ISSN 1070-4272, Russian Journal of Applied Chemistry, 2006, Vol. 79, No. 7, pp. 1134–1137. © Pleiades Publishing, Inc., 2006.
Original Russian Text © V.M. Chernyshev, A.N. Sokolov, V.A. Taranushich, 2006, published in Zhurnal Prikladnoi Khimii, 2006, Vol. 79, No. 7, pp. 1144–1147.

ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Improved Synthesis of 2-Amino-1,2,4-triazolo[1,5-*a*]pyrimidines

V. M. Chernyshev, A. N. Sokolov, and V. A. Taranushich

South-Russian State Technical University, Novocherkassk, Rostov oblast, Russia

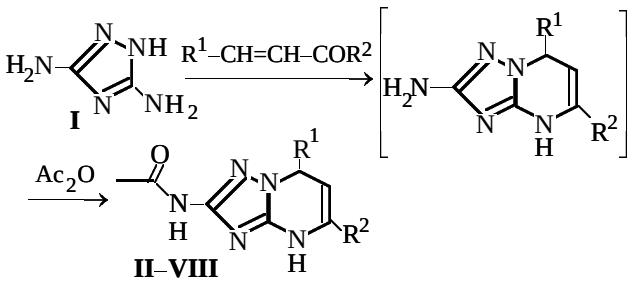
Received May 4, 2006

Abstract—An improved procedure is suggested for preparing 2-amino-1,2,4-triazolo[1,5-*a*]pyrimidines from 3,5-diamino-1,2,4-triazole and unsaturated aromatic ketones, with acetyl protection of the amino group in the step of oxidation of 2-amino-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines.

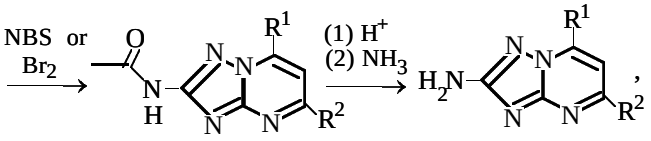
DOI: 10.1134/S1070427206070172

2-Amino-1,2,4-triazolo[1,5-*a*]pyrimidines exhibit a broad spectrum of biological activity and can be used as analgetics [1], blood pressure regulators [2], antibacterial agents [3], and herbicides [4, 5]. The presence of a reactive amino group makes these compounds valuable building blocks in syntheses of biologically active compounds [6, 7].

One of the most convenient routes to 2-amino-1,2,4-triazolo[1,5-*a*]pyrimidines is the cyclocondensation of 3,5-diamino-1,2,4-triazole **I** with α,β-unsaturated ketones [1, 7–11] followed by heteroaromatization of the resulting 2-amino-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines with bromine or *N*-bromosuccinimide (NBS) [11, 12]. An advantage of this route, compared to other methods for forming triazolopyrimidine core, is high regioselectivity and availability of the starting compounds [8, 9]. However, an experimental check showed that the oxidation of the dihydro derivatives is accompanied by formation of a large amount of impurities (presumably azo derivatives), probably because of side oxidation of the amino group. Separation of these impurities involves major loss of the desired 2-amino-1,2,4-triazolo[1,5-*a*]pyrimidines, so that their yield does not exceed 25–30%. We believe that this procedure can be improved by acetyl protection of the amino group in the oxidation step. This possibility was examined in the present study with a series of 2-amino-1,2,4-triazolo[1,5-*a*]-pyrimidines:



I **II**–**VIII**



IX–**XV** **XVI**–**XXII**

where R^1 = Ph, R^2 = Me (**II**, **IX**, **XVI**); R^1 = *p*-Cl·C_6H_4, R^2 = Ph (**III**, **X**, **XVII**); R^1 = Ph, R^2 = *p*-Cl·C_6H_4 (**IV**, **XI**, **XVIII**); R^1 = *p*-MeC_6H_4, R^2 = Ph (**V**, **XII**, **XIX**); R^1 = Ph, R^2 = *p*-MeC_6H_4 (**VI**, **XIII**, **XX**); R^1 = *p*-$MeOC_6H_4$, R^2 = Ph (**VII**, **XIV**, **XXI**); R^1 = R^2 = *p*-MeC_6H_4 (**VIII**, **XV**, **XXII**).

The first step of the suggested scheme involves the condensation of diamine **I** with unsaturated ketones to obtain 2-amino-4,7-dihydro-1,2,4-triazolo[1,5-*a*]-pyrimidines. Since it was difficult to isolate and purify the majority of the dihydro derivatives because of their high solubility, acetyl derivatives **II**–**VIII** were prepared by adding acetic anhydride to the reaction mixture after the condensation completion. The yield of **II**–**VIII** in the one-pot process was 52–90% (see table). These compounds were not described previously and were identified by elemental analysis, ^{1}H NMR spectroscopy, and mass spectrometry.

