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Synthesis of Enamino Ketones from 4,5-Dihydropyrazoles

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Abstract—Enamino ketones were synthesized in 97–99% yield by reactions of 4,5-dihydropyrazoles with 1,3-dicarbonyl compounds.

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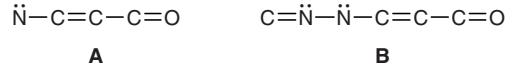
Enamino ketones are versatile and readily accessible synthons for the preparation of a wide series of heterocyclic compounds; in addition, they exhibit biological activity [1–3]. Their chemical reactivity and biological activity strongly depend on the nature of the amine fragment. In the present work we were the first to use 4,5-dihydropyrazoles as initial amine component in the synthesis of enaminones. 4,5-Dihydropyrazoles themselves possess a high synthetic potential, and their derivatives are known to exhibit versatile biological activity [4]; therefore, enhancement of such properties may be expected for enaminones derived therefrom. Moreover, enaminones **B** derived from dihydropyrazoles are characterized by more extended conjugation system as compared to enaminones **A** that have been studied most thoroughly [3]; higher degree of electron density delocalization in the former should increase the stability of structures **B** relative to structures like **A**.

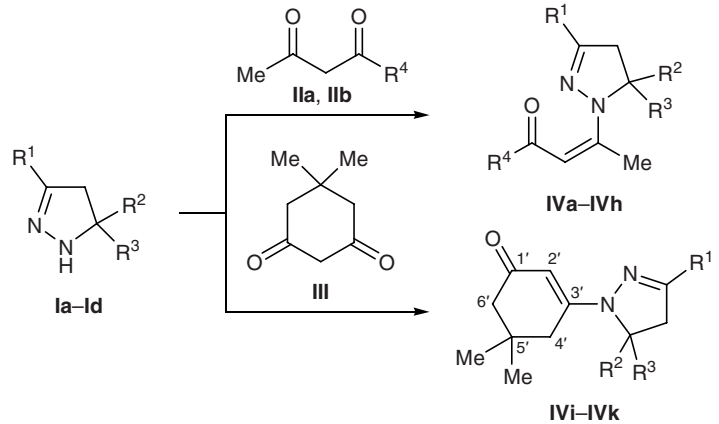


A **B**

By heating equimolar amounts of 4,5-dihydropyrazole **Ia–Id** and dicarbonyl compound **IIa**, **IIb**, or **III** in boiling benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid (no reaction occurred in the absence of a catalyst) with simultaneous removal of liberated water as azeotrope we obtained the corresponding enamino ketones **IVa–IVk** in almost quantitative yield (Scheme 1).

Compounds **IVa–IVk** were isolated as crystalline or viscous oily substances which underwent oxidation on exposure to air and decomposition on attempted

Scheme 1.



I, $R^1 = R^2 = R^3 = H$ (**a**), Me (**c**); $R^3 = Me$, $R^1 = R^2 = H$ (**b**), Et (**d**); **II**, $R^4 = Me$ (**a**), OEt (**b**); **IV**, $R^4 = Me$, $R^1 = R^2 = R^3 = H$ (**a**), Me (**c**); $R^3 = Me$, $R^1 = R^2 = H$ (**b**), Et (**d**); $R^4 = OEt$, $R^1 = R^2 = R^3 = H$ (**e**), Me (**g**), $R^3 = Me$, $R^1 = R^2 = H$ (**f**), Et (**h**); $R^3 = Me$, $R^1 = R^2 = H$ (**i**), Et (**k**), $R^1 = R^2 = R^3 = Me$ (**j**).

vacuum distillation (at a residual pressure of 1–2 mm); however, they can be stored for a long time under argon. Thus the products are less stable than enamino ketones obtained from the same dicarbonyl compounds and secondary cyclic amines, such as piperidine, morpholine, etc.

