NEW METHOD FOR OBTAINING 5-PYRAZOLONES

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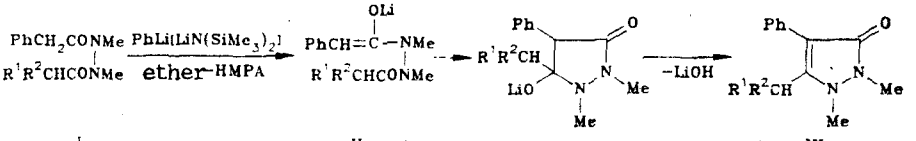
A new preparative method for obtaining 5-pyrazolones from N,N'-dimethyl-N,N'-diacylhydrazines that is based on the intramolecular formation of a $C_{(3)}$—$C_{(4)}$ bond in the pyrazolone molecule was developed.

Compounds of the 5-pyrazolone series are widely known as medicinal preparations and dyes [1]. The methods used to obtain them are based on the construction of the molecule via the formation of $C_{(1)}$—$C_{(5)}$ and $C_{(2)}$—$C_{(3)}$ bonds [1]. We have developed a new preparative method for obtaining 5-pyrazolone derivatives from N,N'-dimethyl-N,N'-diacylhydrazines I that is based on the formation of a $C_{(3)}$—$C_{(4)}$ bond.



I a;c,e II a-c,e III a=c,e

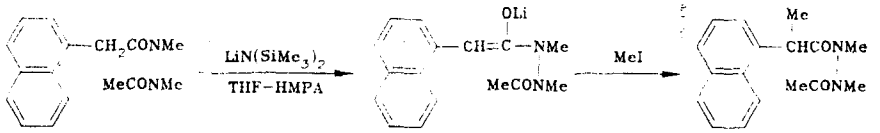
I, III a $R^1=R^2=H$; I b $R^1=Me$, $R^2=H$; c $R^1=R^2=Me$; e $R^1=Ph$, $R^2=H$

The method includes the formation of monoenolate II from I by the action of a strong base. The subsequent intramolecular nucleophilic attack on enolate II at the carbonyl group leads to 5-pyrazolone III.

The presence of bulky substituents attached to the carbonyl group of I, which undergoes nucleophilic attack, hinders the formation of cyclization products. Thus hydrazines Ia, b are converted to 5-pyrazolones IIIa, b in quantitative yields by the action of one equivalent of a strong base, while the more sterically hindered Ic could be converted to 5-pyrazolone IIIc only by the action of two equivalents of a strong base.

If, however, I has bulky substituents attached to the nucleophilic center of the enolate, this hinders the formation of a 5-pyrazolone. Thus the enolate obtained from hydrazine Id does not undergo cyclization on prolonged refluxing in tetrahydrofuran.

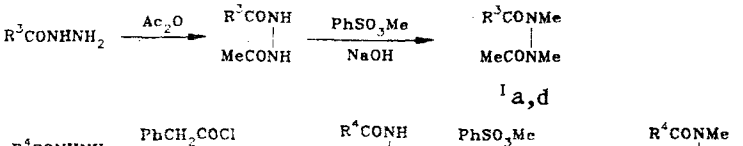
The formation of enolate IId was confirmed by it C-alkylation with methyl iodide by the method in [2].



I d II d IV

The action of two equivalents of hexamethyldisilazanyllithium on hydrazine Ie gives a dienolate, which undergoes the previously described [3+3]-sigmatropic rearrangement to give threo-1,2-1,2-diphenylsuccinic acid N,N'-dimethyldiamide [3]. In addition to a 5-pyrazolone, we isolated a [3−3]-sigmatropic rearrangement product as a side product in the action of one equivalent of a strong base on hydrazide Ie.

The previously undescribed starting Ia-d were obtained by methylation of N,N'-diacylhydrazines:



I a,d

I b,c

Ia R^3=Ph; d R^3= α-naphthyl R^4=Et; c R^4=*i*-Pr

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Compound Ie was obtained by the method in [3].

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-20 spectrometer. The mass spectra were obtained with a Varian MAT-311 A spectrometer at an ionizing voltage of 70 eV, a cathode emission current of 1 mA, and an accelerating voltage of 3 kV. The sample-vaporization temperatures ranged from 30°C to 300°C under linearly programmed conditions. The PMR and ^{13}C NMR spectra were obtained with Bruker WP-200-SY and Varian VXR-400 spectrometers with tetramethylsilane (TMS) as the internal standard. Preparative chromatography of the compounds was carried out on L 40/400 and L 100/160 silica gels. The hexamethyldisilazanyllithium was obtained by the method in [4], while the phenyllithium was obtained by the method in [5].