2-Acetylamino-1,2,4-triazolo[1,5-*a*]pyrimidines **IX**–**XV** were obtained in 84–95% yields (see table) by oxidation of **II**–**VIII** with *N*-bromosuccinimide in ethanol at 50–60°C or with bromine in acetic acid at 15–20°C. In this step, it is very important to maintain the required temperature and reactant ratio. Performing the oxidation at higher temperatures or with excess oxidant results in formation of difficult-to-separate impurities identified by mass spectrometry as brominated derivatives of **IX**–**XV**. Acid hydrolysis of acetyl derivatives **IX**–**XV** gave the desired 2-amino-1,2,4-triazolo[1,5-*a*]pyrimidines **XVI**–**XXII** in almost quan-

Yields and properties of **II**–**XXII**

Compound	Yield, %	mp, °C	Formula*	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
II	86	244–245	$C_{14}H_{15}N_5O$	1.91 s (3H, CH_3), 2.00 s (3H, CH_3), 4.46 d (1H, CH, *J* = 3.2), 5.59 d (1H, CH, *J* = 3.2), 7.18–7.38 m (5H, arom.), 9.50 s (1H, NH), 9.91 s (1H, NH)
III	55	296–298	$C_{19}H_{16}N_5ClO$	2.00 s (3H, CH_3), 5.07 d (1H, CH, *J* = 3.3), 6.12 d (1H, CH, *J* = 3.3), 7.21–7.64 m (9H, arom.), 10.00 s (1H, NH), 10.10 s (1H, NH)
IV	76	257–259	$C_{19}H_{16}N_5ClO$	1.94 s (3H, CH_3), 5.24 d (1H, CH, *J* = 3.5), 6.10 d (1H, CH, *J* = 3.5), 7.21–7.38 m (5H, Ph), 7.46 d (2H, arom., *J* = 8.5), 7.61 d (2H, arom., *J* = 8.5), 10.05 s (1H, NH), 10.12 s (1H, NH)
V	90	264–266	$C_{20}H_{19}N_5O$	1.95 s (3H, CH_3), 2.26 s (3H, CH_3), 5.16 d (1H, CH, *J* = 3.5), 6.04 d (1H, CH, *J* = 3.5), 7.16 m (4H, arom.), 7.40 m (3H, arom.), 7.59 m (2H, arom.), 9.98 s (1H, NH), 10.12 s (1H, NH)
VI	61	228–230	$C_{20}H_{19}N_5O$	1.94 s (3H, CH_3), 2.30 s (3H, CH_3), 5.15 d (1H, CH, *J* = 3.5), 6.08 d (1H, CH, *J* = 3.5), 7.19–7.49 m (9H, arom.), 9.98 s (1H, NH), 10.17 s (1H, NH)
VII	52	259–261	$C_{20}H_{19}N_5O_2$	1.95 s (3H, CH_3), 3.71 s (3H, CH_3O), 5.15 d (1H, CH, *J* = 3.5), 6.04 d (1H, CH, *J* = 3.5), 6.91 d (2H, arom., *J* = 8.5), 7.20 d (2H, arom., *J* = 8.5), 7.39–7.58 m (5H, arom.), 9.97 s (1H, NH), 10.12 s (1H, NH)
VIII	81	273–274	$C_{21}H_{21}N_5O$	1.96 s (3H, CH_3), 2.26 s (3H, CH_3), 2.31 s (3H, CH_3), 5.12 d (1H, CH, *J* = 3.7), 6.03 d (1H, CH, *J* = 3.7), 7.12–7.22 m (6H, arom.), 7.47 d (2H, arom., *J* = 8.2), 9.94 s (1H, NH), 10.11 s (1H, NH)
IX	95 (b)	236–237	$C_{14}H_{13}N_5O$	2.14 s (3H, CH_3), 2.63 s (3H, CH_3), 7.45 s (1H, CH), 7.60 m (3H, arom.), 8.17 m (2H, arom.), 10.86 s (1H, NH)
X	92 (a)	314–315	$C_{19}H_{14}N_5ClO$	2.20 s (3H, CH_3), 7.44–7.70 m (5H, arom.), 8.00 s (1H, CH), 8.32–8.44 m (4H, arom.), 10.86 s (1H, NH)
XI	90 (a), 88 (b)	272–274	$C_{19}H_{14}N_5ClO$	2.18 s (3H, CH_3), 7.58–7.71 m (5H, arom), 8.06 s (1H, CH), 8.32–8.42 m (4H, arom.), 10.92 s (1H, NH)
XII	88 (a)	302–304	$C_{20}H_{17}N_5O$	2.18 s (3H, CH_3), 2.43 s (3H, CH_3), 7.44 d (2H, arom., *J* = 8.0), 7.57–7.59 m (3H, arom.), 8.04 s (1H, CH), 8.24–8.36 m (4H, arom.), 10.94 s (1H, NH)
XIII	91 (a), 90 (b)	276–277	$C_{20}H_{17}N_5O$	2.18 s (3H, CH_3), 2.39 s (3H, CH_3), 7.38 d (2H, arom., *J* = 8.0), 7.57– 7.69 m (3H, arom.), 8.02 s (1H, CH), 8.25–8.28 m (4H, arom.), 10.93 s (1H, NH)
XIV	84 (a)	278–280	$C_{20}H_{17}N_5O_2$	2.18 s (3H, CH_3), 3.88 s (3H, CH_3O), 7.19 d (2H, arom., *J* = 8.9), 7.59 m (3H, arom.), 8.04 s (1H, CH), 8.35–8.42 m (4H, arom.), 10.94 s (1H, NH)
XV	90 (a), 87 (b)	305–306	$C_{21}H_{19}N_5O$	2.18 s (3H, CH_3), 2.40 s (3H, CH_3), 2.43 s (3H, CH_3), 7.36–7.45 m (4H, arom.), 8.00 s (1H, CH), 8.22–8.27 m (4H, arom.), 10.92 s (1H, NH)
XVI	94	249–250**	$C_{12}H_{11}N_5$	2.53 s (3H, CH_3), 6.34 s (2H, NH_2), 7.16 s (1H, CH), 7.58 m (3H, arom.), 8.12 m (2H, arom.)
XVII	90	207–209	$C_{17}H_{12}N_5Cl$	6.52 s (2H, NH_2), 7.54 m (3H, arom.), 7.69 d (2H, arom., *J* = 8.1), 7.84 s (1H, CH), 8.30–8.33 m (4H, arom.)
XVIII	89	220–221***	$C_{17}H_{12}N_5Cl$	6.52 s (2H, NH_2), 7.59–7.62 m (5H, arom.), 7.83 s (1H, CH), 8.24–8.27 m (2H, arom.), 8.24 d (2H, arom., *J* = 8.6)
XIX	93	244–245	$C_{18}H_{15}N_5$	2.42 s (3H, CH_3), 6.47 s (2H, NH_2), 7.43 d (2H, arom., *J* = 8.1), 7.53 m (3H, arom.), 7.78 s (1H, CH), 8.21 d (2H, arom., *J* = 8.1), 8.28 m (2H, arom.)
XX	95	217–219****	$C_{18}H_{15}N_5$	2.38 s (3H, CH_3), 6.45 s (2H, NH_2), 7.35 d (2H, arom., *J* = 8.0), 7.59 m (3H, arom.), 7.76 s (1H, CH), 8.18–8.24 m (4H, arom.)