The IR spectra of enaminones **IVa–IVk** contained absorption bands in the regions 1500–1583 and 1607–1675 cm^{-1}, which correspond to vibrations of the bond system C=N–N–C=CH–C=O; bands in the region 3043–3083 cm^{-1} belong to stretching vibrations of the =C–H bonds. In the ^1H NMR spectra of **IVa–IVd** and **IVi–IVk** we observed a singlet at δ 5.07–5.55 ppm, which was assigned to the NC=CHC=O proton. The corresponding signal in the spectra of enaminones **IVe–IVh** obtained from ethyl acetoacetate was located in a stronger field, at δ 4.58–4.92 ppm. The presence of only one NC=CHC=O signal in the ^1H NMR spectra of compounds **IVa–IVk** suggests that they are formed as a single isomer. Insofar as the =CH proton in **IVa–IVh** shows no couplings with other protons (there are no protons on the neighboring double-bonded carbon atom and nitrogen atom), the isomer configuration cannot be determined reliably. On the other hand, the chemical shifts of the olefinic proton and the position of signals from the double-bonded carbon atoms in the ^{13}C NMR spectra of enaminones derived from acetylacetone (ethyl acetoacetate) and cyclic secondary amines [1], as well as the corresponding data for compounds **IVi–IVk**, led us to presume that enamino ketones **IVa–IVh** are *cis-s-trans* isomers.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded at 26°C on a Bruker DPX-400 spectrometer at 400 and 100 MHz, respectively, from solutions in $CDCl_3$ using HMDS as internal reference. The IR spectra were measured on a Specord 75IR spectrophotometer from samples prepared as thin films or KBr pellets.

Enaminones IVa–IVk (*general procedure*). A mixture of 0.1 mol of dihydropyrazole **Ia–Id**, 0.1 mol of dicarbonyl compound **IIa**, **IIb**, or **III**, and 0.01 g of *p*-toluenesulfonic acid in 50 ml of benzene was heated under reflux in a flask equipped with a Dean–Stark trap until water no longer separated. The solvent was distilled off, and the residue (an oily liquid) was dried until constant weight by keeping at room temperature at a residual pressure of 2 mm.

4-(4,5-Dihydro-1*H*-pyrazol-1-yl)pent-3-en-2-one (IVa). Yield 98%, mp 68°C. IR spectrum, ν, cm^{-1}: 480, 545, 758, 800, 823, 851, 865, 917, 948, 972, 985, 1067, 1100, 1268, 1340, 1384, 1417, 1438, 1525, 1584, 1617, 2915, 2953, 3055. ^1H NMR spectrum, δ, ppm: 2.11 s (3H, MeC=C), 2.65 s (3H, MeC=O), 2.96 t.d (2H, 4-H, $^3J_{4,5}$ = 10.2, $^3J_{3,4}$ = 1.3 Hz), 3.64 t (2H, 5-H, $^3J_{4,5}$ = 10.2 Hz), 5.07 s (1H, C=CH), 6.94 unresolved triplet (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 15.56 (**Me**C=CH), 31.53 (**Me**C=O), 33.26 (C^4), 44.10 (C^5), 96.10 (C=**C**H), 145.38 (C^3), 155.79 (Me**C**=C), 195.48 (C=O). Found, %: C 63.56; H 8.01; N 18.63. $C_8H_{12}N_2O$. Calculated, %: C 63.13; H 7.95; N 18.41.

