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# Three-Component Condensation of 4-Aryl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-2-amines with Formaldehyde and Primary Amines

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**Abstract**—Three-component cyclization of 4-aryl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-2-amines with formaldehyde and primary amines gave the corresponding 6-unsubstituted or 6-aryl-2-alkyl-2,3,4,6-tetrahydro-1*H*-[1,3,5]triazino[1′,2′:3,4][1,3,5]triazino[1,2-*a*]benzimidazoles.

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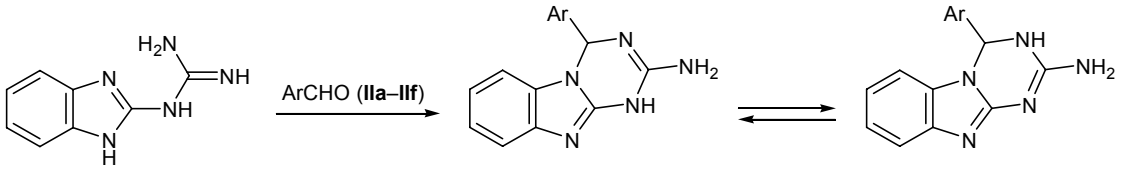
Reactions of substituted guanidines [1] and 2-aminobenzimidazoles [2] with formaldehyde and primary amines provide a synthetic route to hydrogenated 1,3,5-triazine derivatives. In the present work we performed analogous reaction with 4-aryl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-2-amines **IIIa**–**IIIf** which are readily available via condensation of 1-(1*H*-benzimidazol-2-yl)guanidine (**I**) with aromatic aldehydes **IIa**–**IIf** (Scheme 1). Martin et al. [3] previously proposed two procedures for the synthesis of these compounds, and the products were assigned the structure of tautomeric 4-aryl-3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-2-amines **IVa**–**IVf** on the basis of only IR spectra and elemental analyses. We examined their $^1$H NMR spectra in DMSO-$d_6$ and found that the CH and NH proton signals appear as two singlets, which corresponds to tautomeric structure of 4-aryl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]-triazin-2-amines **III**, whereas the CH and NH protons in the triazine ring of tautomers **IV** should resonate as two doublets. The melting points of **IIIa** and **IIIb** coincided with those reported in [3] for **IVa** and **IVb**.

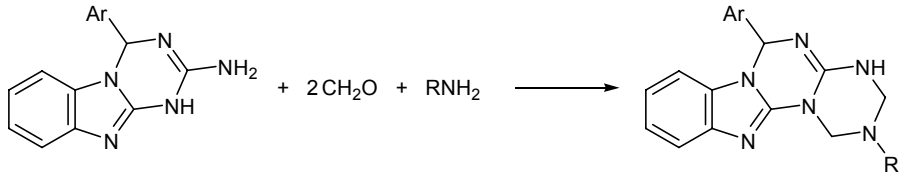
**Scheme 1.**




**I** **IIIa–IIIf** **IVa–IVf**

Ar = Ph (**a**), 4-MeOC$_6$H$_4$ (**b**), 2-MeOC$_6$H$_4$ (**c**), 4-FC$_6$H$_4$ (**d**), pyridin-3-yl (**e**), pyridin-4-yl (**f**).

