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SYNTHESIS OF 2-UNSUBSTITUTED 2,3,5,6,7,8-HEXAHYDRO-PYRAZOLO[4,3-*d*][1,2]DIAZEPINONE-8-CARBOXYLATES

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Abstract – Substituted 2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxy-lates were prepared in good to excellent yields from ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)-methylidene]-4,5-dihydro-5-oxo-1*H*-pyrazol-3-yl}propenoate with 1,2-disubstituted hydrazines by heating in an alcohol.

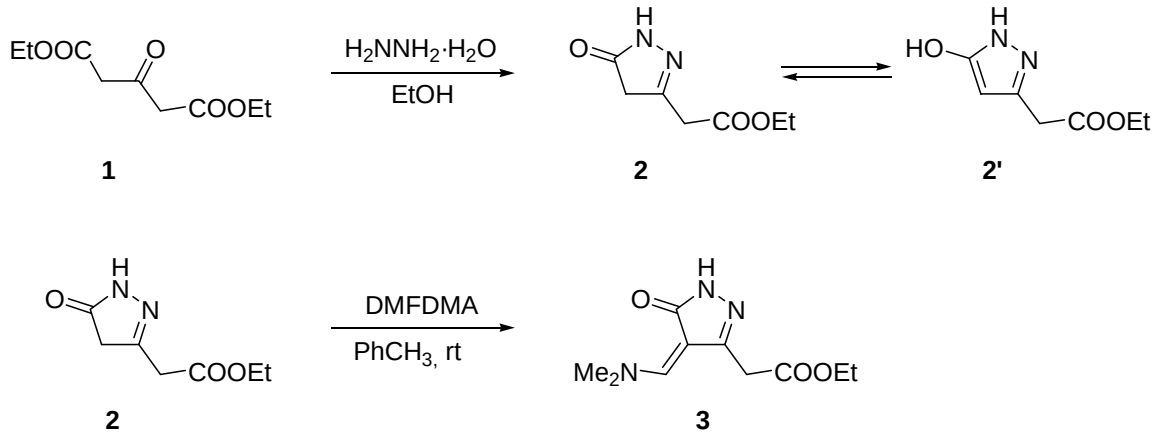
INTRODUCTION

In connection with our interest in alkyl 3-dimethylaminopropenoates and related enaminones as building blocks for the preparation of various heterocyclic systems and functionalized heterocycles, such as heteroaryl-substituted α-amino- and α-hydroxy acid derivatives, fused pyridones, pyrimidones, pyranones and related systems,[1–3] including some naturally occurring alkaloids,[4–11] and on application in combinatorial synthesis,[12–14] we reported recently some transformations of alkyl [(*Z*)-4-dimethylamino-methylidene-4,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazol-3-yl]acetate with *N*-nucleophiles into 2*H*-pyrazolo[4,3-*c*]pyridine-7-carboxylates[15,16] and (substituted pyrazol-3-yl)pyrimidones and (pyrazol-3-yl)pyranones.[17]

While pyrazolo[3,4-*d*][1,2]diazepines have been obtained by cycloaddition of 2-diazopropane to 1,2-diazepine derivatives,[18–23] isomeric pyrazolo[4,3-*d*][1,2]diazepines are mentioned in the literature only once. Namely, in the heterocyclization of 5-ethynylpyrazole-4-carbohydrazides under the influence of CuCl, an unexpected formation of a diazepinone and dehydrodimerisation into the corresponding bis(pyrazolo[4,3-*d*][1,2]diazepinone) has been described.[24] Recently, substituted 2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepinone-8-carboxylates have been prepared in our laboratory.[25] In this paper, we describe the preparation of 2-unsubstituted-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]-diazepinone-8-carboxylates.

RESULTS AND DISCUSSION

Ethyl 2-(4,5-dihydro-5-oxo-1*H*-pyrazol-3-yl)acetate (**2**), prepared from diethyl acetone-1,3-dicarboxylate (**1**) and hydrazine hydrate in EtOH at rt,[26] was transformed with *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) in toluene at rt into ethyl (*Z*)-2-{4-[(dimethylamino)methylidene]-4,5-dihydro-5-oxo-1*H*-pyrazol-3-yl}acetate (**3**) in 76% yield (Scheme 1).



