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SYNTHESIS OF 3,5-DIARYL-4-BENZYLIDENE-AMINO-1,2,4-TRIAZOLES AND 4-AMINO-3,5-DIARYL-1,2,4-TRIAZOLES

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A one-pot reaction leading to 3,5-diaryl-4-benzylideneamino-1,2,4-triazoles is described, the key step of which is the reaction of arenecarbohydrazonoyl chloride with benzylidenehydrazide. Compounds obtained in this way were hydrolyzed to 4-amino-3,5-diaryl-1,2,4-triazoles.

Keywords: 4-amino-3,5-diaryl-1,2,4-triazole, 3,5-diaryl-4-benzylideneamino-1,2,4-triazole, benzylidene-hydrazide, cyclization.

Methods for the synthesis of heterocyclic compounds containing a nitrogen–nitrogen bond often start from hydrazonyl compounds. For instance, tetrazoles have been prepared by the reaction of 1-chloro-2,3-diazabutadienes with the azide anion [1, 2]. Similarly 1,2,4-triazoles were obtained by the reaction of 1-chloro-2,3-diazabutadienes with ammonia or amines [3].

Recently we have described the reaction of 1-chloro-2,3-diazabutadienes with titanium tetrachloride which gives dihydro-1,2,4,5-tetrazines [4].

1-Chloro-2,3-diazabutadienes are readily synthesized in three steps. Interac-tion of carboxylic esters and hydrazine hydrate yields hydrazides, which react with aromatic aldehydes to afford arylidenehydrazides **1** [5]. Transformation of the latter with chlorinating agents, e.g., PCl_5, $SOCl_2$ or $POCl_3$, finally gives the target chlorides [6].

Results and Discussion

In this work we studied the synthesis of 1,2,4-triazole derivatives from 1,3-chloro-2,3-diazabutadienes. Starting hydrazonyl chlorides were synthesized *in situ* from arylidenehydrazides **1** and $POCl_3$. 1-Chloro-2,3-diazabutadienes **2** were found to undergo condensation *in situ* with unreacted hydrazides **1** to 4-arylideneamino-1,2,4-triazoles **3** in boiling toluene in the presence of acetonitrile (Scheme and Table 1).

Acetonitrile facilitates the formation of carbocation by increasing the polarity of the reaction media.

4-Arylideneamino-1,2,4-triazoles **3** were hydrolyzed in boiling aqueous methanol in the presence of hydrochloric acid to yield 4-amino-1,2,4-triazoles **4** (Scheme and Table 1).

