Chemistry of Heterocyclic Compounds, Vol. 50, No. 4, July, 2014 (Russian Original Vol. 50, No. 4, April, 2014)

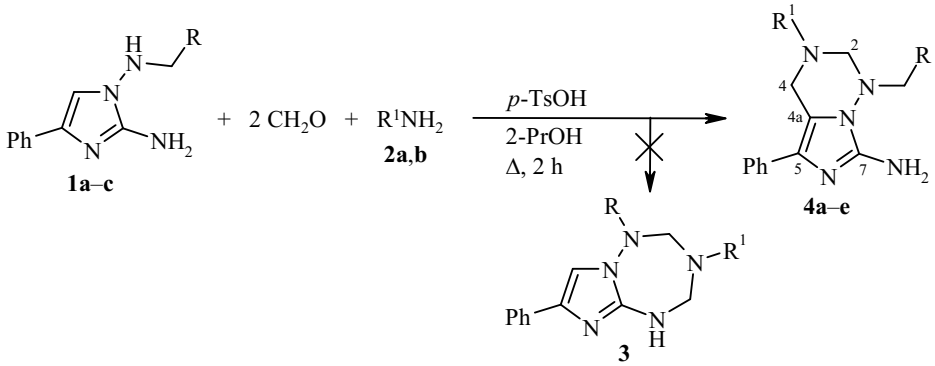
NEW METHOD FOR SYNTHESIS OF THE HETEROCYCLIC SYSTEM – 1,2,3,4-TETRAHYDROIMIDAZO[5,1-*f*][1,2,4]TRIAZIN-7-AMINE

D. Yu. Vandyshev[1], Kh. S. Shikhaliev[1]*, A. Yu. Potapov[1], S. I. Firgang[2], and M. Yu. Krysin[1]

Keywords: 1,2-diaminoimidazoles, formaldehyde, imidazotetrazepines, primary amines, 1,2,3,4-tetrahydroimidazo[5,1-*f*][1,2,4]triazin-7-amines.

Imidazotriazines are used as dyes, luminophores, and corrosion inhibitors [1, 2]. Earlier these compounds were obtained on the basis of diaminopyridinium salts, and this was not economically feasible. We decided to study an alternative method for the preparation of imidazotriazines starting from 1,2-diaminoimidazoles.

In the course of the investigations we found that 1,2,3,4-tetrahydroimidazo[5,1-*f*][1,2,4]triazin-7-amines **4a**-**e** are formed during the reaction of 1,2-diaminoimidazoles **1a**-**c**, obtained by the reaction between benzaldehyde guanylhydrazones and halo ketones [1], with formaldehyde and primary amines **2a**,**b**.



1a, **4a**,**d** R = 4-MeC_6H_4;
1b, **4b**,**e** R = 2-$MeOC_6H_4$; **1c**, **4c** R = Ph;
2a, **4a**,**b** R^1 = $PhCH_2$; **2b**, **4c**–**e** R^1 = $MeO(CH_2)_2$

*To whom correspondence should be addressed, e-mail: chocd261@chem.vsu.ru.

[1]Voronezh State University, 1 Universitetskaya Sq., Voronezh 394006, Russia.
[2]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky Ave., Moscow 119991, Russia; e-mail: galina_stashina@chemical-block.com.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 638-640, April, 2014. Original article submitted February 24, 2014.

