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Reaction of 4-Aryl-2-aminobuta-1,3-diene-1,1,3-tricarbonitriles with CH-Nucleophiles: I. Synthesis of 5-Aryl-2,4-diamino-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydro-5*H*-chromeno-[2,3-*b*]pyridine-3-carbonitriles

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Abstract—5-Aryl-2,4-diamino-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles were synthesized from 4-aryl-2-aminobuta-1,3-diene-1,1,3-tricarbonitriles and dimedone.

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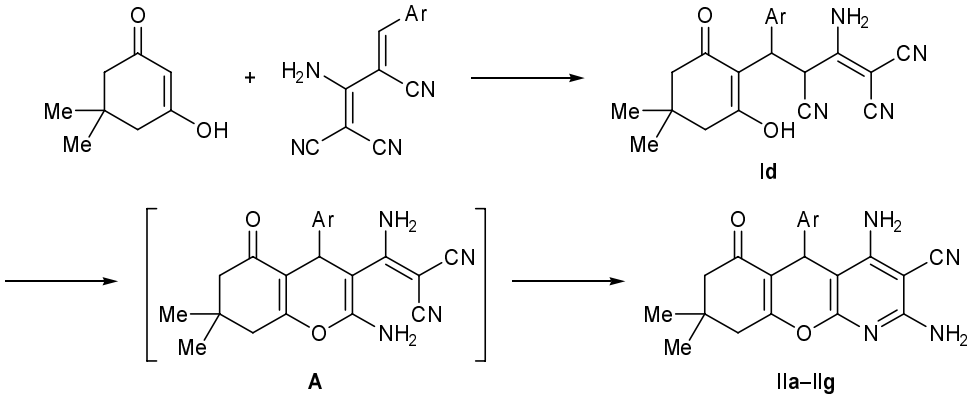
Interest in 4*H*-pyrans originates from their potential biological activity [1–7]. Pyran derivatives on the basis of dimedone exhibit antiallergic [1] and fungicide [2] activity. One of the main synthetic approaches to 2-aminopyrans is based on reactions of β-dicarbonyl compounds with tetracyanoethylene [8–11] or arylmethylidene derivatives of malononitrile and cyanoacetic acid [12–15]. Among β-dicarbonyl compounds capable of reacting with α,β-unsaturated nitriles, a specific place is occupied by cyclic diketones, namely cyclohexane-1,3-diones. The latter are strong CH acids, and they undergo enolization to a considerable extent; therefore, they readily react with α,β-unsaturated nitriles to give 2-aminochromenes [2, 15–20]. Despite a large number of publications on this topic [1–20], there are no data on reactions involving arylmethylidene derivatives of malononitrile dimer, although this reaction (at least its initial step, the formation of aminochromene) should follow an analogous scheme. In addition, the presence of an aminodicyanoethylene fragment could give rise to further transformations leading to fused heterocyclic systems.

We have found that 4-aryl-2-aminobuta-1,3-diene-1,1,3-tricarbonitriles react with dimedone in alcohol in the presence of a catalytic amount of a base to give 5-aryl-2,4-diamino-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **IIa**–**IIg**. A probable reaction scheme includes addition

Scheme 1.



Ar = Ph (**a**), 2-ClC_6H_4 (**b**), 2-Cl-6-FC_6H_3 (**c**), 3-BrC_6H_4 (**d**), 4-FC_6H_4 (**e**), 4-$Me_2NC_6H_4$ (**f**), 3,4-$(MeO)_2C_6H_3$ (**g**).

of dimedone as CH acid at the activated double bond of arylmethylidene derivative of malononitrile dimer to form Michael adduct which undergoes intramolecular cyclization with participation of the hydroxy and cyano groups. The presence of an amino group in the δ-position with respect to the cyano group in intermediate aminochromene **I** favors its subsequent heterocyclization with formation of pyridine ring.

Initially, the reaction was carried out according to a standard procedure, by heating the reactants in boiling ethanol in the presence of piperidine. In this case, the reaction took 2–3 days, and the yields were poor (20–30%). With a view to raise the yield and shorten the reaction time we examined the effect of the solvent and catalyst. The best yields (60–80%) were obtained with the use of sodium isopropoxide as catalyst and isopropyl alcohol as solvent; simultaneously, the reaction time shortened to 6–12 h.

