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Five-Membered 2,3-Dioxo Heterocycles: CIII.* Spiro Heterocyclization of 4,5-Diaroyl-1*H*-pyrrole-2,3-diones with 3-Aminobut-2-enenitrile

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Abstract—1-Aryl-4,5-diaroyl-1*H*-pyrrole-2,3-diones reacted with 3-aminobut-2-enenitrile to produce 1,6-diaryl-4-aroyl-3-hydroxy-8-methyl-2-oxo-1,7-diazaspiro[4.4]nona-3,6,8-triene-9-carbonitriles.

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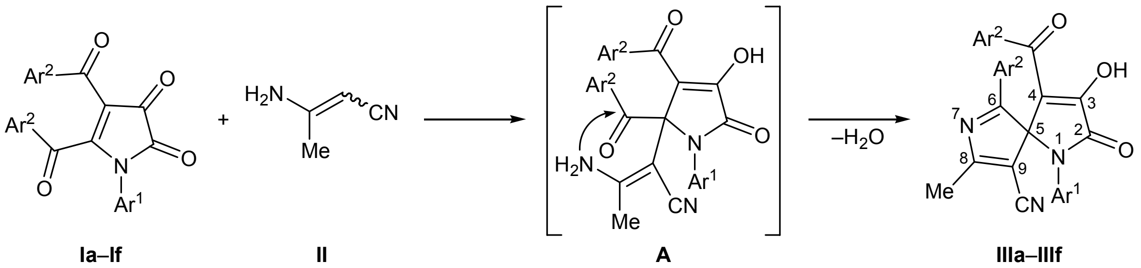
Nucleophilic spiro heterocyclizations and recyclizations of monocyclic 1*H*-pyrrole-2,3-diones by the action of binucleophiles provide a convenient synthetic route to various five-, six-, and seven-membered aza heterocycles and fused, bridged, and spiro heterocyclic systems [2, 3]. We previously found that reactions of 4,5-diaroyl-1*H*-pyrrole-2,3-diones with ethyl 3-amino-3-phenylprop-2-enoate lead to the formation of substituted ethyl 1,7-diazaspiro[4.4]nona-3,6,8-triene-9-carboxylates via addition of nucleophilic enamine centers (β-CH group of the enamine fragment and amino group) to C^5 in the pyrrole ring and 5-aroyl carbonyl carbon atom and subsequent elimination of water [4]. In order to develop a procedure for the synthesis of 1,7-diazaspiro[4.4]nona-3,6,8-triene-9-carbonitriles, in the present work we examined reactions of the same 4,5-diaroyl-1*H*-pyrrole-2,3-diones with 3-aminobut-2-enenitrile.

By heating equimolar amounts of 1-aryl-4,5-diaroyl-1*H*-pyrrole-2,3-diones [5] **Ia**–**If** and 3-aminobut-2-enenitrile (**II**) [6] in boiling anhydrous benzene for 2–3 h (TLC monitoring) we obtained the corresponding 4-aroyl-1,6-diaryl-3-hydroxy-8-methyl-2-oxo-1,7-diazaspiro[4.4]nona-3,6,8-triene-9-carbonintriles **IIIa**–**IIIf** in good yields (Scheme 1). Compounds **IIIa**–**IIIf** were isolated as light yellow high-melting crystalline substances which were readily soluble in alcohols and chlorinated hydrocarbons and insoluble in alkanes and water. They showed a positive color test (cherry color) for enolic hydroxy group on treatment with an alcoholic solution of iron(III) chloride.

The IR spectra of **IIIa**–**IIIf** contained absorption bands typical of stretching vibrations of enolic hydroxy group (broad band at 3158–3192 cm^{-1}), cyano group (2205–2211 cm^{-1}), and lactam (C^2=O, 1689–1703 cm^{-1}) and ketone carbonyl groups (1660–

Scheme 1.



Ar^1 = Ph, Ar^2 = 2,5-$Me_2C_6H_3$ (**a**); Ar^1 = 4-MeC_6H_4, Ar^2 = Ph (**b**), 4-MeC_6H_4 (**c**), 2,5-$Me_2C_6H_3$ (**d**);
Ar^1 = 4-$MeOC_6H_4$, Ar^2 = Ph (**e**), 4-MeC_6H_4 (**f**).

