Russian Journal of Organic Chemistry, Vol. 37, No. 10, 2001, pp. 1509–1511. Translated from Zhurnal Organicheskoi Khimii, Vol. 37, No. 10, 2001, pp. 1578–1579.

SHORT COMMUNICATIONS

Reactivity with Respect to Bases of 5-Hydroxy-7-oxo-6-azabicyclo[3.2.1]octane-1,2,2-tricarbonitriles

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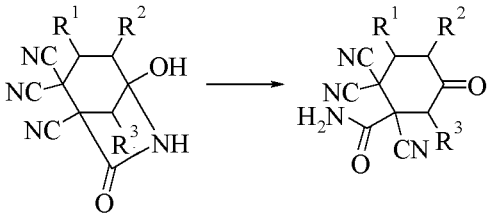
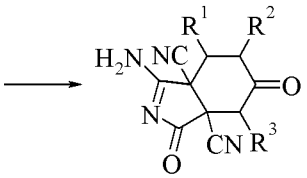
Received July 25, 2001

We reported formerly on the synthesis of 5-hydroxy-7-oxo-6-azabicyclo[3.2.1]octane-1,2,2-tricarbonitriles (Ia–f) from tetracyanoethylene and appropriate α,β-unsaturated ketones [1, 2]. We found that at treating the azabicyclic compounds **Ia–f** with various bases, in particular amines, pyrrolidine ring underwent opening yielding 5-oxo-1,2,2-tricyano-1-cyclohexanecarboxamides (**IIa–d**) that further cyclized into 3-amino-1,6-dioxo-3a,4,5,6,7,7a-hexahydro-1H-isoindole-3a,7a-dicarbonitriles (**IIIa–f**). The conversion is affected by the reaction temperature and amount of the base brought into reaction. The use of equimolar quantity of sodium alcoholate in the corresponding alcohol at room temperature led to heterolytic cleavage of the N–C bond in azabicyclic compounds **Ia–f** to afford carboxamides **IIa–d**. At heating azabicycles **Ia–f** to 50–60°C in the presence of 2–3-fold excess of sodium alcoholate occurred intramolecular reaction between the carboxamide group with *cis*-cyano group yielding hexahydroisoindoledicarbonitriles **IIIa–f**.



Ia–e **IIa–e**



IIIa–e

R^1 = Ph, R^2 = R^3 = H (a); R^1 = Ph, R^2 = Me, R^3 = H (**b**); R^1 = Ph, R^2 = H, R^3 = Me (**c**); R^1 = 4-$MeOC_6H_4$, R^2 = H, R^3 = Me (**d**); R^1 = 4-$MeOC_6H_4$, R^2 = R^3 = Me (**e**); R^1 = $MeOC_6H_4$, R^2 = H, R^3 = *i*-Pr (**f**).

When the reaction is carried out in amine solution (diethylamine, triethylamine) the azabicycles **Ia–f** within 30–60 s give rise to 3-amino-1,6-dioxo-3a,4,5,6,7,71-hexahydro-1*H*-isoindole-3a,7a-dicarbonitriles **IIIa–f** in 64–82% yield. The structure of compounds **IIa–d** and **IIIa–f** was proved by IR, ^{1}H NMR, and mass spectra.

The progress of reaction was monitored and the purity of compounds synthesized was checked by TLC on Silufol UV-254 plates (development in iodine vapor). IR spectra were recorded on spectrophotometer UR-20 from mulls in mineral oil. ^{1}H NMR spectra were registered on spectrometer Bruker AM-300 (300 MHz) in DMSO-d_6.

5-Oxo-3-phenyl-1,2,2-tricyano-1-cyclohexanecarboxamide (IIa). To a solution of 0.01 mol of sodium in 20 ml of anhydrous ethanol was added 0.01 mol of azabicycle **Ia**, and the mixture was stirred at room temperature till complete dissolution. In 10–15 min separated a precipitate that was filtered off and washed with ethanol.

Yield 57%, mp 195–196°C (decomp.). IR spectrum, ν, cm^{-1}: 3395, 3280 (NH_2), 2270 (C≡N), 1730, 1700 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.17 d.d (1H, $CHC\underline{H}_2$), 2.68 d.d (1H, CH_2CCN), 2.71 t (1H, $CHC\underline{H}_2$), 3.01 d.d (1H, CH_2CCN), 3.66 d.d (1H, $C\underline{H}Ph$), 6.48 s (1H, $CONH_2$), 6.51 s (1H, $CONH_2$), 7.51 d (2H, H^o), 7.68 m (3H, $H^{m,p}$). Found, %: C 65.85; H 4.23; N 19.06. $C_{16}H_{12}N_4O_2$. Calculated, %: C 65.75; H 4.14; N 19.17.