When the reaction was performed in benzene using morpholine as catalyst, we succeeded in isolating intermediate Michael adduct **Id**. Its IR spectrum contained absorption bands belonging to amino and enol hydroxy group in the region 3200–3400 cm^{-1} (broad band), those typical of conjugated (2220 cm^{-1}) and unconjugated cyano groups (2270 cm^{-1}), and carbonyl absorption band at 1630 cm^{-1}. Compound **Id** showed in the ^1H NMR spectrum a signal at δ 12.2 ppm from the enol OH proton, two signals at δ 8.2 and 8.3 ppm characteristic of the enamino group, doublets at δ 5.2 (CHAr) and 4.6 ppm (CHCN), and signals from protons in the aromatic substituent and two methyl groups. Presumably, low polarity of benzene favored spontaneous crystallization of Michael adduct **Id** from the reaction mixture. The structure of compounds **IIa**–**IIg** was confirmed by the IR, ^1H NMR, and mass spectra.

EXPERIMENTAL

The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates (spots were detected under UV light, by treatment with iodine vapor, or by heating). The IR spectra were recorded on a UR-20 spectrometer from samples dispersed in mineral oil. The ^1H NMR spectra were measured on a Bruker DAX-500 spectrometer at 500 MHz using DMSO-d_6 as solvent. The molecular weights were determined from the mass spectra which were obtained on a Finnigan MAT Incos-50 mass spectrometer (electron impact, 70 eV).

2,4-Diamino-8,8-dimethyl-6-oxo-5-phenyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (IIa). A catalytic amount of sodium isopropoxide was added to a mixture of 100 ml of isopropyl alcohol, 0.01 mol of 2-amino-4-phenylbuta-1,3-diene-1,1,3-tricarbonitrile, and 0.01 mol of dimedone. The mixture was heated for 6 h under reflux, and the precipitate was filtered off, washed with isopropyl alcohol, and recrystallized from ethanol–acetonitrile. Yield 2.56 g (71%), mp 283–284°C (decomp.). IR spectrum, ν, cm^{-1}: 3450, 3370, 3300, 3190 (NH_2); 2210 (C≡N); 1640 (C=O). ^1H NMR spectrum, δ, ppm: 0.85 s (3H, CH_3), 1.05 s (3H, CH_3), 2.05 d (1H, CH_2), 2.3 d (1H, CH_2), 2.45 d (1H, CH_2CO), 2.6 d (1H, CH_2CO), 4.9 s (1H, C**H**Ph), 6.45 s (2H, NH_2), 6.5 s (2H, NH_2), 7.1 t (1H, H_{arom}), 7.2 t (2H, H_{arom}), 7.3 d (2H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 360 (18) $[M]^+$, 283 (100) $[M - Ph]^+$.

Compounds **IIb**–**IIg** were synthesized in a similar way.

2,4-Diamino-5-(2-chlorophenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-*b*]-pyridine-3-carbonitrile (IIb). Yield 2.44 g (62%), mp 279–280°C (decomp.). IR spectrum, ν, cm^{-1}: 3460, 3380, 3310, 3180 (NH_2); 2210 (C≡N); 1640 (C=O). ^1H NMR spectrum, δ, ppm: 0.9 s (3H, CH_3), 1.05 s (3H, CH_3), 2.05 d (1H, CH_2), 2.25 d (1H, CH_2), 2.45 d (1H, CH_2CO), 2.6 d (1H, CH_2CO), 5.05 s (1H, C**H**C_6H_4), 5.9 s (2H, NH_2), 6.4 s (2H, NH_2), 7.2 t (1H, H_{arom}), 7.2 t (1H, H_{arom}), 7.3 d (1H, H_{arom}), 7.5 d (1H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 394 (16) $[M]^+$, 359 (42) $[M - Cl]^+$, 283 (100) $[M - C_6H_4Cl]^+$.

2,4-Diamino-5-(2-chloro-6-fluorophenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydro-5*H*-chromeno-[2,3-*b*]pyridine-3-carbonitrile (IIc). Yield 2.63 g (64%), mp 293–294°C (decomp.). IR spectrum, ν, cm^{-1}: 3460, 3360, 3255 (NH_2); 2220 (C≡N); 1640 (C=O). ^1H NMR spectrum, δ, ppm: 0.95 s (3H, CH_3), 1.05 s (3H, CH_3), 2.05 d (1H, CH_2), 2.25 d (1H, CH_2), 2.45 d (1H, CH_2CO), 2.6 d (1H, CH_2CO), 5.2 s (1H, C**H**C_6H_3), 5.7 s (2H, NH_2), 6.45 s (2H, NH_2), 7.1 t (1H, H_{arom}), 7.25 m (2H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 412 (26) $[M]^+$, 377 (69) $[M - Cl]^+$, 357 (5) $[M - Cl - F]^+$, 283 (100) $[M - C_6H_3ClF]^+$.