It was supposed that as in the case of 2-aminobenzimidazole, where the reaction took place through the exo- and endocyclic nitrogen atoms [3], the reaction should take place preferentially at the two amino groups with the formation of the imidazotetrazepine ring **3**. Analysis of the ^{1}H NMR spectra of the products of this multicomponent reaction showed that the two-proton singlet of the NH_2 group remains, the characteristic signal for the proton of the amino group in the hydrazine fragment NHR and the signal for the proton of the imidazole ring are absent, but broadened signals for the CH_2 group of the triazine ring appear at 3.56-3.95 and 4.10-4.45 ppm. The ^{13}C NMR spectra of compounds **4a-e** contain characteristic signals for the carbon atom of the imidazole ring C–NH_2 at 144.7 ppm and for the bridgehead carbon atom of the imidazotriazine ring (C-4a) at 113.5 ppm. The signals for the carbon atoms of the methylene groups in the triazine ring resonate in the more upfield region at 49.9-50.6 and 66.5-70.6 ppm. On the basis of the data from ^{1}H NMR spectroscopy and mass spectrometry the obtained compounds were assigned the structure of 1-R-3-R^1-5-phenyl-1,2,3,4-tetrahydro-imidazo[5,1-*f*][1,2,4]triazin-7-amines **4a-e**, and it was concluded that the aminomethylation reaction takes place at the amino group of the hydrazine fragment and at the carbon atom of the imidazole ring, as also in the case of 3-aminopyrazoles [4]. The relatively low yields of the reaction products (44-65%) can be explained by the side formation of aminoformaldehyde resins.

Thus, a new three-component method has been developed for the preparation of tetrahydroimidazole systems based on the reaction of 1,2-diaminoimidazoles with primary amines and formaldehyde.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer (500 and 126 MHz, respectively) in DMSO-d_6 with TMS as internal standard. Mass spectra were recorded on an LKB-9000 spectrometer with EI ionization. Elemental analysis was performed on a Carlo Erba NA 1500 instrument. Melting points were determined on a Stuart SMP30 apparatus.

5-Phenyl-1,2,3,4-tetrahydroimidazo[5,1-*f*][1,2,4]triazin-7-amines 4a-e (General Method). A mixture of the diaminoimidazole **1a-c** [1] (5 mmol), 40% aqueous solution of formaldehyde (10 mmol), the amine **2a**,**b (**5 mmol), and 2-PrOH (5 ml) was refluxed for 2 h in the presence of *p*-TsOH·H_2O (50 mg). The precipitate was filtered off and recrystallized from 2-PrOH. The obtained imidazotriazines were light-yellow powdered substances.

3-Benzyl-1-(4-methylbenzyl)-5-phenyl-1,2,3,4-tetrahydroimidazo[5,1-*f*][1,2,4]triazin-7-amine (4a). Yield 50%, mp 204-205°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25 (3H, s, CH_3); 3.50 (2H, s, NC$\underline{H}_2$Ar); 3.68 (2H, br. s, 4-CH_2); 3.95-4.31 (4H, m, 2-CH_2, NC$\underline{H}_2$Ph); 5.49 (2H, s, NH_2); 7.00 (2H, d, *J* = 7.9, H Ar); 7.05-7.12 (3H, m, H Ar); 7.29-7.47 (9H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.1 (CH_3); 50.1 (4-CH_2); 56.9 ($\underline{C}H_2$Ph); 58.3 ($\underline{C}H_2$Ar); 66.9 (2-CH_2); 113.6 (C-4a); 123.7, 125.1, 126.5, 127.7, 128.7, 128.8, 129.1, 129.6, 130.3, 133.1, 136.0, 137.0 (C Ar); 138.1 (C-5); 144.7 (C-7). Mass spectrum, *m*/*z* (I_{rel}, %): 410 $[M+H]^+$ (100). Found, %: C 76.18; H 6.63; N 17.06. $C_{26}H_{27}N_5$. Calculated, %: C 76.25; H 6.65; N 17.10.