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In the same way were prepared and purified compounds **IIb–d.**

4-Methyl-5-oxo-3-phenyl-1,2,2-tricyano-1-cyclohexanecarboxamide (IIb). Yield 46%, mp 174–175°C. IR spectrum, ν, cm^{-1}: 3385, 3290 (NH_2), 2270 (C≡N), 1725, 1700 (C=O). ^1H NMR spectrum, δ, ppm: 0.96 d (3H, CH_3), 2.87 d (1H, $COCH_2$), 3.70 d (1H, $COCH_2$), 4.07 m (1H, CHMe), 4.32 d (1H, CHPh), 7.50–7.70 m (5H, Ph). Found, %: C 66.55; H 4.64; N 17.21. $C_{17}H_{14}N_4O_2$. Calculated, %: C 66.71; H 4.65; N 17.19.

6-Methyl-5-oxo-3-phenyl-1,2,2-tricyano-1-cyclohexanecarboxamide (IIc). Yield 49%, mp 174–175°C. IR spectrum, ν, cm^{-1}: 3385, 3290 (NH_2), 2270 (C≡N), 1725, 1700 (C=O). ^1H NMR spectrum, δ, ppm: 1.21 d (3H, $CHCH_3$), 2.74 d.d (1H, $COCH_2$), 3.58 t (1H, $COCH_2$), 3.98 q (1H, COCHMe), 4.02 d.d (1H, CHPh), 6.55 s (1H, $CONH_2$), 6.60 s (1H, $CONH_2$), 7.60 m (5H, Ph). Found, %: C 66.55; H 4.64; N 17.21. $C_{17}H_{14}N_4O_2$. Calculated, %: C 66.66; H 4.61; N 17.29.

6-Methyl-3-(4-methoxy-3-nitrophenyl)-5-oxo-1,2,2-tricyano-1-cyclohexanecarboxamide (IId). Yield 41%, mp 169–170°C. IR spectrum, ν, cm^{-1}: 3400, 3295 (NH_2), 2265 (C≡N), 1720, 1700 (C=O). ^1H NMR spectrum, δ, ppm: 0.98 d (3H, CH_3), 2.79 d.d (1H, CH_2CO), 3.56 t (1H, CH_2CO), 3.84 s (3H, OCH_3), 4.01 q (1H, $CHCH_3$), 4.21 d.d (1H, CHAr), 6.60 s (1H, $CONH_2$), 7.11 d (2H, H^m), 7.56 d (2H, H^o). Found, %: C 64.22; H 4.70; N 16.58. $C_{18}H_{16}N_4O_3$. Calculated, %: C 64.13; H 4.77; N 16.69.

3-Amino-1,6-dioxo-4-phenyl-3a,4,5,6,7,7a-hexahydro 1*H*-isoindole-3a,7a-dicarbonitrile (IIIa). (a). To a solution of 0.02 mol of sodium in 20 ml of anhydrous ethanol was added 0.01 mol of azabicycle **Ia**, and the mixture was stirred at 50–60°C for 5 min. The solution was cooled, the precipitate was filtered off, washed with dioxane and ethyl ether. Yield of compound **IIIa** 58%, mp 202–203°C (decomp.). IR spectrum, ν, cm^{-1}: 3385, 3290 (NH_2), 2270 (C≡N), 1725, 1700 (C=O). ^1H NMR spectrum, δ, ppm: 2.30 d.d (1H, $CHCH_2$), 2.64 d.d (1H, CH_2CCN), 2.79 t (1H, $CHCH_2$), 3.09 d.d (1H, CH_2CCN), 3.94 d.d (1H, CHPh), 7.60–7.70 m (5H, Ph), 8.05 s (1H, NH), 9.95 s (1H, NH). Found, %: C 65.85; H 4.23; N 19.06. $C_{16}H_{12}N_4O_2$). Calculated, %: C 65.75; 4.14; N 19.17.

(b) In 10 ml of diethylamine was dissolved 0.01 mol of azabicycle **Ia**. After 10–15 min separated a precipitate of compound **IIIa** that was filtered off, washed with water, dioxane, ethyl ether, and recrystallized from dioxane. Yield 73%.

Compounds **IIIb–f** were prepared in a similar way.