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* For communication CII, see [1].

1669 cm^{-1}). Compounds **IIIa**–**IIIf** displayed in the ^{1}H NMR spectra signals from protons in the aromatic rings and substituents therein, a three-proton singlet from the 8-Me group at δ 2.24–2.26 ppm, and a broadened singlet from the enolic hydroxy proton at δ 11.47–12.45 ppm. In the ^{13}C NMR spectrum of **IIIa** we observed signals from carbon atoms in aromatic and aliphatic substituents, $C^3=C^4$ and $C^8=C^9$ ethylene fragments, aroyl carbonyl group (δ_C 186.98 ppm), lactam carbonyl group (δ_C 165.01 ppm), nitrile group (δ_C 113.54 ppm), and C^6 (δ_C 168.80 ppm) and a signal at δ_C 81.16 ppm belonging to the spiro carbon atom. The positions of signals in the ^{13}C NMR spectrum of **IIIa** were very similar to those found for ethyl 4-benzoyl-3-hydroxy-1-(4-methylphenyl)-2-oxo-6,8-diphenyl-1,7-diazaspiro[4.4]nona-3,6,8-triene-9-carboxylate whose structure was determined by X-ray analysis [4].

Presumably, the described reaction involves initial addition of the β-CH group in the enamine fragment of **II** to C^5 of pyrroledione **I** and subsequent intramolecular cyclization via nucleophilic attack by the primary amino group in intermediate **A** on the aroyl carbonyl carbon atom attached to C^5 of the pyrrole ring and elimination of water (Scheme 1). This reaction may be regarded as one more example of direct spiro heterocyclization of 4,5-diaroyl-1*H*-pyrrole-2,3-diones by the action of acyclic enamines, and it provides a synthetic route to new functional derivatives of the difficultly accessible 1,7-diazaspiro[4.4]nona-3,6,8-triene system.

EXPERIMENTAL

The IR spectra were recorded on a Perkin Elmer Spectrum Two spectrometer from samples dispersed in mineral oil. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-400 instrument at 400 and 100 MHz, respectively, using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The reaction conditions were optimized using a Waters Acquity UPLC system (BEH C18 column, grain size 1.7 μm; eluents methanol–water and acetonitrile–water, flow rate 0.3–0.5 mL/s; ESI MS Xevo TQD detector). The purity of the products was checked by UPLC and TLC (Silufol; benzene, ethyl acetate–benzene, 1 : 5; development with iodine vapor).

4-(2,5-Dimethylbenzoyl)-6-(2,5-dimethylphenyl)-3-hydroxy-8-methyl-2-oxo-1-phenyl-1,7-diazaspiro-[4.4]nona-3,6,8-triene-9-carbonitrile (IIIa). A solution of 1.0 mmol of compound **Ia** and 1.0 mmol of enamine **II** in 20 mL of anhydrous benzene was heated for 2 h under reflux, the progress of the reaction being monitored by UPLC. When the reaction was complete, the mixture was evaporated by half, the residue was diluted with an equal volume of petroleum ether (bp 40–70°C) and cooled, and the precipitate was filtered off and recrystallized from toluene. Yield 74%, mp 201–202°C. IR spectrum, ν, cm^{-1}: 3158 (OH), 2211 (CN), 1700 (C^2=O), 1669 (4-C=O). ^{1}H NMR spectrum, δ, ppm: 2.02 s (3H, CH_3), 2.24 s (3H, CH_3), 2.25 s (3H, CH_3), 2.27 s (3H, CH_3), 2.34 s (3H, CH_3), 6.87–7.44 m (11H, H_{arom}), 12.45 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 16.93 (Me), 20.49 (Me), 21.08 (Me), 21.18 (Me), 81.16 (C^5), 103.20 (C^9), 113.54 (CN), 114.07 (C^4), 125.68–143.75, 152.97 (C^8), 165.01 (C^2), 168.80 (C^6), 177.73 (C^3), 186.99 (4-CO). Found, %: C 76.57; H 5.45; N 8.44. $C_{32}H_{27}N_3O_3$. Calculated, %: C 76.63; H 5.43; N 8.38.