3-Benzyl-1-(2-methoxybenzyl)-5-phenyl-1,2,3,4-tetrahydroimidazo[5,1-*f*][1,2,4]triazin-7-amine (4b). Yield 65%, mp 210-212°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.56 (2H, s, NC$\underline{H}_2$Ar); 3.81 (2H, s, OCH_3); 3.90 (2H, br. s, 4-CH_2); 4.30-4.45 (4H, m, 2-CH_2, NC$\underline{H}_2$Ph); 5.59 (2H, s, NH_2); 6.24 (1H, dd, *J* = 6.1, *J* = 7.4, H Ar); 6.59 (1H, t, *J* = 7.3, *J* = 7.4, H Ar); 7.00 (2H, d, *J* = 8.2, H Ar); 7.09-7.12 (3H, m, H Ar); 7.23-7.27 (3H, m, H Ar); 7.32 (1H, dd, *J* = 7.6, *J* = 7.9, H Ar); 7.37-7.49 (3H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 50.6 (4-CH_2); 52.8 ($\underline{C}H_2$Ph); 55.7 (OCH_3); 58.2 ($\underline{C}H_2$Ar); 66.5 (2-CH_2); 111.4 (C-3 Ar); 113.5 (C-4a); 120.6, 123.7, 124.7, 125.0, 126.2, 127.8, 128.7, 128.9, 129.9, 130.0, 132.0, 136.1 (C Ar); 138.2 (C-5); 144.7 (C-7); 158.1 (C-2 Ar). Mass spectrum, *m*/*z* (I_{rel}, %): 426 $[M+H]^+$ (100). Found, %: C 73.30; H 6.38; N 16.44. $C_{26}H_{27}N_5O$. Calculated, %: C 73.39; H 6.40; N 16.46.

1-Benzyl-3-(2-methoxyethyl)-5-phenyl-1,2,3,4-tetrahydroimidazo[5,1-*f*][1,2,4]triazin-7-amine (4c). Yield 44%, mp 180-181°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.68-2.72 (2H, m, NC$\underline{H}_2$$CH_2$); 3.19 (3H, s, OCH_3); 3.32-3.34 (2H, m, CH_2C$\underline{H}_2$O); 3.49 (2H, s, NC$\underline{H}_2$Ph); 3.60 (2H, br. s, 4-CH_2); 4.25 (2H, br. s, 2-CH_2); 5.50 (2H, s, NH_2); 7.11 (1H, dt, *J* = 7.4, *J* = 7.3, H Ph); 7.31-7.42 (5H, m, H Ph); 7.50 (2H, dd, *J* = 8.3, *J* = 8.2, H Ph); 7.56 (2H, d, *J* = 7.0, H Ph). ^{13}C NMR spectrum, δ, ppm: 49.9 (4-CH_2); 53.6 (N$\underline{C}H_2CH_2$); 57.1 (OCH_3); 58.3 ($\underline{C}H_2$Ph); 67.9 ($CH_2\underline{C}H_2O$); 70.5 (2-CH_2); 113.6 (C-4a); 124.8, 125.1, 126.5, 128.2, 128.7, 130.4, 136.1

(C Ar); 136.5 (C-5); 144.7 (C-7). Mass spectrum, *m/z* (I_{rel}, %): 363 $[M]^+$ (100). Found, %: C 69.31; H 6.91; N 19.24. $C_{21}H_{25}N_5O$. Calculated, %: C 69.40; H 6.93; N 19.27.

3-(2-Methoxyethyl)-1-(4-methylbenzyl)-5-phenyl-1,2,3,4-tetrahydroimidazo[5,1-*f*][1,2,4]triazin-7-amine (4d). Yield 48%, mp 183-185°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, ArC$\underline{H}_3$); 2.63-2.71 (2H, m, NC$\underline{H}_2$CH$_2$); 3.21 (3H, s, OCH$_3$); 3.38 (2H, s, CH$_2$C$\underline{H}_2$O); 3.49-3.65 (2H, m, NC$\underline{H}_2$Ar); 3.56 (2H, br. s, 4-CH$_2$); 4.10 (2H, br. s, 2-CH$_2$); 5.50 (2H, s, NH$_2$); 7.11 (1H, dd, *J* = 7.4, *J* = 7.3, H Ar); 7.20 (2H, d, *J* = 7.8, H Ar); 7.32 (2H, dd, *J* = 7.6, *J* = 7.9, H Ar); 7.44 (2H, d, *J* = 7.9, H Ar); 7.50 (2H, d, *J* = 7.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.2 (Ar$\underline{C}$H$_3$); 49.9 (4-CH$_2$); 53.7 (N$\underline{C}$H$_2$CH$_2$); 56.8 (OCH$_3$); 58.3 ($\underline{C}$H$_2$Ar); 67.9 (CH$_2\underline{C}$H$_2$O); 70.5 (2-CH$_2$); 113.5 (C-4a); 124.8, 125.0, 126.5, 128.7, 129.3, 130.4, 133.4, 136.1 (C Ar); 137.3 (C-5); 144.7 (C-7). Mass spectrum, *m/z* (I_{rel}, %): 374.49 $[M+H]^+$ (100). Found, %: C 69.89; H 7.20; N 18.52. $C_{22}H_{27}N_5O$. Calculated, %: C 70.00; H 7.21; N 18.55.