Scheme 1

The structure of compound (**3**) was determined by HMBC 2D NMR spectral data showing the coupling constant between $C_{(5)}$ carbon atom and methylidene proton, $^{3}J_{C\text{-}H}$ = 8 Hz, thus indicating *trans* orientation of methylidene proton and carbonyl group around the exocyclic double bond or (*Z*)-configuration around the exocyclic double bond. (Figure 1)

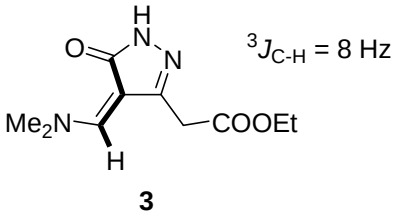
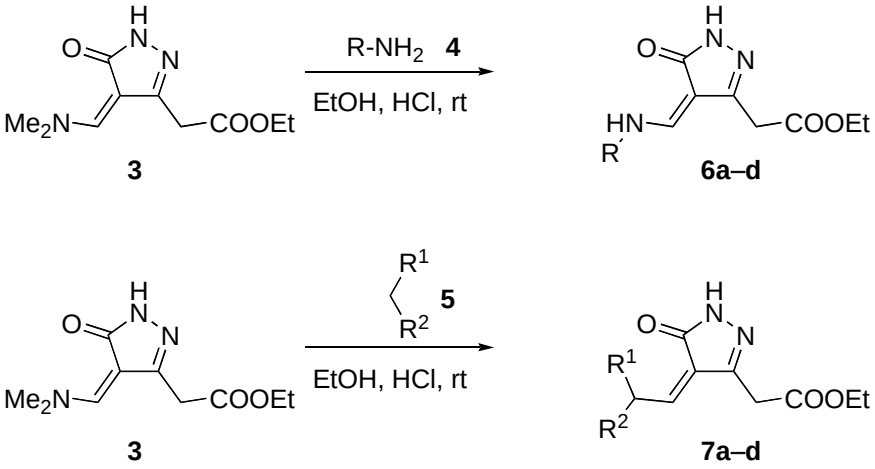


Figure 1

In the reaction of **3** with *N*- and *C*- nucleophiles in EtOH at rt in the presence of equimolar amount of hydrochloric acid, the dimethylamino group was substituted to give compounds (**6a**–**d**) and (**7a**–**d**), respectively. Since the starting compound (**3**) is soluble in water in the presence of hydrochloric acid, the reactions can be carried out also in water with essentially the same yields, as reactions in EtOH, and simple isolation of the products. (Scheme 2, Table 1)

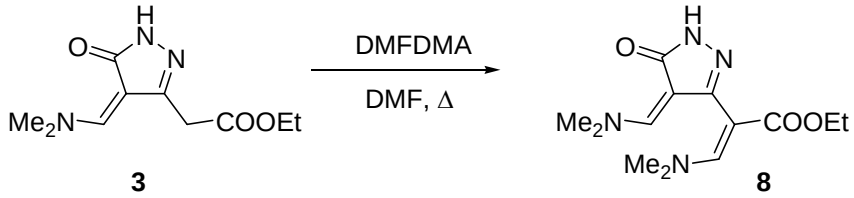


Scheme 2

Table 1

Product	R	Yield	Product	R^1CHR^2	Yield
3+4a→6a	CH_2CH_2COOEt	**51%**	**3+5a→7a**	6-hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl	**66%**
3+4b→6b	4-nitrophenyl	**90%**	**3+5b→7b**	6-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl	**80%**
3+4c→6c	4-bromophenyl	**77%**	**3+5c→7c**	3-hydroxy-1-oxo-1*H*-inden-2-yl	**66%**
3+4d→6d	4-methylphenyl	**79%**	**3+5d→7d**	5-hydroxy-1,3-diphenyl-1*H*-pyrazol-4-yl	**61%**