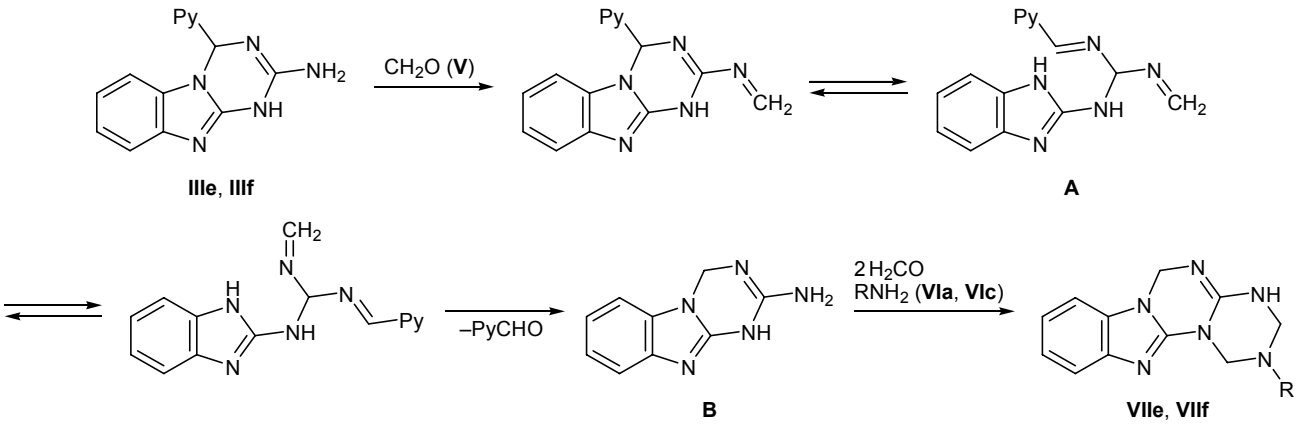
**Scheme 2.**




**IIIa–IIId** **V** **VIa–VId** **VIIa–VIId**

**III**, **VII**, Ar = Ph (**a**), 4-MeOC$_6$H$_4$ (**b**), 2,5-(MeO)$_2$C$_6$H$_3$ (**c**), 4-FC$_6$H$_4$ (**d**); **VI**, **VII**, R = PhCH$_2$ (**a**), puridin-3-ylmethyl (**b**), 2-morpholinoethyl (**c**), PhCH$_2$CH$_2$ (**d**).

**Scheme 3.**




**III**, Py = pyridin-3-yl (**e**), pyridin-4-yl (**f**); **VIa**, **VIIe**, R = $PhCH_2$; **VIc**, **VIIf**, R = 2-morpholinoethyl.

Reactions of 4-aryl-1,4-dihydrobenzo[4,5]imidazo-[1,2-*a*][1,3,5]triazin-2-amines **IIIa**–**IIId** with formaldehyde (**V**) and primary amines **VIa**–**VId** lead to fusion of a new triazine ring to the existing one with formation of 2-alkyl-6-aryl-2,3,4,6-tetrahydro-1*H*-[1,3,5]triazino[1′,2′:3,4][1,3,5]triazino[1,2-*a*]benzimidazoles **VIIa**–**VIId** (Scheme 2). The reaction occurred most smoothly when a mixture of equimolar amounts of the reactants was heated in boiling dioxane containing a small amount (10%) of dimethylformamide. The products separated from the reaction mixture on cooling (yield 54–85%). Unlike initial 4-aryl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-2-amines **IIIa**–**IIId**, the $^1$H NMR spectra of **VIIa**–**VIId** lacked signals assignable to protons of exo- and endocyclic amino groups, but contained two singlets belonging to methylene protons and signals from protons in the corresponding aliphatic amine fragments and NH group in the newly formed triazine ring.

When the above three-component condensation was performed with 4-[pyridin-3(or 4)-yl]-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-2-amines **IIIe** and **IIIf**, the only isolated products were those containing no pyridine fragment, 2-alkyl-2,3,4,6-tetrahydro-1*H*-[1,3,5]triazino[1′,2′:3,4][1,3,5]triazino[1,2-*a*]benzimidazoles **VIIe** and **VIIf**. Unlike compounds **VIIa**–**VIId** which displayed in the $^1$H NMR spectra signals from the $C^6H$ proton (δ 6.6–7.0 ppm) and protons in the aromatic ring attached to $C^6$, in the spectra of **VIIe** and **VIIf** we observed only a singlet at δ 5.3 ppm due to methylene protons ($C^6H_2$). Presumably, loss of the pyridine fragment occurs via opening of the triazine ring with formation of intermediate **A**, rotation about the C–N bond therein, and cyclization to triazinobenzimidazole **B** with elimination of pyridinecarbaldehyde. The subsequent three-component condensation of **B** with formaldehyde and primary amine yields final product **VIIe** or **VIIf** (Scheme 3).