4-(5-Methyl-4,5-dihydro-1*H*-pyrazol-1-yl)pent-3-en-2-one (IVb). Yield 98%, viscous oily substance. IR spectrum, ν, cm^{-1}: 497, 543, 773, 809, 867, 933, 960, 1052, 1065, 1100, 1167, 1265, 1313, 1340, 1352, 1409, 1516, 1633, 2921, 2960, 3043. ^1H NMR spectrum, δ, ppm: 1.13 d (3H, 5-Me, ^3J = 6.5 Hz), 2.00 s (3H, MeC=C), 2.44 d.d.d (1H, 4-H_A, ^2J = 18.3, $^3J_{4,5}$ = 3.2, $^3J_{3,4}$ = 1.9 Hz), 2.52 s (3H, MeC=O), 3.05 d.d.d (1H, 4-H_B, ^2J = 18.3, $^3J_{4,5}$ = 10.6, $^3J_{3,4}$ = 1.5 Hz), 4.23 m (1H, 5-H), 5.17 s (1H, C=CH), 6.82 unresolved triplet (3-H). ^{13}C NMR spectrum, δ_C, ppm: 15.87 (5-Me), 18.44 (**Me**C=C), 31.65 (**Me**C=O), 41.88 (C^4), 52.29 (C^5), 95.66 (C=**C**H), 144.86 (C^3), 155.16 (Me**C**=C), 195.33 (C=O). Found, %: C 64.92; H 8.40; N 16.58. $C_9H_{14}N_2O$. Calculated, %: C 65.03; H 8.49; N 16.85.

4-(3,5,5-Trimethyl-4,5-dihydro-1*H*-pyrazol-1-yl)-pent-3-en-2-one (IVc). Yield 97%, colorless crystals, mp 78°C. IR spectrum, ν, cm^{-1}: 537, 592, 675, 727, 767, 838, 933, 955, 1000, 1050, 1062, 1133, 1153, 1183, 1237, 1313, 1333, 1358, 1400, 1425, 1442, 1500, 1617, 2900, 2958. ^1H NMR spectrum, δ, ppm: 1.57 s (6H, 5-Me), 2.01 s (3H, 3-Me), 2.10 s (3H, MeC=C), 2.63 s (3H, MeC=O), 2.80 s (2H, 4-H), 5.55 s (1H, C=CH). ^{13}C NMR spectrum, δ_C, ppm: 16.09 (**Me**C=C), 17.22 (3-Me), 26.30 (5-Me), 32.16 (**Me**C=O), 55.36 (C^4), 64.60 (C^5), 95.46 (C=**C**H), 152.80 (C^3), 156.15 (Me**C**=C), 195.19 (C=O). Found, %: C 68.46; H 9.84; N 14.81. $C_{11}H_{18}N_2O$. Calculated, %: C 68.01; H 9.34; N 14.42.

4-(3,5-Diethyl-5-methyl-4,5-dihydro-1*H*-pyrazol-1-yl)pent-3-en-2-one (IVd). Yield 98%, viscous oily substance. IR spectrum, ν, cm^{-1}: 547, 600, 680, 792, 835, 979, 1059, 1097, 1181, 1307, 1349, 1373, 1420, 1455, 1528, 1630, 2886, 2964, 2980. ^1H NMR spectrum, δ, ppm: 0.82 t (3H, 5-$CH_2C\mathbf{H}_3$, ^3J = 7.3 Hz), 1.14 t (3H, 3-$CH_2C\mathbf{H}_3$, ^3J = 7.5 Hz), 1.55 s (3H, 5-Me), 1.65 m (1H, 3-CH_A), 2.08 s (3H, MeC=C), 2.16 m (1H, 3-CH_B), 2.32 q (2H, 3-CH_2, ^3J = 7.5 Hz) 2.64 s (3H, MeC=O), 2.69 d (1H, 4-H_A, ^2J = 17.9 Hz),

2.89 d (1H, 4-H_B, ^2J = 17.9 Hz), 5.50 s (1H, C=CH). ^{13}C NMR spectrum, δ_C, ppm: 8.10 (5-CH_2**C**H_3), 10.64 (3-CH_2**C**H_3), 17.11 (5-Me), 23.52 (5-CH_2), 25.27 (**Me**C=C), 31.26 (3-CH_2), 31.96 (**Me**C=O), 50.13 (C^4), 67.92 (C^5), 100.31 (C=**C**H), 156.94 (C^3), 157.42 (Me**C**=C), 195.02 (C=O). Found, %: C 70.46; H 9.82; N 12.17. $C_{13}H_{22}N_2O$. Calculated, %: C 70.23; H 9.97; N 12.60.