Table. (Contd.)

Compound	Yield, %	mp, °C	Formula*	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
XXI	91	238–240	$C_{18}H_{15}N_5O$	3.87 s (3H, CH_3O), 6.46 s (2H, NH_2), 7.15 d (2H, arom., *J* = 8.9), 7.55 m (3H, arom.), 7.77 s (1H, CH), 8.27–8.35 m (4H, arom.)
XXII	92	187–188	$C_{19}H_{17}N_5O$	2.38 s (3H, CH_3), 2.42 s (3H, CH_3), 6.51 s (2H, NH_2), 7.35 d (2H, arom., *J* = 8.1), 7.41 d (2H, arom., *J* = 8.1), 7.74 s (1H, CH), 8.18 d (2H, arom., *J* = 8.1), 8.19 d (2H, arom., *J* = 8.1)

* The results of the C, H, N analysis were consistent with the calculated composition within ±0.32%; the mass spectra of all the compounds contain a strong $[M + H]^+$ peak.
** mp 245–250°C [4].
*** mp 210–211°C [11].
**** mp 220–222°C [11].

titative yield (see table). The overall yield of **XVI**–**XXII** based on **I** was 40–70%. Compounds **IX**–**XXII** were identified by elemental analysis, ^{1}H NMR spectroscopy, and mass spectrometry (see table).

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 LCQ Deca XP MAX device in the electrospray mode with positive polarization at direct inlet of 0.5 mg ml^{-1} solutions of the compounds in acetonitrile. Elemental analysis was performed with a Perkin–Elmer 2400 analyzer. The melting points were determined by the capillary method with a PTP device.