Compound (**3**) reacts with DMFDMA in boiling DMF to give ethyl (*E*)-3-(dimethylamino)-2-{(*Z*)-4-[(dimethylamino)methylidene]-4,5-dihydro-5-oxo-1*H*-pyrazol-3-yl}propenoate (**8**) in 70% yield. Fortunately, annular *N*-methylation did not take place under these conditions. (Scheme 3)



Scheme 3

The structure of compound (**8**) was determined by HMBC 2D NMR spectral data showing the $^3J_{C\text{-}H}$ = 8 Hz and $^3J_{C\text{-}H}$ = 5 Hz indicating (*Z*)-orientation around exocyclic double bond and (*E*)-orientation on the side chain attached at 3'-position. (Figure 2) These orientations are in agreement with previously observed properties in 1-phenyl substituted derivatives.[25]

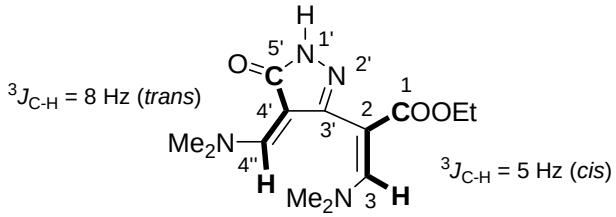
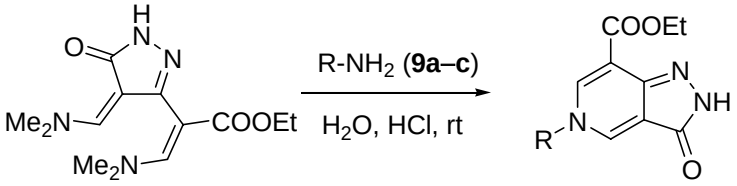


Figure 2

Since compound (**8**) was soluble in water, the reactions of **8** with primary amines (**9a**–**c**) were carried out in water at rt in the presence of hydrochloric acid, to precipitate pyrazolo[4,3-*c*]pyridine derivatives (**10a**–**c**) after 12 hours in good yields and in analytical purity (Scheme 4).