1-(2-Methoxybenzyl)-3-(2-methoxyethyl)-5-phenyl-1,2,3,4-tetrahydroimidazo[5,1-*f*](1,2,4)triazin-7-amine (4e). Yield 52%, mp 189-192°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.73-2.79 (2H, m, NC$\underline{H}_2$CH$_2$); 3.33 (3H, s, CH$_2$CH$_2$OC$\underline{H}_3$); 3.58 (2H, т, *J* = 5.0, *J* = 5.0, CH$_2$C$\underline{H}_2$O); 3.70 (2H, br. s, 4-CH$_2$); 3.85 (2H, s, ArOC$\underline{H}_3$); 4.25-4.48 (4H, m, 2-CH$_2$, NC$\underline{H}_2$Ar); 5.55 (2H, s, NH$_2$); 7.00 (1H, dd, *J* = 7.4, *J* = 7.3, H Ar); 7.07-7.13 (2H, m, H Ar); 7.30-7.39 (4H, m, H Ar); 7.51 (2H, d, *J* = 7.7, H Ar). ^{13}C NMR spectrum , δ, ppm: 50.0 (4-CH$_2$); 52.6 (N$\underline{C}$H$_2$CH$_2$); 53.7 (ArO$\underline{C}$H$_3$); 55.8 (CH$_2$CH$_2$O$\underline{C}$H$_3$); 58.4 ($\underline{C}$H$_2$Ar); 67.9 (CH$_2\underline{C}$H$_2$O); 70.6 (2-CH$_2$); 111.6 (C-3 Ar); 113.5 (C-4a); 120.8, 124.1, 124.7, 125.0, 126.2, 128.7, 130.1, 132.3 (C Ar); 136.1 (C-5); 144.7 (C-7); 158.3 (C-2 Ar). Mass spectrum, *m/z* (I_{rel}, %): 394 $[M+H]^+$ (100). Found, %: C 67.10; H 6.90; N 17.76. $C_{22}H_{27}N_5O_2$. Calculated, %: C 67.15; H 6.92; N 17.80.

The work was carried out with support from the Ministry of Education and Science of the Russian Federation (state contract 02.G25.31.0007).

REFERENCES

1. A. V. Ivashchenko, V. T. Lazareva, E. K. Prudnikova, S. P. Ivashchenko, and V. G. Rumyantsev, *Khim. Geterotsikl. Soedin.*, 236 (1982). [*Chem. Heterocycl. Compd.*, **18**, 185 (1982).]
2. D. S. Werner, H. Dong, M. Kadalbajoo, R. S. Laufer, P. A. Tavares-Greco, B. R. Volk, M. J. Mulvihill, and A. P. Crew, *Tetrahedron Lett.*, **51**, 3899 (2010).
3. Kh. S. Shikhaliev, D. V. Kryl'skii, A. Yu. Potapov, M. Yu. Krysin, and I. N. Trefilova, *Izv. Vuzov. Khimiya i Khim. Tekhnologiya*, **47**, 149 (2004).
4. A. V. Dolzhenko, A. V. Dolzhenko, and W.-K. Chui, *Heterocycles*, **75**, 1575 (2008).