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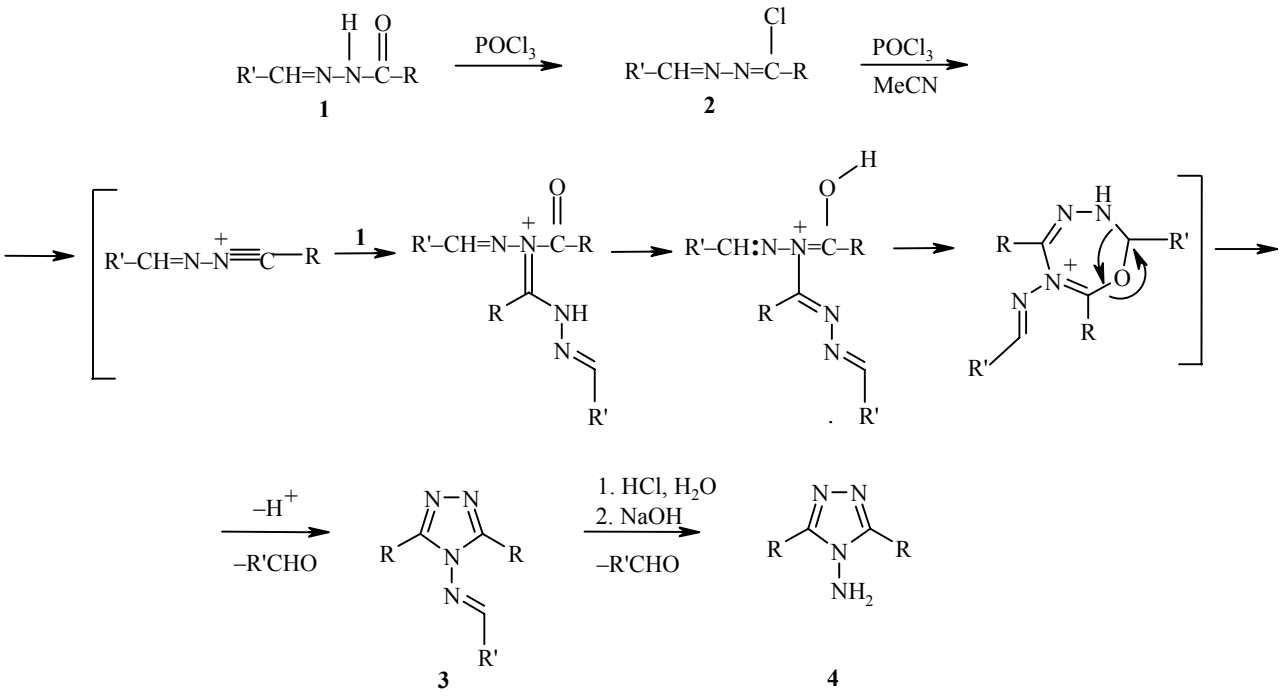
TABLE 1. Characteristics of 4-Arylideneamino-1,2,4-triazoles **3** and 4-Amino-1,2,4-triazoles **4**

Compounds **3**, **4**	R	R'	**3**		**4**	
			Yield, %	mp, °C	Yield, %	mp, °C
a	Ph	Ph	83	145-147*	93	268-269*[2]
b	3- MeC_6H_4	Ph	92	152-153	91	242-244*[3]
c	3-ClC_6H_4	Ph	78	165-166	88	210-212
d	3-$MeOC_6H_4$	Ph	90	143-145	90	245-246*[4]
e	3-$NO_2C_6H_4$	Ph	71	189-190	86	>250
f	Ph	2-MeC_6H_4	81	172-174	—	—

* Isolated as a trihydrate (microanalysis).
*[2] Ref. [7] mp 269°C.
*[3] Ref. [8] mp 176-177°C.
*[4] Ref. [9] mp 244°C.

Scheme



EXPERIMENTAL

Toluene was distilled from sodium prior to use and stored over sodium. $POCl_3$ was distilled. ^1H NMR spectra were recorded on a Varian Unity-Nova 300 spectrometer (300 MHz) as solutions in methanol-d_4. Mass spectra were recorded on the GC-MS QP-2000 Schimadzu spectrometer.

3,5-Diaryl-4-arylideneamino-1,2,4-triazoles (3a–f). General procedure: Arylidene arenecarbohydrazide (**1**) (0.018 mol), acetonitrile 3 ml, and $POCl_3$ (0.018 mol) in 50 ml of toluene were refluxed for 14 hours with exclusion of moisture. The mixture was cooled and poured on 50 g of ice. The gluey precipitate was separated. After its crystallization from $CHCl_3$ 3,5-diaryl-4-arylideneamino-1,2,4-triazole (**3**) was obtained.

4-Amino-3,5-diaryl-1,2,4-triazoles (4a–e). General procedure*:* 3,5-Diaryl-4-benzylidene- amino-1,2,4-triazole (**3**) (1.0 mmol) was dissolved in 20 ml of ethanol, then 20 ml of 10% hydrochloric acid was added. The mixture was refluxed for 2 hours, diluted with 20 ml of water and filtered. The filtrate was alkalyzed with 10% NaOH and then the precipitate was collected. After crystallization from ethanol 4-amino-3,5-diaryl-1,2,4-triazole (**4**) was obtained.