The results of elementary analysis for C, H, and N were in agreement with the calculated values.

N-Acetyl-N′-phenylacetylhydrazine ($C_{10}H_{12}N_2O_2$). Acetic anhydride [10.2 g (0.1 mole)] of acetic anhydride was added dropwise with stirring to a solution of 15 g (0.1 mole) of phenylacetic acid hydrazide in 60 ml of acetic acid, after which the mixture was stirred for 30 min, and the resulting precipitate was removed by filtration, washed with ether, and dried to give 16.2 g (84%) of a product with mp 164-166°C (from AcOH). PMR spectrum ($CDCl_3$): 2.0 (3H, s, CH_3), 3.62 (2H, s, CH_2), 7.31 (5H, m, arom.), 8.59 (1H, s, NH), 8.67 ppm (1H, s, NH).

N′-Acetyl-N′-α-naphthylacetylhydrazine ($C_{14}H_{14}N_2O_2$). This compound was obtained in the same way as N-acetyl-N′-phenylacetylhydrazine from 20 g (0.1 mole) of α-naphthylacetic acid hydrazide and 10.2 g (0.1 mole) of acetic anhydride. The procedure gave 21 g (87%) of a product with mp 175-178°C (from AcOH). PMR spectrum (d_6-DMSO): 1.84 (3H, s, CH_3), 3.95 (2H, s, CH_2), 7.5-8.12 (7H, m, arom.), 9.77 (1H, broad s, NH), 10.08 ppm (1H, broad s, NH).

N-Propionyl-N′-phenylacetylhydrazine ($C_{11}H_{14}N_2O_2$). A 15.5-g (0.1 mole) sample of phenylacetyl chloride was added with stirring and cooling (with cold water) in the course of 20 min to a solution of 8.8 g (0.1 mole) of propionic acid hydrazide and 10.6 g (0.1 mole) of sodium carbonate in 75 ml of water, after which the mixture was stirred for 30 min. The resulting precipitate was removed by filtration, washed with water, and dried to give 14.4 g (70%) of a product with mp 154-156°C (from AcOH). PMR spectrum (d_6-DMSO): 1.01 (3H, t, CH_3), 2.11 (2H, q, CH_2), 3.45 (2H, s, CH_2), 7.25-7.30 (5H, m, arom.), 10.04 ppm (2H, broad s, NH).

N-Isobutyryl-N′-phenylacetylhydrazine ($C_{12}H_{16}N_2O_2$). This compound was obtained in the same way as N-propionyl-N′-phenylacetylhydrazine from 10.2 g (0.1 mole) of isobutyric acid hydrazide and 15.5 g (0.1 mole) of phenylacetyl chloride. Workup gave 16.4 g (75%) of a product with mp 188-190°C (from AcOH). PMR spectrum (d_6-DMSO): 1.03 (6H, d, CH_3, J_{CH-CH_3} = 6.68 Hz), 2.44 (1H, m, CH), 3.46 (2H, s, CH_2), 7.3 (5H, s, arom.), 9.95 ppm (2H, broad s, N—H).

N,N′-Dimethyl-N-acetyl-N′-phenylacetylhydrazine (Ia, $C_{12}H_{16}N_2O_2$). A 69-g (0.4 mole) sample of methyl benzenesulfonate and 40% NaOH solution were added in 10-ml portions each in the course of 5 min with stirring to a heated (to 90°C) solution of 19.2 g (0.1 mole) of N-acetyl-N′-phenylacetylhydrazine and 8 g (0.2 mole) of NaOH in 300 ml of water in such a way that the medium was always alkaline, after which the mixture was stirred for 30 min, cooled to room temperature, and extracted with chloroform (3 × 50 ml). The solvent was evaporated, and the residue was chromatographed [L 40/100 silica gel, CCl_4—ethyl acetate (4:1)] to give 17.6 g (80%) of a product with mp 64-66°C. IR spectrum: 1685 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 1.76 (3H, s, CH_3), 3.07 (3H, s, NCH_3), 3.13 (3H, s, NCH_3), 3.64 (2H, s, CH_2), 7.23-7.32 ppm (5H, m, arom.).

N,N′-Dimethyl-N-propionyl-N′-phenylacetylhydrazine (Ib, $C_{13}H_{18}N_2O_2$). This compound was obtained in the same way as Ia from 20.6 g (0.1 mole) of N-propionyl-N′-phenylacetylhydrazine and 69 g (0.4 mole) of methyl benzenesulfonate. Workup gave 15.2 g (65%) of an oily product. IR spectrum: 1690 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 0.98 (3H, t, CH_3), 2.01 (2H, q, CH_2), 3.07 (3H, s, NCH_3), 3.10 (3H, s, NCH_3), 3.62 (2H, s, CH_2), 7.2-7.31 ppm (5H, m, arom.).