Ethyl 3-(4,5-dihydro-1*H*-pyrazol-1-yl)but-2-enoate (IVe). Yield 97%, viscous oily substance. IR spectrum, ν, cm^{-1}: 483, 525, 648, 709, 833, 903, 925, 998, 1047, 1118, 1158, 1272, 1342, 1358, 1420, 1567, 1593, 1675, 2905, 2938, 2983, 3083. ^{1}H NMR spectrum, δ, ppm: 1.25 t (3H, CH_2C**H**$_3$, ^3J = 7.2 Hz), 2.61 s (3H, MeC=C), 2.93 t.d (2H, 4-H, $^3J_{4,5}$ = 10.1, $^3J_{3,4}$ = 1.1 Hz), 3.58 t (2H, 5-H, $^3J_{4,5}$ = 10.1 Hz), 4.10 q (2H, OCH_2, ^3J = 7.2 Hz), 4.58 s (1H, C=CH), 6.85 unresolved triplet (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 14.50 (CH_2**C**H_3), 15.36 (**Me**C=C), 33.47 (C^4), 44.47 (C^5), 58.51 (OCH_2), 86.28 (C=**C**H), 144.26 (C^3), 156.53 (Me**C**=C), 168.58 (C=O). Found, %: C 59.20; H 7.54; N 15.96. $C_9H_{14}N_2O_2$. Calculated, %: C 59.32; H 7.74; N 15.37.

Ethyl 3-(5-methyl-4,5-dihydro-1*H*-pyrazol-1-yl)-but-2-enoate (IVf). Yield 98%, viscous oily substance. IR spectrum, ν, cm^{-1}: 483, 532, 642, 715, 775, 802, 842, 883, 933, 950, 1023, 1041, 1092, 1122, 1250, 1292, 1308, 1322, 1342, 1350, 1400, 1550, 1580, 1667, 2833, 2858, 2883, 2915, 2957, 3058. ^{1}H NMR spectrum, δ, ppm: 1.22 d (3H, 5-Me, ^3J = 6.18 Hz), 1.25 t (3H, CH_2C**H**$_3$, ^3J = 7.1 Hz), 2.51 d.d.d (1H, 4-H_A, ^2J = 18.0, $^3J_{4,5}$ = 3.5, $^3J_{3,5}$ = 1.9 Hz), 2.60 s (3H, MeC=C), 3.13 d.d.d (1H, 4-H_B, ^2J = 18.0, $^3J_{4,5}$ = 10.7, $^3J_{3,5}$ = 1.6 Hz), 4.10 q.d (OCH_A, ^2J = 2.1, ^3J = 7.1 Hz), 4.23 m (1H, 5-H), 4.76 s (1H, C=CH), 6.68 t (3-H, ^3J = 1.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.55 (**C**$H_3$$CH_2$), 15.64 (5-Me), 18.54 (**Me**C=C), 42.04 (C^4), 52.02 (C^5), 58.51 (OCH_2), 85.81 (C=**C**H), 143.17 (C^3), 155.64 (Me**C**=C), 168.77 (C=O). Found, %: C 61.38; H 8.57; N 14.38. $C_{10}H_{16}N_2O_2$. Calculated, %: C 61.20; H 8.22; N 14.27.

Ethyl 3-(3,5,5-trimethyl-4,5-dihydro-1*H*-pyrazol-1-yl)but-2-enoate (IVg). Yield 99%, mp 96°C. IR spectrum, ν, cm^{-1}: 628, 725, 798, 842, 888, 907, 958, 983, 1000, 1040, 1095, 1125, 1100, 1247, 1317, 1358, 1377, 1422, 1558, 1640, 1670, 2915, 2933, 2980. ^{1}H NMR spectrum, δ, ppm: 1.25 t (3H, C**H**$_3$$CH_2$, ^3J = 7.1 Hz), 1.56 s (6H, 5-Me), 1.98 s (3H, 3-Me), 2.54 s (3H, MeC=C), 2.75 s (2H, 4-H), 4.06 q (OCH_2, ^3J = 7.1 Hz), 4.92 s (C=CH). ^{13}C NMR spectrum, δ_C, ppm: 14.97 (**C**$H_3$$CH_2$), 16.21 (3-Me), 17.18 (**Me**C=C), 26.10 (5-Me), 55.50 (C^4), 58.42 (OCH_2), 64.45 (C^5), 85.52 (C=**C**H), 150.02 (C^3), 155.99 (Me**C**=C), 168.65 (C=O). Found, %: C 64.34; H 9.06; N 12.37. $C_{12}H_{20}N_2O_2$. Calculated, %: C 64.26; H 8.99; N 12.49.