2,4-Diamino-5-(3-bromophenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-*b*]-pyridine-3-carbonitrile (IId). Yield 3.78 g (86%), mp 292–293°C (decomp.). IR spectrum, ν, cm^{-1}: 3440, 3390, 3300, 3190 (NH_2); 2220 (C≡N); 1640 (C=O). ^1H NMR spectrum, δ, ppm: 0.85 s (3H, CH_3), 1.05 s (3H, CH_3), 2.1 d (1H, CH_2), 2.25 d (1H, CH_2), 2.5 d (1H, CH_2CO), 2.6 d (1H, CH_2CO), 4.95 s (1H,

C**H**C_6H_4), 6.4 s (4H, NH_2), 7.2 m (2H, H_{arom}), 7.3 d (1H, H_{arom}), 7.6 m (1H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 440 (6), 438 (10) $[M]^+$, 283 (100) $[M - C_6H_4Br]^+$.

2,4-Diamino-5-(4-fluorophenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-*b*]-pyridine-3-carbonitrile (IIe). Yield 2.75 g (73%), mp 276–277°C (decomp.). IR spectrum, ν, cm^{-1}: 3490, 3400, 3310, 3180 (NH_2); 2220 (C≡N); 1640 (C=O). ^1H NMR spectrum, δ, ppm: 0.85 s (3H, CH_3), 1.05 s (3H, CH_3), 2.05 d (1H, CH_2), 2.25 d (1H, CH_2), 2.5 d (1H, CH_2CO), 2.55 d (1H, CH_2CO), 4.95 s (1H, C**H**C_6H_4), 6.35 s (2H, NH_2), 6.4 s (2H, NH_2), 7.0 t (2H, H_{arom}), 7.3 t (2H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 378 (26) $[M]^+$, 359 (2) $[M - F]^+$, 283 (100) $[M - C_6H_4F]^+$.

2,4-Diamino-5-(4-dimethylaminophenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydro-5*H*-chromeno-[2,3-*b*]pyridine-3-carbonitrile (IIf). Yield 2.38 g (59%), mp 286–287°C (decomp.). IR spectrum, ν, cm^{-1}: 3435, 3415, 3390, 3245, 3190 (NH_2); 2210 (C≡N); 1640 (C=O). ^1H NMR spectrum, δ, ppm: 0.8 s (3H, CH_3), 1.05 s (3H, CH_3), 2.05 d (1H, CH_2), 2.25 d (1H, CH_2), 2.5 d (1H, CH_2CO), 2.55 d (1H, CH_2CO), 2.8 s [6H, $N(CH_3)_2$], 4.75 s (1H, C**H**C_6H_4), 6.2 s (2H, NH_2), 6.35 s (2H, NH_2), 6.55 d (2H, H_{arom}), 7.05 d (2H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 403 (100) $[M]^+$, 283 (51) $[M - C_6H_4NMe_2]^+$.

2,4-Diamino-5-(3,4-dimethoxyphenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydro-5*H*-chromeno-[2,3-*b*]pyridine-3-carbonitrile (IIg). Yield 2.22 g (53%), mp 280–282°C (decomp.). IR spectrum, ν, cm^{-1}: 3410, 3380, 3240, 3190 (NH_2); 2210 (C≡N); 1640 (C=O). ^1H NMR spectrum, δ, ppm: 0.9 s (3H, CH_3), 1.05 s (3H, CH_3), 2.05 d (1H, CH_2), 2.25 d (1H, CH_2), 2.5 d (1H, CH_2CO), 2.55 d (1H, CH_2CO), 3.15 s (6H, CH_3O), 4.85 s (1H, C**H**C_6H_3), 6.3 s (2H, NH_2), 6.35 s (2H, NH_2), 6.7 d (1H, H_{arom}), 6.8 d (1H, H_{arom}), 7.0 d (1H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 420 (100) $[M]^+$, 283 (42) $[M - C_6H_3(OMe)_2]^+$.

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