Compounds **VIIa**–**VIIf** were isolated as white crystalline substances which were poorly soluble in most organic solvents and soluble in DMF and DMSO on heating.

## EXPERIMENTAL

The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using chloroform–methanol (5 : 1) as eluent. The $^1$H NMR spectra were recorded on a Bruker AC-300 spectrometer (300 MHz) from solutions in DMSO-$d_6$ using tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV) were obtained on an LKB 9000 instrument. The elemental compositions were determined on a Carlo Erba NA 1500 analyzer.

**2-Alkyl-6-aryl-2,3,4,6-tetrahydro-1*H*-[1,3,5]triazino[1′,2′:3,4][1,3,5]triazino[1,2-*a*]benzimidazoles VIIa–VIIf (*general procedure*).** A mixture of 0.005 mol of compound **IIIa**–**IIIf**, 0.011 mol of a 40% solution of formaldehyde (**V**), 0.005 mol of amine **VIa**–**VId**, and 5 ml of dioxane containing 10% of DMF was heated for 30 min under reflux. The precipitate was filtered off and recrystallized from dimethylformamide.

**2-Benzyl-6-phenyl-2,3,4,6-tetrahydro-1*H*-[1,3,5]-triazino[1′,2′:3,4][1,3,5]triazino[1,2-*a*]benzimidazole (VIIa).** Yield 1.5 g (76%), mp 237–239°C. $^1$H NMR spectrum, δ, ppm: 3.60 s (2H, $PhCH_2$), 4.25 s and 4.35 s (2H each, 1-H, 3-H), 6.60 s (1H, 6-H), 6.58–6.91 m (7H, $H_{arom}$), 6.93 t (1H, $C_6H_4$, $J$ = 8.0 Hz),

7.28 d (1H, $C_6H_4$, $J$ = 8.0 Hz), 7.31–7.69 m (5H, Ph), 7.93 s (1H, 4-H). Found, %: C 73.25; H 5.67; N 21.26. $m/z$ 394 $[M]^+$. $C_{24}H_{22}N_6$. Calculated, %: C 73.07; H 5.62; N 21.30. $M$ 394.48.

**6-(4-Methoxyphenyl)-2-(pyridin-3-ylmethyl)-2,3,4,6-tetrahydro-1*H*-[1,3,5]triazino[1′,2′:3,4]-[1,3,5]triazino[1,2-*a*]benzimidazole (VIIb).** Yield 1.45 g (68%), mp 253–255°C. $^1$H NMR spectrum, δ, ppm: 3.78 s (3H, $CH_3O$), 4.04 s (2H, $N^2CH_2$), 4.30 s and 4.38 s (2H each, 1-H, 3-H), 6.60 s (1H, 6-H), 6.85–7.02 m (3H, $C_5H_4N$, $H_{arom}$), 7.07–7.56 m (6H, $H_{arom}$), 7.76 d (1H, $C_5H_4N$, $J$ = 8.0 Hz), 7.95 s (1H, 4-H), 8.46 d (1H, $C_5H_4N$, $J$ = 8.0 Hz), 8.65 s (1H, $C_5H_4N$). Found, %: C 67.81; H 5.49; N 23.10. $m/z$ 425 $[M]^+$. $C_{24}H_{23}N_7O$. Calculated, %: C 67.75; H 5.45; N 23.04. $M$ 425.50.