Ethyl 3-(3,5-diethyl-5-methyl-4,5-dihydro-1*H*-pyrazol-1-yl)but-2-enoate (IVh). Yield 97%, viscous oily substance. IR spectrum, ν, cm^{-1}: 455, 533, 567, 632, 733, 800, 898, 932, 992, 1057, 1110, 1130, 1175, 1272, 1318, 1343, 1392, 1428, 1468, 1583, 1642, 1667, 2892, 2950, 2987. ^{1}H NMR spectrum, δ, ppm: 0.76 m (3H, 5-CH_2C**H**$_3$), 1.07 m (3H, 3-CH_2C**H**$_3$), 1.18 m (3H, OCH_2C**H**$_3$), 1.47 s (3H, 5-Me), 1.58 m (1H, 5-CH_A), 2.11 m (1H, 5-CH_B), 2.24 m (2H, 3-CH_2), 2.54 s (3H, MeC=C), 2.60 d (1H, 4-H_A, ^2J = 17.7 Hz), 2.81 d (1H, 4-H_B, ^2J = 17.7 Hz), 4.02 q.d (OCH_2, ^2J = 1.7, ^3J = 7.1 Hz), 4.92 s (C=CH). ^{13}C NMR spectrum, δ_C, ppm: 8.20 (5-CH_2**C**H_3), 10.72 (3-CH_2**C**H_3), 14.61 (OCH_2**C**H_3), 16.81 (5-Me), 23.46 (5-CH_2), 25.27 (MeC=C), 30.98 (3-CH_2), 50.03 (C^4), 58.28 (OCH_2), 67.68 (C^5), 84.13 (C=**C**H), 155.40 (C^3), 156.65 (Me**C**=C), 169.09 (C=O). Found, %: C 66.25; H 9.29; N 11.02. $C_{14}H_{24}N_2O_2$. Calculated, %: C 66.63; H 9.59; N 11.10.

5,5-Dimethyl-3-(5-methyl-4,5-dihydro-1*H*-pyrazol-1-yl)cyclohex-2-en-1-one (IVi). Yield 97%, viscous oily substance. IR spectrum, ν, cm^{-1}: 433, 457, 497, 665, 697, 717, 797, 817, 853, 883, 900, 933, 947, 987, 1007, 1060, 1073, 1097, 1140, 1163, 1180, 1233, 1260, 1353, 1413, 1540, 1626, 2833, 2940, 3053. ^{1}H NMR spectrum, δ, ppm: 1.13 s (3H, 5′-Me), 1.18 s (3H, 5′-Me), 1.29 d (3H, 5-Me, ^3J = 6.1 Hz), 2.21 m (2H, 4′-H), 2.59 d.d.d (1H, 4-H_A, ^2J = 18.1, ^3J = 3.5, 1.7 Hz), 2.67 s (2H, 6′-H), 3.22 d.d.d (1H, 4-H_B, ^2J = 18.1, ^3J = 10.1, ^3J = 1.4 Hz), 4.28 m (1H, 5-H), 5.17 s (1H, C=CH), 6.91 unresolved triplet (3-H). ^{13}C NMR spectrum, δ_C, ppm: 18.21 (5-Me), 28.01 (5′-Me), 28.26 (5′-Me), 32.00 ($C^{5'}$), 39.71 (C^4), 41.58 ($C^{4'}$), 49.64 ($C^{6'}$), 51.65 (C^5), 96.79 ($C^{2'}$), 144.45 (C^3), 157.15 ($C^{3'}$), 196.06 (C=O). Found, %: C 69.64; H 8.45; N 13.26. $C_{12}H_{18}N_2O$. Calculated, %: C 69.87; H 8.79; N 13.58.

