in 20 ml of ethanol was added to a solution of 10 mmol of 5-alkyl-4-amino-4*H*-1,2,4-triazole-3-thiol **I**–**VI** and 10 mmol of KOH in 40 ml of aqueous ethanol. The mixture was heated for 30 min under reflux, cooled, and diluted with 50–60 ml of water, and the colorless precipitate was filtered off, washed with water, and recrystallized from ethanol.

3-Alkyl-6-arylamino-7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazines XIXn, XXc, and XXIl. A mixture of 10 mmol of (5-alkyl-4-amino-4*H*-1,2,4-triazol-3-ylsulfanyl)acetamide **XIIIn**, **XIVc**, or **XVIIIl** and 20–30 ml of $POCl_3$ was heated for 2–3 h under reflux. Excess $POCl_3$ was evaporated under reduced pressure, and 50 ml of a 10% solution of KOH was added to the oily residue. After crystallization, the precipitate was filtered off, washed with water, and recrystallized from ethanol–DMF.

6-Arylamino-3-methyl-7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazine hydrochlorides XXg and XXl. A mixture of 10 mmol of acetanilide **XIVg** or **XIVl** and 20–30 ml of $POCl_3$ was heated for 2–3 h under reflux. Excess $POCl_3$ was evaporated under reduced pressure, and the oily residue was ground with 50 ml of diethyl ether. After crystallization, the precipitate was filtered off and recrystallized from ethanol–DMF.

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