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Synthesis of 8,10-Dimethyl-1,10b-dihydro[1,3,5]triazino-[2,1-*a*]isoindole-2,4,6(3*H*)-trione by Direct Arylation of 1,3,5-Triazine-2,4(1*H*,3*H*)-dione

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Abstract—Direct arylation of 1,3,5-triazine-2,4(1*H*,3*H*)-dione with mesitylene afforded a novel fused heterocyclic system, 8,10-dimethyl-1,10b-dihydro[1,3,5]triazino[2,1-*a*]isoindole-2,4,6(3*H*)-trione.

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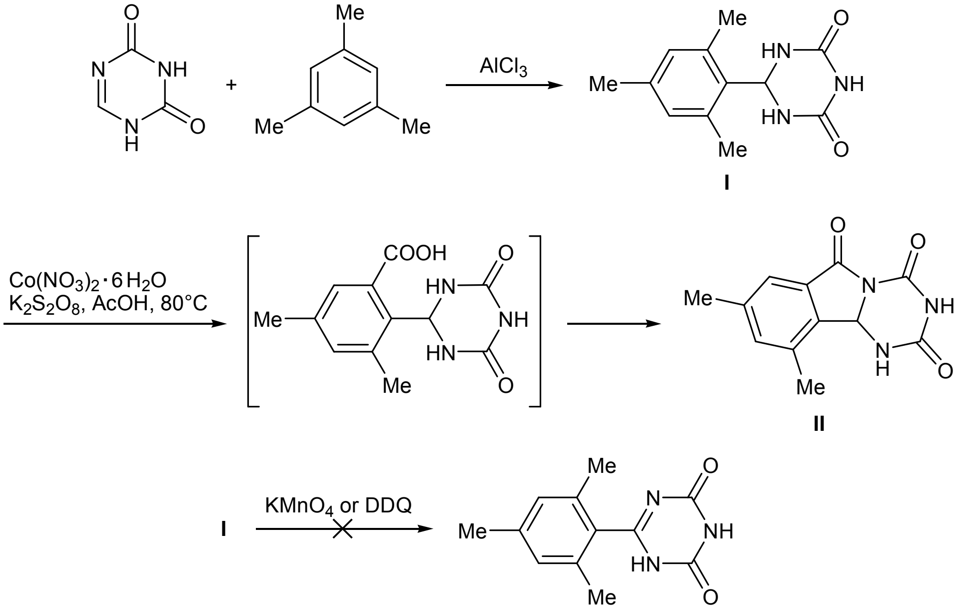
Nitrogen-containing polynuclear heterocycles are widely used as chemosensors for anions [1], liquid crystals [2], photo- and electroluminescent materials [3], ligands for complexation with metals [4], and antiviral [5] and antitumor agents [6]. Taking into account that the scope of practical application of fused hetarenes is limited by their synthetic accessibility, an important problem is development of new methods for the preparation of such heterocyclic systems [7]. Among potential methods, the approach based on direct nucleophilic substitution of hydrogen at an activated carbon atom (S_N^H) seems to be the most promising from the viewpoint of the “green chemistry” principles [8]. The S_N^H methodology is the most appropriate for π-deficient azines such as pyrimidines [9] or 1,2,4-triazines [10], and it ensures one-step direct functionalization of an unsubstituted carbon atom in an azine molecule with fragments of π-excessive or CH-active compounds with formation of S_N^H products which in some cases are capable of undergoing subsequent condensation to give polynuclear heteroaromatic systems [11]. Only a few reactions of azines with unactivated arenes have been reported; examples are reactions of pyrimidine and quinazoline with polynuclear arenes [12, 13] and reaction of 5,6-diphenyl-1,2,4-triazin-3(2*H*)-one(or thione) with benzene [14] in the presence of Lewis acids.

Although 1,3,5-triazines are the most π-deficient heterocycles among the azine series, which readily react with various carbon-centered nucleophiles to give S_NAr^i [15–19] or S_N^H products [20, 21], only recently we have obtained products of direct arylation of 1,3,5-triazines in reactions of 1,3,5-triazine-2,4(1*H*,3*H*)-dione with arenes in the presence of $AlCl_3$ as Lewis acid [22].