4-Benzylideneamino-3,5-diphenyl-1,2,4-triazole (3a·3H$_2$O). ^{1}H NMR spectrum, ppm: 7.70-7.41 (13H, m, Ph); 8.02 (2H, m, H-2, H-6 in PhCH=N); 8.58 (1H, s, N=C–H). Mass spectrum (*m/z*, I_{rel}, %): 324 (M^+ - 3H_2O), 221. Found, %: C 66.52; H 5.53; N 14.43. $C_{21}H_{16}N_4 \cdot 3H_2O$. Calculated, %: C 66.67; H 5.82; N 14.81.

4-Benzylideneamino-3,5-bis(3-methylphenyl)-1,2,4-triazole (3b). ^{1}H NMR spectrum, ppm: 2.36 (3H, s, CH_3); 2.43 (3H, s, CH_3); 7.45-7.65 (11H, m, Ar); 8.01 (2H, m, H-2, H-6 in N=CH–Ph); 8.59 (1H, s, N=C–H). Mass spectrum (*m/z*, I_{rel}, %): 352 (M^+), 249. Found, %: C 78.13; H 5.55; N 15.69. $C_{23}H_{20}N_4$. Calculated, %: C 78.41; H 5.68; N 15.91.

4-Benzylideneamino-3,5-bis(3-chlorophenyl)-1,2,4-triazole (3c). ^{1}H NMR spectrum, ppm: 7.50-7.56 (6H, m, Ar); 7.65 (1H, t, J = 7.8 Hz, H-4 in N=CH–Ph); 7.79-7.84 (4H, m, Ar); 7.94 (2H, s, Ar); 8.50 (1H, s, N=C–H). Mass spectrum (*m/z*, I_{rel}, %): 392 (M^+), 289, 255. Found, %: C 63.83; H 3.35; N 14.20. $C_{21}H_{14}Cl_2N_4$. Calculated, %: C 64.14; H 3.56; N 14.25.

4-Benzylideneamino-3,5-bis(3-methoxyphenyl)-1,2,4-triazole (3d). ^{1}H NMR spectrum, ppm: 3.81 (3H, s, OCH_3); 3.84 (3H, s, OCH_3); 7.21-7.61 (9H, m, Ar); 7.17 (2H, m, Ar); 8.01 (2H, m, H-2, H-6 in PhCH=N); 8.58 (1H, s, N=C–H). Mass spectrum (*m/z*, I_{rel}, %): 384 (M^+), 281. Found, %: C 71.53; H 5.04; N 14.25. $C_{23}H_{20}N_4O_2$. Calculated, %: C 71.88; H 5.21; N 14.58.

4-Benzylideneamino-3,5-bis(3-nitrophenyl)-1,2,4-triazole (3e). ^{1}H NMR spectrum, ppm: 7.54 (2H, dd, J = 7.8, J' = 7.2 Hz, H-3, H-5 in N=CH–Ph); 7.65 (1H, t, J = 7.8 Hz, H-4 in N=CH–Ph); 7.70 (2H, dd, J = 8.4, J' = 7.8 Hz, H-5 in 3-$NO_2C_6H_4$); 7.82 (2H, d, J = 8.4 Hz, H-4 in 3-$NO_2C_6H_4$); 8.24 (1H, s, N=C–H); 8.33 (2H, m, H-2, in N=CH–Ph); 8.36 (2H, d, J = 7.8 Hz, H-6 in 3-$NO_2C_6H_4$); 8.94 (2H, s, H-2 in 3-$NO_2C_6H_4$). Mass spectrum (*m/z*, I_{rel}, %): 414 (M^+), 311. Found, %: C 60.71; H 3.45; N 20.10. $C_{21}H_{14}N_6O_4$. Calculated, %: C 60.87; H 3.38; N 20.29.