N,N′-Dimethyl-N-isobutyryl-N′-phenylacetylhydrazine (Ic, $C_{14}H_{20}N_2O_2$). This compound was obtained in the same way as Ia from 21.8 g (0.1 mole) of N-isobutyryl-N′-phenylacetylhydrazine and 69 g (0.4 mole) of methyl benzenesulfonate. Workup gave 17.2 g (70%) of an oily product. IR spectrum: 1690 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 1.08 (3H, d, CH_3, J_{CH-CH_3} = 6.6 Hz), 1.13 (3H, d, CH_3, J_{CH-CH_3} = 6.8 Hz), 2.82 (1H, m, CH), 3.03 (3H, s, NCH_3), 3.17 (3H, s, NH_3), 3.64 (2H, s, CH_2), 7.3 ppm (5H, m, arom.).

N,N′-Dimethyl-N-acetyl-N′-α-naphthylacetylhydrazine (Id, $C_{16}H_{18}N_2O_2$). This compound was obtained in the same way as Ia from 24.2 g (0.1 mole) of N-acetyl-N′-α-naphthylacetylhydrazine and 69 g (0.4 mole) of methyl benzenesulfonate. Workup gave 21.6 g (80%) of a product with mp 94-96°C. IR spectrum: 1690 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 1.77 (3H, s, CH_3), 3.07 (3H, s, NCH_3), 3.14 (3H, s, NCH_3), 4.03 (1H, d, *a*-H, J_{ab} = 12.21 Hz), 4.19 (1H, d, b-H), 7.31-8.05 ppm (7H, m, arom.).

1,2,3-Trimethyl-4-phenyl-5-pyrazolone (IIIa, $C_{12}H_{14}N_2O$). A solution of a mixture of 2.2 g (10 mmole) of Ia and 1.8 g (10 mmole) of hexamethylphosphoric triamide (HMPT) in 5 ml of THF was added at −78°C with stirring in an argon atmosphere to a solution of 10 mmole of phenyllithium* in 15 ml of ether, after which the mixture was stirred for 30 min, warmed up to room temperature, and refluxed for 1 h. It was then cooled and treated with 5 ml of 2 N Hcl, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 ml). The combined organic layers were dried with Na_2SO_4 and evaporated, and the residue was chromatographed (L 100/160 silica gel, isopropyl alcohol) to give 1.9 g (95%) of IIIa with mp 72-74°C (from ethyl acetate). IR spectrum: 1720 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 2.28 (3H, s, 3-CH_3), 3.29 (3H, s, 2-CH_3), 3.39 (3H, s, 1-CH_3), 7.23-7.38 ppm (5H, m, arom.). ^{13}C NMR spectrum ($CDCl_3$): 11.19 (3-CH_3), 28.8 (2-CH_3), 33.25 (1-CH_3), 108.91 [$C_{(4)}$], 126.0 [$CH_{(Ph)}$], 128.3 [$CH_{(Ph)}$], 128.49 [$CH_{(Ph)}$], 131.73 [$C_{(Ph)}$], 147.32 [$C_{(3)}$], 164.47 ppm [$C_{(5)}$]. Mass spectrum: M^+ 202.

1,2-Dimethyl-3-ethyl-4-phenyl-5-pyrazolone (IIIb, $C_{13}H_{16}N_2O$). This compound was obtained in the same way as IIIa from 2.34 g (10 mmole) of Ib and 10 mmole of phenyllithium. Workup gave 2 g (94%) of a product with mp 84-86°C (from ethyl acetate). IR spectrum: 1725 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 1.26 (3H, t, CH_3), 2.66 (2H, q, CH_2), 3.28 (3H, s, 2-CH_3), 3.39 (3H, s, 1-CH_3), 7.23-7.45 ppm (5H, m, arom.). ^{13}C NMR spectrum ($CDCl_3$): 13.34 (CH_3), 18.31 (CH_2), 29.05 (2-CH_3), 33.56 (1-CH_3), 109.24 [$C_{(4)}$], 126.31 [$CH_{(Ph)}$], 128.28 [$CH_{(Ph)}$], 131.8 [$C_{(Ph)}$], 153.28 [$C_{(3)}$], 165.01 ppm [$C_{(5)}$]. Mass spectrum: 216.