The arylation of 1,3,5-triazine with electron-rich mesitylene was the most efficient. The use of 5–6 equiv of $AlCl_3$ increased the yield of 6-(2,4,6-trimethylphenyl)-1,3,5-triazinane-2,4-dione (**I**) to 75%. Attempted aromatization of **I** by standard methods, in particular by the action of potassium permanganate in neutral or acid medium or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded no corresponding oxidation products. When a milder oxidant, a mixture of $Co(NO_3)_2\cdot 6H_2O$ and $K_2S_2O_8$ in acetic acid [23], was used, no aromatization of **I** was observed, but a new fused heterocyclic system was formed, 8,10-dimethyl-1,10b-dihydro[1,3,5]triazino[2,1-*a*]isoindole-2,4,6(3*H*)-trione (**II**). Presumably, the reaction involved oxidation of one methyl group in the mesitylene fragment to carboxy group [24, 25] and subsequent intramolecular condensation at the triazine nitrogen atom (Scheme 1).

The structure of **II** was confirmed by the NMR, IR, and mass spectra. Its ^1H NMR spectrum contained signals from only two methyl groups at δ 2.45 and 2.68 ppm, and two carbonyl carbon signals were observed in the ^{13}C NMR spectrum at δ_C 157.6

Scheme 1.



and 164.8 ppm. Compound **II** displayed in the IR spectrum a broadened carbonyl absorption band in the region of 1644 cm^{-1}. The molecular ion peak in the mass spectrum of **II** had an *m*/*z* value corresponding to the assumed structure.

Thus we were the first to obtain a new polynuclear heterocyclic system, 8,10-dimethyl-1,10b-dihydro-[1,3,5]triazino[2,1-*a*]isoindole-2,4,6(3*H*)-trione (**II**) by direct arylation of 1,3,5-triazine-2,4(1*H*,3*H*)-dione with mesitylene.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker DRX-400 spectrometer using tetramethylsilane as internal reference. The melting points were measured on a Boetius melting point apparatus. The mass spectrum was obtained on a Bruker Daltonics MicrOTOF-Q II instrument (Bremen, Germany). The elemental compositions were determined on a Perkin Elmer 2400 Series II CHN analyzer. The IR spectra were recorded on a Bruker Alpha spectrometer with Fourier transform.

6-(2,4,6-Trimethylphenyl)-1,3,5-triazinane-2,4-dione (I) [22]**.** A mixture of 200 mg (1.53 mmol) of 1,3,5-triazine-2,4(1*H*,3*H*)-dione hydrate, 1000 mg (7.50 mmol) of $AlCl_3$, and 3 mL of 1,3,5-trimethylbenzene was stirred for 18 h at room temperature. The mixture was then treated with 20 mL of water and 5 mL of 2 N aqueous HCl, the organic layer was separated and added to 5–10 mL of ethanol, and the precipitate was filtered off, washed with ethanol, and recrystallized from aqueous acetic acid (1:1). Yield 75%, colorless crystals, mp 275–276°C. IR spectrum, ν, cm^{-1}: 3385, 3063, 2918, 1691, 1401, 1360, 1260, 1206, 1020, 768, 754. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 2.25 s (3H, CH_3), 2.38 s (6H, CH_3), 6.05 s (1H, 6-H), 6.80 s (2H), 7.56 s (2H, NH), 9.14 s (1H, NH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ_C, ppm: 20.3, 20.9, 60.4, 130.3, 131.2, 137.8, 138.0, 153.6. Found, %: C 61.95; H 6.52; N 17.80. $C_{12}H_{15}N_3O_2$. Calculated, %: C 61.79; H 6.48; N 18.01.

8,10-Dimethyl-1,10b-dihydro[1,3,5]triazino-[2,1-*a*]isoindole-2,4,6(3*H*)-trione (II). Following the procedure described in [23], compound **I**, 1 mmol, was dissolved in 6 mL of acetic acid, 2 mL of an aqueous solution of a mixture of 5 mmol (1.46 g) of $Co(NO_3)_2\cdot 6H_2O$ and 2.5 mmol (0.68 g) of $K_2S_2O_8$ was added, and the mixture was stirred for 2.5 h at 80°C. The precipitate of cobalt hydroxide was filtered off, the filtrate was evaporated on a rotary evaporator, the residue was treated with 5 mL of water, and the precipitate was filtered off, washed with water, and dried. Yield 57%, mp 275°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 2.45 s (3H, CH_3), 2.68 s (3H, CH_3), 6.37–6.39 m (1H, 6-H), 7.20 m (1H, CH), 7.28 m (1H, CH), 7.39 s (1H, NH), 11.23 s (1H, NH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ_C, ppm: 18.6, 21.8, 82.1, 122.9, 124.1, 133.4, 138.5, 145.5, 146.3, 148.8, 157.6, 164.8. Mass spectrum: *m*/*z* 245 $[M]^+$. Found, %: C 58.55; H 4.62; N 17.25.

$C_{12}H_{11}N_3O_3$. Calculated, %: C 58.77; H 4.52; N 17.13. *M* 245.24.

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