**6-(2,5-Dimethoxyphenyl)-2-(2-morpholinoethyl)-2,3,4,6-tetrahydro-1*H*-[1,3,5]triazino[1′,2′:3,4]-[1,3,5]triazino[1,2-*a*]benzimidazole (VIIc).** Yield 1.3 g (54%), mp 178–180°C. $^1$H NMR spectrum, δ, ppm: 2.40 t (2H, 2-$CH_2C\mathbf{H}_2$), 2.55 m (4H, $CH_2NCH_2$), 2.85 t (2H, 2-$CH_2$, $J$ = 8.0 Hz), 3.55 m (4H, $CH_2OCH_2$), 3.69 s and 3.72 s (3H each, $CH_3O$), 4.25 s and 4.35 s (2H each, 1-H, 3-H), 6.60 s (1H, 6-H), 6.70 d (1H, $C_6H_4$, $J$ = 8.0 Hz), 6.77 t (1H, $C_6H_4$, $J$ = 8.0 Hz), 6.74 d (1H, $H_{arom}$, $J$ = 8.0 Hz), 6.93 m (2H, $C_6H_4$), 7.03 s (1H, $H_{arom}$), 7.21 d (1$H_{arom}$, $J$ = 8.0 Hz), 7.85 s (1H, 4-H). Found, %: C 62.74; H 6.51; N 20.48. $m/z$ 477 $[M]^+$. $C_{25}H_{31}N_7O_3$. Calculated, %: C 62.88; H 6.54; N 20.53. $M$ 477.57.

**6-(4-Fluorophenyl)-2-(2-phenylethyl)-2,3,4,6-tetrahydro-1*H*-[1,3,5]triazino[1′,2′:3,4][1,3,5]triazino[1,2-*a*]benzimidazole (VIId).** Yield 1.8 g (85%), mp 219–221°C. $^1$H NMR spectrum, δ, ppm: 2.55 t (2H, PhC$\mathbf{H}_2$), 2.85 t (2H, 2-$CH_2$, $J$ = 8.5 Hz), 4.25 s and 4.35 s (2H each, 1-H, 3-H), 6.68 s (1H, 6-H), 6.53–6.76 m (7H, $H_{arom}$), 6.77 t (1H, $H_{arom}$, $J$ = 8.0 Hz), 6.88–7.24 m (5H, $H_{arom}$), 7.55 s (1H, 4-H). Found, %: C 70.30; H 5.49; N 19.78. $m/z$ 426 $[M]^+$. $C_{25}H_{23}FN_6$. Calculated, %: C 70.41; H 5.44; N 19.70. $M$ 426.50.

**2-Benzyl-2,3,4,6-tetrahydro-1*H*-[1,3,5]triazino-[1′,2′:3,4][1,3,5]triazino[1,2-*a*]benzimidazole (VIIe).** Yield 1.2 g (75%), mp 256–258°C. $^1$H NMR spectrum, δ, ppm: 3.58 s (2H, PhC$\mathbf{H}_2$), 4.25 s and 4.35 s (2H each, 1-H, 3-H), 5.30 s (2H, 6-H), 6.55–6.93 m (5H, $H_{arom}$), 6.95 m (2H, $C_6H_4$), 7.15 t (1H, $C_6H_4$, $J$ = 8.0 Hz), 7.25 d (1H, $C_6H_4$, $J$ = 8.0 Hz), 7.56 s (1H, 4-H). Found, %: C 67.68; H 5.66; N 26.48. $m/z$ 318 $[M]^+$. $C_{18}H_{18}N_6$. Calculated, %: C 67.91; H 5.70; N 26.40. $M$ 318.38.

**2-(2-Morpholinoethyl)-2,3,4,6-tetrahydro-1*H*-[1,3,5]triazino[1′,2′:3,4][1,3,5]triazino[1,2-*a*]benzimidazole (VIIf).** Yield 1.1 g (64%), mp 248–250°C. $^1$H NMR spectrum, δ, ppm: 2.35 br.t (2H, 2-$CH_2C\mathbf{H}_2$), 2.55 m (4H, $CH_2NCH_2$), 2.85 t (2H, 2-$CH_2$, $J$ = 7.5 Hz), 3.55 m (4H, $CH_2OCH_2$), 4.25 s and 4.35 s (2H each, 1-H, 3-H), 5.30 s (2H, 6-H), 6.94 m (2H, $C_6H_4$), 7.15 t (1H, $C_6H_4$, $J$ = 8.0 Hz), 7.25 d (1H, $C_6H_4$, $J$ = 8.0 Hz), 7.56 s (1H, 4-H). Found, %: C 59.63; H 6.82; N 28.64. $m/z$ 341 $[M]^+$. $C_{17}H_{23}N_7O$. Calculated, %: C 59.81; H 6.79; N 28.72. $M$ 341.42.

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