1,2-Dimethyl-3-isopropyl-4-phenyl-5-pyrazolone (IIIc, $C_{14}H_{18}N_2O$). This compound was obtained in the same way as IIIa from 1.23 g (5 mmole) of Ic and 10 mmole of phenyllithium. Workup gave 0.6 g (50%) of a product with mp 54-56°C (from ethyl acetate). IR spectrum: 1730 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 1.25 (6H, d, CH_3, J_{CH-CH_3} = 7 Hz), 3.21 (1H, m, CH), 3.35 (3H, s, 2-CH_3), 3.39 (3H, s, 1-CH_3), 7.3-7.4 ppm (5H, m, arom.). ^{13}C NMR spectrum ($CDCl_3$): 20.01 (CH_3), 25.98 (3-CH), 28.88 (2-CH_3), 34.77 (1-CH_3), 109.68 [$C_{(4)}$], 126.83 [$CH_{(Ph)}$], 128.22 [$CH_{(Ph)}$], 130.24 [$CH_{(Ph)}$], 132.20 [$C_{(Ph)}$], 156.05 [$C_{(3)}$], 165.12 ppm [$C_{(5)}$]. Mass spectrum: M^+ 230.

N,N′-Dimethyl-N-acyl-N′-2-α-naphthylpropionylhydrazine (IV, $C_{15}H_{16}N_2O_2$). A mixture of 2.7 g (20 mmole) of Id and 1.8 g (10 mmole) of hexamethylphosphoric triamide (HMPT) in 5 ml of THF was added with stirring in an argon atmosphere at 20°C to a solution of 10 mmole of hexamethyldisilazanyllithium in 15 ml of THF, and the mixture was stirred for 20 min. A solution of 1.55 g (11 mmole) of methyl iodide in 5 ml of THF was then added all at once, and the mixture was refluxed for 30 min. It was then cooled and treated with 10 ml of 10% sodium sulfite solution, the organic layer was separated, and the aqueous layer was extracted with chloroform (2 × 10 ml). The combined organic layers were dried with Na_2SO_4, the solvent was evaporated, and the residue was chromatographed (L 40/100 silica gel, chloroform) to give 2.27 g (80%) of IV in the form of an oil. IR spectrum: 1695 cm^{-1} (C=O). PMR spectrum† ($CDCl_3$): 0.8, 1.26, 2.04 (3H, s, CH_3); 2.51, 2.58, 2.61 (3H, d, $CHCH_3$, J_{CHCH_3} = 6.6 Hz); 2.84, 3.03, 3.12 (3H, s, NCH_3); 3.03, 3.10, 3.23 (3H, s, NCH_3); 4.44, 4.58, 4.69 (1H, q, $CHCH_3$); 7-8.0 ppm (7H, m, arom.). Mass spectrum: M^+ 284.

1,2-Dimethyl-3-benzyl-4-phenyl-5-pyrazolone (IIIe, $C_{18}H_{18}N_2O$). A solution of a mixture of 2.93 g (10 mmole) of Ie and 1.8 g (10 mmole) of hexamethylphosphoric triamide (HMPT) in 5 ml of THF was added with stirring at −78°C in an argon atmosphere to a solution of 10 mmole of phenyllithium in 15 ml of ether, after which it was warmed up to room temperature and then refluxed for 1 h. It was then cooled and treated with 5 ml of 2 N HCl, and the precipitated threo-1,2-diphenylsuccinic acid N,N′-dimethyldiamide* was removed by filtration. The residual solution was extracted with ethyl acetate (2 × 10 ml), the organic layer was dried with Na_2SO_4, the solvent was evaporated, and the residue was worked up as in the case of IIIa to give 0.59 g (20%) of threo-1,2-diphenylsuccinic acid N,N′-dimethyldiamide and 0.83 g (30%) of IIIe with mp 97-99°C. IR spectrum: 1690 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 3.16 (3H, s, 3-CH_3), 3.43 (3H, s, 1-CH_3), 4.06 (2H, s, CH_2), 7.20-7.50 ppm (10H, m, arom.). ^{13}C NMR spectrum ($CDCl_3$): 29.01 (2-CH_3), 30.95 (3-CH_2), 33.67 (1-CH_3), 110.81 [$C_{(4)}$], 126.62 [$CH_{(Ph)}$], 127.05 [$CH_{(Ph)}$], 127.88 [$CH_{(Ph)}$], 128.47 [$CH_{(Ph)}$], 129.05 [$CH_{(Ph)}$], 131.57 [$C_{(Ph)}$], 136.37 [$C_{(Ph)}$], 148.11 ppm [$C_{(3)}$]. Mass spectrum: M^+ 278.

LITERATURE CITED

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*Here and subsequently, hexamethyldisilazanyllithium could be used in place of phenyllithium.

†The physicochemical constants were presented in [3].

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