5,5-Dimethyl-3-(3,5,5-trimethyl-4,5-dihydro-1*H*-pyrazol-1-yl)cyclohex-2-en-1-one (IVj). Yield 97%, viscous oily substance. IR spectrum, ν, cm^{-1}: 413, 460, 500, 533, 593, 687, 741, 793, 820, 833, 860, 880, 900, 925, 953, 990, 1013, 1033, 1107, 1137, 1144, 1240, 1271, 1367, 1420, 1543, 1613, 2867, 2953. ^{1}H NMR spectrum, δ, ppm: 1.08 s (6H, 5′-Me), 1.55 s (6H, 5-Me), 2.00 s (3H, 3-Me), 2.13 s (2H, 4′-H), 2.61 s (2H, 4-H), 2.81 s (2H, 6′-H), 5.37 s (1H, 2′-H). ^{13}C NMR spectrum, δ_C, ppm: 16.74 (3-Me), 26.61

(5-Me), 29.43 (5′-Me), 33.16 ($C^{5'}$), 42.34 ($C^{4'}$), 50.30 ($C^{6'}$), 55.87 (C^{4}), 65.50 (C^{5}), 97.02 ($C^{3'}$), 154.31 (C^{3}), 158.91 ($C^{2'}$), 197.34 (C=O). Found, %: C 71.31; H 9.14; N 11.53. $C_{14}H_{22}N_2O$. Calculated, %: C 71.76; H 9.46; N 11.95.

3-(3,5-Diethyl-5-methyl-4,5-dihydro-1*H*-pyrazol-1-yl)-5,5-dimethylcyclohex-2-en-1-one (IVk). Yield 98%, viscous oily substance. IR spectrum, ν, cm^{-1}: 420, 472, 500, 547, 592, 673, 687, 727, 740, 799, 820, 860, 879, 925, 987, 1020, 1053, 1107, 1237, 1240, 1251, 1287, 1357, 1413, 1453, 1547, 1607, 2872, 2960. ^{1}H NMR spectrum, δ, ppm: 0.78 t (3H, 5-$CH_2C\mathbf{H}_3$, ^3J = 7.1 Hz), 1.07 s (6H, 5′-Me), 1.15 t (3H, 3-$CH_2C\mathbf{H}_3$, ^3J = 7.6 Hz), 1.54 s (3H, 5-Me), 1.63 m (1H, 5-CH_A), 2.16 s (2H, 4′-H), 2.21 m (1H, 5-CH_B), 2.33 m (2H, 3-CH_2), 2.67 m (2H, 6′-H), 2.70 d (1H, 4-H_A, ^2J = 17.9 Hz), 2.90 d (1H, 4-H_B, ^2J = 17.9 Hz), 5.39 s (1H, C=CH). ^{13}C NMR spectrum, δ_C, ppm: 8.0 (5-$CH_2\mathbf{C}H_3$), 10.63 (3-$CH_2\mathbf{C}H_3$), 23.43 (5-Me), 25.11 (5-CH_2), 28.19 (5′-Me), 28.71 (5′-Me), 30.55 (3-CH_2), 32.26 ($C^{5'}$), 41.35 ($C^{4'}$), 49.37 (C^{4}), 49.85 ($C^{6'}$), 68.10 (C^{5}), 103.21 ($C^{2'}$), 158.56 (C^{3}), 159.03 ($C^{3'}$), 196.92 (C=O). Found, %: C 73.16; H 9.87; N 10.43. $C_{16}H_{26}N_2O$. Calculated, %: C 73.24; H 9.99; N 10.68.

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