2-Acetylamino-4,7-dihydro-1,2,4-triazolo[1,5-*a*]-pyrimidines II–VIII. A mixture of 1 g (0.01 mol) of **I**, 0.01 mol of appropriate unsaturated ketone, and 4 ml of anhydrous DMF was refluxed for 20 min, after which 1.39 g (0.0136 mol) of Ac_2O was added, and the mixture was refluxed for an additional 3 min. Then the mixture was cooled, 4 ml of acetonitrile was added, and the precipitate of the target product was filtered off and washed with 20 ml of acetone. Compounds **II**–**VIII** were purified by twofold refluxing with 5 ml of acetonitrile.

2-Acetylamino-1,2,4-triazolo[1,5-*a*]pyrimidines IX–XV. (a) To a stirred mixture of 0.003 mol of acetyl derivative **III**–**VIII** and 0.27 g (0.0044 mol) of sodium acetate in 20 ml of ethanol, 0.52 g (0.003 mol) of *N*-bromosuccinimide was added in 0.1-g portions over a period of 10 min at 50–60°C. Then the mixture was refluxed for 15 min and diluted with 15–20 ml of water; the precipitate was filtered off, washed with 20 ml of water, and crystallized from DMF–ethanol (1 : 3).

(b) To a solution of 0.003 mol of **II**, **IV**, **VII**, or **VIII** and 0.27 g (0.0044 mol) of sodium acetate in 10–15 ml of acetic acid, 0.48 g (0.003 mol) of Br_2 was added dropwise over a period of 5 min at 15–20°C. The solution was stirred for 30 min and diluted with 15–20 ml of water. The precipitate was filtered off, washed with water (20 ml), and crystallized from DMF–ethanol (1 : 3).

2-Amino-1,2,4-triazolo[1,5-*a*]pyrimidines XVI–XXII. Concentrated HCl (1 ml) was added to a suspension of 0.0014 mol of **IX**–**XV** in 10 ml of ethanol; the mixture was refluxed for 40 min, the solvent was distilled off, and the residue was neutralized with aqueous NH_3 to pH 6–8. The precipitate was filtered off and crystallized from DMF–ethanol, 1 : 3.

CONCLUSIONS

(1) Successive reactions of 3,5-diamino-1.2.4-triazole with α,β-unsaturated aromatic ketones and acetic anhydride allow one-pot synthesis of 2-acetylamino-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines in 52–90% yield.

(2) The acetyl protection of the amino group in 2-amino-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines in the step of their oxidation with *N*-bromosuccinimide or bromine prevents oxidation of the amino group and allows the overall yield of 2-amino-1,2,4-triazolo[1,5-*a*]pyrimidines to be increased to 40–70% based on 3,5-diamino-1,2,4-triazole.

REFERENCES

1. Desenko, S.M., Orlov, V.D., Lipson, V.V., et al., *Khim.-Farm. Zh.*, 1994, vol. 28, no. 3, pp. 19–21.
2. Rusinov, V.L., Petrov, A.Yu., Pilicheva, T.L., et al., *Khim.-Farm. Zh.*, 1986, vol. 20, no. 2, pp. 178–182.

3. Rusinov, V.L., Myasnikov, A.V., Pilicheva, T.L., et al., *Khim.-Farm. Zh.*, 1990, vol. 24, no. 1, pp. 39–42.
4. US Patent 5 127 936.
5. US Patent 4 822 404.
6. Berecz, G., Reiter, J., Argay, G., and Kálmán, A., *J. Heterocyclic Chem.*, 2002, vol. 39, no. 2, pp. 319–325.
7. Lipson, V.V., Desenko, S.M., Borodina, V.V., et al., *Zh. Org. Khim.*, 2005, no. 1, pp. 115–120.
8. Desenko, S.M. and Orlov, V.D., *Azageterotsikly na osnove aromaticheskikh nepredel'nykh ketonov* (Aza Heterocycles Derived from Aromatic Unsaturated Ketones), Kharkov: Folio, 1998.
9. Desenko, S.M., *Khim. Geterotsikl. Soedin.*, 1995, no. 2, pp. 147–159.
10. Lipson, V.V., Desenko, S.M., Orlov, V.D., et al., *Khim. Geterotsikl. Soedin.*, 2000, no. 1, pp. 1542–1549.
11. Desenko, S.M., Kolos, N.N., Tueni, M., and Orlov, V.D., *Khim. Geterotsikl. Soedin.*, 1990, no. 7, pp. 938–941.
12. Desenko, S.M., Orlov, V.D., and Lipson, V.V., *Khim. Geterotsikl. Soedin.*, 1990, no. 12, pp. 1638–1642.