4-(2-Methylbenzylideneamino)-3,5-diphenyl-1,2,4-triazole (3f). ^{1}H NMR spectrum, ppm: 2.03 (3H, s, CH_3); 7.18 (1H, d, J = 7.8 Hz, H-3 in ArCH=N); 7.31 (1H, dd, J = 7.2, J' = 7.5 Hz, H-5 in ArCH=N); 7.41 (1H, d, J = 7.5 Hz, H-6 in ArCH=N); 7.45-7.51 (6H, m, Ar); 7.91-7.96 (5H, m, Ar); 8.43 (1H, s, N=C–H). Mass spectrum (*m/z*, I_{rel}, %): 338 (M^+), 221. Found, %: C 77.78; H 5.19; N 16.47. $C_{22}H_{18}N_{14}$. Calculated, %: C 78.11; H 5.33; N 16.57.

4-Amino-3,5-diphenyl-1,2,4-triazole (4a). ^{1}H NMR spectrum, ppm: 4.89 (2H, s, NH_2); 7.56-7.54 (6H, m, H-2, H-4, H-6; Ph); 7.99 (4H, dd, J = 6.0, J' = 7.2 Hz, H-3, H-5, Ph). Mass spectrum (*m/z*, I_{rel}, %): 236 (M^+), 133. Found, %: C 71.31; H 5.21; N 23.51. $C_{14}H_{12}N_4$. Calculated, %: C 71.19; H 5.08; N 23.73.

4-Amino-3,5-bis(3-methylphenyl)-1,2,4-triazole (4b). ^{1}H NMR spectrum, ppm: 2.44 (6H, s, CH_3); 4.82 (2H, s, NH_2); 7.33 (2H, d, J = 7.5 Hz, H-4, Ar); 7.42 (2H, dd, J = 7.8, J' = 7.5 Hz, H-5, Ar); 7.73 (2H, d, J = 7.5 Hz, H-6, Ar); 7.77 (2H, s, H-2, Ar). Mass spectrum (*m/z*, I_{rel}, %): 264 (M^+), 147. Found, %: C 72.96; H 5.87; N 21.02. $C_{16}H_{16}N_4$. Calculated, %: C 72.73; H 6.06; N 21.21.

4-Amino-3,5-bis(3-chlorophenyl)-1,2,4-triazol*e* (4c). ^{1}H NMR spectrum, ppm: 4.88 (2H, s, NH_2); 7.52-7.60 (4H, m, H-4, H-5, Ar); 7.97 (2H, d, J = 7.9 Hz, H-6, Ar); 8.08 (2H, s, H-2, Ar). Mass spectrum (*m/z*, I_{rel}, %): 304 (M^+), 167. Found, %: C 55.41; H 3.41; N 18.19. $C_{14}H_{10}Cl_2N_4$. Calculated, %: C 55.10; H 3.28; N 18.37.

4-Amino-3,5-bis(3-methoxyphenyl)-1,2,4-triazole (4d). ^{1}H NMR spectrum, ppm: 3.88 (6H, s, OCH_3); 4.88 (2H, s, NH_2); 7.12 (2H, d, J = 8.1 Hz, H-4, Ar); 7.47 (2H, dd, J = 8.1, J' = 8.1 Hz, H-5, Ar); 7.57 (2H, d, J = 8.1 Hz, H-6, Ar); 7.90 (2H, s, H-2, Ar). Mass spectrum (*m/z*, I_{rel}, %): 296 (M^+), 163. Found, %: C 64.98; H 5.37; N 18.70. $C_{16}H_{16}N_4O_2$. Calculated, %: C 64.86; H 5.41; N 18.92.

4-Amino-3,5-bis(3-nitrophenyl)-1,2,4-triazole (4e). ^{1}H NMR spectrum, ppm: 4.80 (2H, s, NH_2); 7.82-7.93 (4H, m, H-4, H-5, Ar); 8.42 (2H, d, J = 7.8 Hz, H-6, Ar); 9.01 (2H, s, H-2; Ar). Mass spectrum (*m/z*, I_{rel}, %): 326 (M^+), 178. Found, %: C 51.71; H 3.18; N 25.65. $C_{14}H_{10}N_6O_4$. Calcuted, %: C 51.53; H 3.07; N 25.77.

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