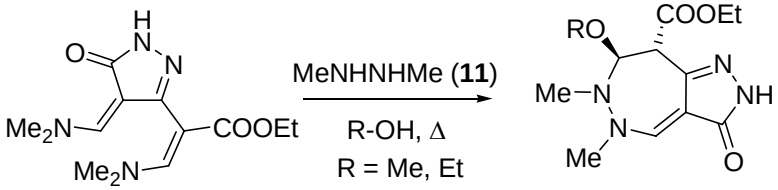


8 **10a–c**

R = **a**: Me, **b**: CH_2CN, **c**: quinolin-3-yl

Scheme 4

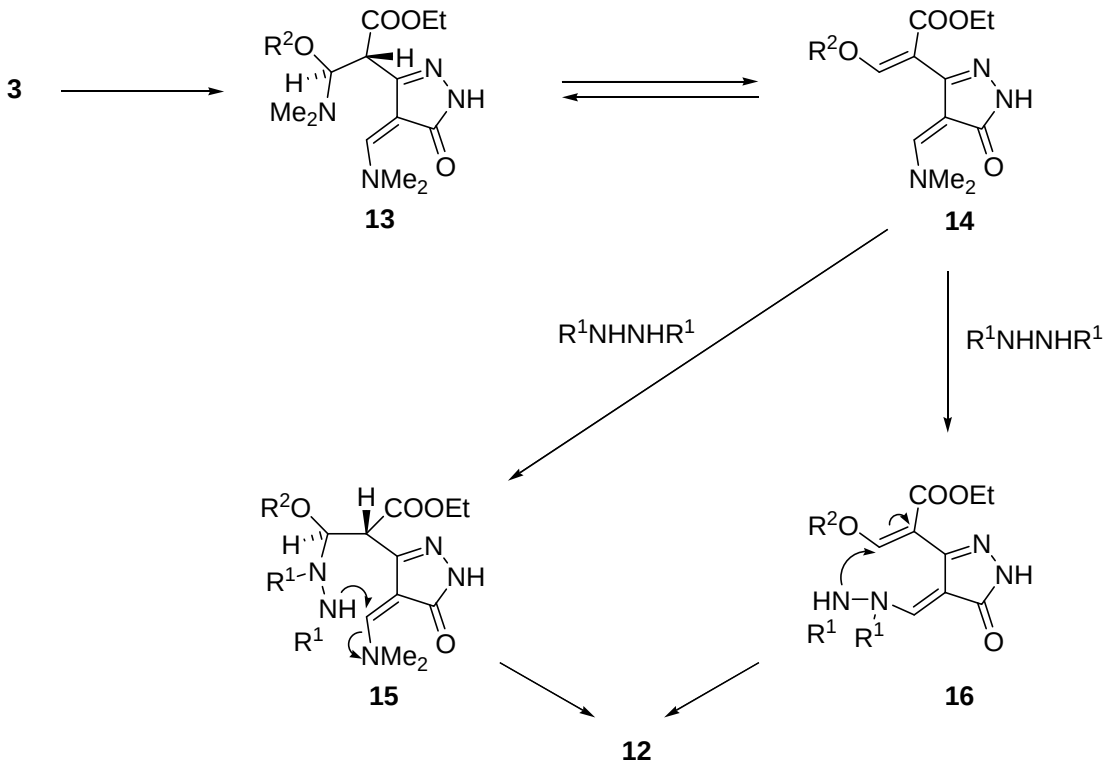
Compound (**8**) reacts with 1,2-dimethylhydrazine (**11**) by heating in MeOH or EtOH at reflux temperature for several hours to give 2,3,5,6,7,8-hexahydropyrazolo[4,3-*c*]diazepine-8-carboxylates (**12a**,**b**).



8 **12a,b**

Scheme 5

The mechanism of the transformation of **12** is unknown so far, however, the possible explanation is either the formation of aminal (**13**) or enol ether (**14**) as intermediates in the presence of an alcohol. In the reaction with 1,2-disubstituted hydrazine, (Scheme 6) the corresponding intermediates (**15** and **16**) are formed, which cyclises into the final product (**12**).



Scheme 6

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H NMR, ^{13}C NMR and 2D NMR HMBC, NOESY spectra were obtained on a Bruker Avance DPX 300 (300 MHz) spectrometer with DMSO-d_6 or $CDCl_3$ as solvent and TMS as internal standard (δ in ppm, J in Hz). IR spectra were recorded with Perkin–Elmer Spectrum BX FTIR and BIO RAD Excalibur Series FTS 3000 MX FTIR spectrophotometers (KBr discs, ν in cm^{-1}). MS spectra were obtained on an Autospeck Q spectrometer. The microanalyses for C, H, and N were obtained on a Perkin Elmer CHN *Analyser* 2400 and Perkin Elmer Series II CHN *Analyser* 2400.

Ethyl 2-(4,5-dihydro-5-oxo-1*H*-pyrazol-3-yl)acetate (2)

A solution of diethyl 3-oxopentanedioate (**1a**) (1.8 mL, 10 mmol) hydrazine hydrate (0.53 mL, 11 mmol) in EtOH (5 mL) were stirred at rt for 2 h. Water (3 mL) was added to a reaction mixture and EtOH was partially evaporated. The residue was cooled to -30°C and white crystals were filtered off. Yield: 93% (1.584 g). R (cm^{-1}): 2630, 1740, 1610, 1500, 1200, 1170, 970, 780, 670, 550. ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H, J = 7.1, OCH_2CH_3); 3.63 (s, 2H, CH_2); 4.20 (q, 2H, J = 7.1, OCH_2CH_3); 5.54 (s, 1H, 4–H); 8.36 (br s, 2H, NH, OH).