3-Amino-5-methyl-1,6-dioxo-4-phenyl-3*a*,4,5,6,7,7*a*-hexahydro-1*H*-isoindole-3*a*,7*a*-dicarbonitrile (IIIb). Yield 59% (*a*), 64% (*b*), mp 210–211°C (decomp.). IR spectrum, ν, cm^{-1}: 3360, 3265 (NH_2), 2270 (C≡N), 1720, 1705 (C=O). ^1H NMR spectrum, δ, ppm: 1.14 d (3H, $CHCH_3$), 2.80 d (1H, CH_2), 3.68 d (1H, CH_2), 3.92 m (1H, CHMe), 4.14 d (1H, CHPh), 7.60–7.70 m (5H, Ph), 8.03 s (1H, NH), 9.86 s (1H, NH). Found, %: C 66.59; H 4.63; N 18.26. $C_{17}H_{14}N_4O_2$. Calculated, %: C 66.66; H 4.61; N 18.29.

3-Amino-7-methyl-1,6-dioxo-4-phenyl-3*a*,4,5,6,7,7*a*-hexahydro-1*H*-isoindole-3*a*,7*a*-dicarbonitrile (IIIc). Yield 65% (*a*), 71% (*b*), mp 211–212°C (decomp.). IR spectrum, ν, cm^{-1}: 3365, 3265 (NH_2), 2270 (C≡N), 1720, 1700 (C=O). ^1H NMR spectrum, δ, ppm: 1.26 d (3H, $CHCH_3$), 2.88 d.d (1H, CH_2), 3.74 t (1H, CH_2), 3.88 q (1H, CHMe), 4.02 t (1H, CHPh), 7.60–7.70 m (5H, Ph), 8.00 s (1H, NH), 9.79 s (1H, NH). Found, %: C 66.56; H 4.67; N 18.28. $C_{17}H_{14}N_4O_2$. Calculated, %: C 66.66; H 4.61; N 18.29.

3-Amino-1,6-dioxo-7-methyl-4-(4-methoxyphenyl)-3*a*,4,5,6,7,7*a*-hexahydro-1*H*-isoindole-3*a*,7*a*-dicarbonitrile (IIId). Yield 44% (*a*), 74% (*b*), mp 164–165°C. IR spectrum, ν, cm^{-1}: 3365, 3265 (NH_2), 2270 (C≡N), 1720, 1700 (C=O). ^1H NMR spectrum, δ, ppm: 1.36 d (3H, $CHCH_3$), 2.97 d.d (1H, CH_2), 3.66 t (1H, CH_2), 3.89 q (1H, CHMe), 3.95 d.d (1H, CHAr), 7.06 d (2H, H^m), 7.43 d (2H, H^o), 8.13 s (1H, NH), 9.71 s (1H, NH). Found, %: C 64.41; H 4.68; N 16.59. $C_{18}H_{16}N_4O_3$. Calculated, %: C 64.28; H 4.79; N16.66.

3-Amino-4,7-dimethyl-1,6-dioxo-4-(4-methoxyphenyl)-3*a*,4,5,6,7,7*a*-hexahydro-1*H*-isoindole-3*a*,7*a*-dicarbonitrile (IIIe). Yield 42% (*a*), 77% (*b*), mp 138–139°C. IR spectrum, ν, cm^{-1}: 3360, 3275 (NH_2), 2265 (C≡N), 1720, 1705 (C=O). ^1H NMR spectrum, δ, ppm: 1.13 d (3H, $CHCH_3$), 1.44 d (3H, $CHCH_3$), 2.92 m (1H, $ArCHCHCH_3$), 3.12 q (1H, CHMe), 3.84 d.d (1H, CHAr), 3.86 s (3H, CH_3O), 7.12 d (2H, H^m), 7.51 d (2H, H^o), 8.16 s (1H, NH), 9.94 s (1H, NH). Found, %: C 65.03; H 5.13; N 16.06. $C_{19}H_{18}N_4O_3$. Calculated, %: C 65.13; H 5.18; N 15.99.

3-Amino-1,6-dioxo-7-isopropyl-4-(4-methoxyphenyl)-3*a*,4,5,6,7,7*a*-hexahydro-1*H*-isoindole-3*a*,7*a*-dicarbonitrile (IIIf). Yield 63% (*a*), 82% (*b*),

mp 211–221°C (decomp.). IR spectrum, ν, cm^{-1}: 3360, 3275 (NH_2), 2265 (C≡N), 1720, 1705 (C=O). ^1H NMR spectrum, δ, ppm: 1.05 d (6H, $2CH_3$), 2.44 m (1H, $CHMe_2$), 3.01 t (1H, CH_2), 3.64 t (1H, CH_2), 3.76 d (1H, CHPr-*i*), 3.84 s (3H, CH_3O), 3.91 t (1H, CHAr), 7.11 d (2H, H^m), 7.49 d (2H, H^o), 8.12 s (1H, NH), 9.84 s (1H, NH). Found, %: C 65.88; H 5.51; N 15.44. $C_{20}H_{20}N_4O_3$. Calculated, %: C 65.92; H 5.53; N 15.38.

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