Compounds **IIIb**–**IIIf** were synthesized in a similar way.

4-Benzoyl-3-hydroxy-8-methyl-1-(4-methylphenyl)-2-oxo-6-phenyl-1,7-diazaspiro[4.4]nona-3,6,8-triene-9-carbonitrile (IIIb). Yield 77%, mp 152–153°C. IR spectrum, ν, cm^{-1}: 3192 (OH), 2205 (CN), 1694 (C^2=O), 1665 (4-C=O). ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 2.30 s (3H, CH_3), 6.80–7.92 m (14H, H_{arom}), 11.47 br.s (1H, OH). Found, %: C 75.84; H 4.57; N 9.11. $C_{29}H_{21}N_3O_3$. Calculated, %: C 75.80; H 4.61; N 9.14.

3-Hydroxy-8-methyl-4-(4-methylbenzoyl)-1,6-bis(4-methylphenyl)-2-oxo-1,7-diazaspiro[4.4]nona-3,6,8-triene-9-carbonitrile (IIIc). Yield 72%, mp 145–146°C. IR spectrum, ν, cm^{-1}: 3163 (OH), 2209 (CN), 1701 (C^2=O), 1667 (4-C=O). ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 2.26 s (3H, CH_3), 2.36 s (6H, CH_3), 6.81–7.82 m (12H, H_{arom}), 12.06 br.s (1H, OH). Found, %: C 76.41; H 5.14; N 8.57. $C_{31}H_{25}N_3O_3$. Calculated, %: C 76.37; H 5.17; N 8.62.

4-(2,5-Dimethylbenzoyl)-6-(2,5-dimethylphenyl)-3-hydroxy-8-methyl-1-(4-methylphenyl)-2-oxo-1,7-diazaspiro[4.4]nona-3,6,8-triene-9-carbonitrile (IIId). Yield 70%, mp 187–188°C. IR spectrum, ν, cm^{-1}: 3168 (OH), 2211 (CN), 1703 (C^2=O), 1665 (4-C=O). ^{1}H NMR spectrum, δ, ppm: 2.01 s (3H, CH_3), 2.23 s (3H, CH_3), 2.24 s (3H, CH_3), 2.29 s (6H, CH_3), 2.33 s (3H, CH_3), 6.81–7.38 m (10H, H_{arom}), 12.28 br.s (1H, OH). Found, %: C 76.82; H 5.63; N 8.17. $C_{33}H_{29}N_3O_3$. Calculated, %: C 76.87; H 5.67; N 8.15.

4-Benzoyl-3-hydroxy-1-(4-methoxyphenyl)-8-methyl-2-oxo-6-phenyl-1,7-diazaspiro[4.4]nona-3,6,8-triene-9-carbonitrile (IIIe). Yield 81%, mp 147–148°C. IR spectrum, ν, cm^{-1}: 3185 (OH), 2206 (CN), 1689 (C^2=O), 1660 (4-C=O). ^1H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 3.71 s (3H, OCH_3), 6.74–7.96 m (14H, H_{arom}), 12.19 br.s (1H, OH). Found, %: C 73.29; H 4.41; N 8.81. $C_{29}H_{21}N_3O_4$. Calculated, %: C 73.25; H 4.45; N 8.84.

3-Hydroxy-1-(4-methoxyphenyl)-8-methyl-4-(4-methylbenzoyl)-6-(4-methylphenyl)-2-oxo-1,7-diazaspiro[4.4]nona-3,6,8-triene-9-carbonitrile (IIIf). Yield 83%, mp 190–192°C. IR spectrum, ν, cm^{-1}: 3181 (OH), 2205 (CN), 1690 (C^2=O), 1661 (4-C=O). ^1H NMR spectrum, δ, ppm: 2.26 s (3H, CH_3), 2.37 s (6H, CH_3), 3.72 s (3H, OCH_3), 6.80–7.82 m (12H, H_{arom}), 12.35 br.s (1H, OH). Found, %: C 73.87; H 5.03; N 8.30. $C_{31}H_{25}N_3O_4$. Calculated, %: C 73.94; H 5.00; N 8.34.

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