Ethyl (*Z*)-2-{4-[(dimethylamino)methylene]-4,5-dihydro-5-oxo-1*H*-pyrazol-3-yl}acetate (3)

To a suspension of ethyl 2-(4,5-dihydro-5-oxo-1*H*-pyrazol-3-yl)acetate (**39**) (170 mg, 1 mmol) in toluene (2 mL), DMFDMA (0.3 mL, 2 mmol) was added and mixture was stirred at rt for 2 h. Product precipitated was filtered off and recrystallised from toluene/EtOH. Yield: 76% (172 mg). mp 135–138°C. *Anal*. Calcd for $C_{10}H_{15}N_3O_3$ (225.24): C 53.32; H 6.71; N 18.66. Found: C 53.13; H 6.78; N 18.40. IR (cm^{-1}): 3430, 3150, 1720, 1670, 1590, 1540, 1410, 1210, 1140, 820, 740, 660, 550. ^{1}H NMR ($CDCl_3$): δ 1.26 (t, 3H, *J* = 7.1, OCH_2CH_3); 3.31 (s, 3H, NMe); 3.51 (s, 2H, CH_2); 3.85 (s, 3H, NMe); 4.17 (q, 2H, *J* = 7.1, OCH_2CH_3); 8.90 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 14.9; 34.7; 43.4; 47.8; 61.2; 97.4; 147.7; 154.2; 165.4; 170.7. $^3J_{C\text{-}H}$ = 8 Hz.

Synthesis of ethyl (Z)-2-{4,5-dihydro-5-oxo-4-[(substituted amino)methylidene]-1*H*-pyrazol-3-yl}acetates (6a–d):

Ethyl (*Z*)-2-{4-[(dimethylamino)methylene]-4,5-dihydro-5-oxo-1*H*-pyrazol-3-yl}acetate (**3**) (113 mg, 0.5 mmol) was added to a water solution of amine (**4c**, **14b–d**) (0.5 mmol in 1 mL) and hydrochloric acid (1 equiv.) and left at rt for 12 h. Product precipitated, was filtered off and recrystallised from appropriate solvent.

Ethyl (*Z*)-3-(3-(2-ethoxycarbonylmethyl-5-oxo-1*H*-pyrazol-4-ylideneamino)propanoate (6a)

From **3** and ethyl β-alaninate hydrochloride (**4a**) (77 mg, 0.5 mmol). Yeld: 51% (75 mg). mp 128–129°C (toluene/EtOH). *Anal*. Calcd for $C_{13}H_{19}N_3O_5$ (297.31): C 52.52; H 6.44; N 14.13. Found: C 52.51; H 6.58; N 14.02. IR (cm^{-1}): 3160, 1740, 1720, 1670, 1590, 1540, 1390, 1340, 1250, 1200, 1180, 1100, 1030, 850, 790, 660, 600. ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H, *J* = 7.1, OCH_2CH_3); 1.28 (t, 3H, *J* = 7.2, OCH_2CH_3); 2.67 (t, 2H, *J* = 6.2, CH_2CH_2); 3.55 (s, 2H, CH_2); 3.70 (t, 2H, *J* = 6.2, CH_2CH_2); 4.18 (q, 2H, *J* = 7.1, OCH_2CH_3); 4.19 (q, 2H, *J* = 7.2, OCH_2CH_3); 7.73 (s, 1H, =CH); 8.68 (br s, 1H, NH); 9.82 (br s, 1H, NH).

Ethyl (*Z*)-2-{4,5-dihydro-4-[(4-nitrophenylamino)methylidene]-5-oxo-1*H*-pyrazol-3-yl}acetate (6b)

From **3** and 4-nitroaniline (**14b**) (69 mg, 0.5 mmol). Yield: 90% (143 mg). mp 222–224°C (EtOH). *Anal*. Calcd for $C_{14}H_{14}N_4O_5$ (318.28): C 52.83; H 4.43; N 17.60. Found: C 52.79; H 4.50; N 17.50. IR (cm^{-1}): 3160, 1730, 1690, 1590, 1520, 1340, 1290, 1200, 1110, 840, 750, 640. ^{1}H NMR (DMSO-d_6): δ 1.20 (t, 3H, *J* = 7.1, OCH_2CH_3); 3.70 (s, 2H, CH_2); 4.11 (q, 2H, *J* = 7.1, OCH_2CH_3); 7.68–7.73 (m, 2H, Ph);

8.26–8.31 (m, 2H, Ph); 8.61 (s, 1H, =CH); 11.31 (br s, 1H, NH).

Ethyl (*Z*)-2-{4-[(4-bromophenylamino)methylene]-4,5-dihydro-5-oxo-1*H*-pyrazol-3-yl}acetate (6c)

From **3** and 4-bromoaniline (**14c**) (104 mg, 0.5 mmol). Yield: 77% (135 mg). mp 208–211°C (toluene/EtOH). *Anal*. Calcd for $C_{14}H_{14}N_3O_3Br$ (352.18): C 47.74; H 4.01; N 11.93. Found: C 47.97; H 4.13; N 11.86. IR (cm^{-1}): 3150, 1730, 1680, 1620, 1580, 1480, 1300, 1200, 1070, 810, 790, 760, 670, 500. ^1H NMR ($CDCl_3$): δ 1.28 (t, 3H, *J* = 7.1, OCH_2CH_3); 3.64 (s, 2H, CH_2); 4.20 (q, 2H, *J* = 7.1, OCH_2CH_3); 7.08–7.13 (m, 2H, Ph); 7.51–7.56 (m, 2H, Ph); 8.18 (s, 1H, =CH); 8.82 (br s, 1H, NH); 9.53 (br s, 1H, NH).

Ethyl (*Z*)-2-{4,5-dihydro-5-oxo-4-[(*p*-toluidino)methylene]-1*H*-pyrazol-3-yl}acetate (6d)

From **3** and 4-methylaniline hydrochloride (**14d**) (72 mg, 0.5 mmol). Yield: 79% (114 mg). mp 197–199°C (toluene/EtOH). *Anal*. Calcd for $C_{15}H_{17}N_3O_3$ (287.31): C 62.71; H 5.96; N 14.63. Found: C 62.54; H 6.19; N 14.57. IR (cm^{-1}): 3140, 1720, 1690, 1610, 1580, 1520, 1310, 1200, 1070, 810, 790, 760, 660, 510. ^1H NMR ($CDCl_3$): δ 1.28 (t, 3H, *J* = 7.1, OCH_2CH_3); 2.36 (s, 3H, Me); 3.63 (s, 2H, CH_2); 4.20 (q, 2H, *J* = 7.1, OCH_2CH_3); 7.10–7.14 (m, 2H, Ph); 7.20–7.23 (m, 2H, Ph); 8.18 (s, 1H, =CH); 8.82 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 14.9; 21.2; 34.3; 61.3; 101.3; 118.1; 131.0; 135.3; 137.3; 145.3; 146.0; 169.0; 170.5. $^3J_{C\text{-}H}$ = 8 Hz.

Synthesis of ethyl (Z)-2-{4,5-dihydro-5-oxo-4-[(substituted)methylidene]-1*H*-pyrazol-3-yl}acetates (7a–d)

A mixture of ethyl (*Z*)-2-{4-[(dimethylamino)methylene]-4,5-dihydro-5-oxo-1*H*-pyrazol-3-yl}acetate (**3**) (113 mg, 0.5 mmol), *C*-nucleophile (**5a–d**) (0.5 mmol), hydrochloric acid (1 equiv.) in EtOH (2 mL) were allowed to stand at rt for 12 h. Product precipitated, was filtered off and recrystallised from appropriate solvent.

Ethyl (*Z*)-2-[4,5-dihydro-4-(6-hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-ylmethylidene)-5-oxo-1*H*-pyrazol-3-yl]acetate (7a)

From **3** and barbituric acid (**5a**) (64 mg, 0.5 mmol). Yield: 66% (100 mg). mp >350°C (EtOH). *Anal*. Calcd for $C_{12}H_{12}N_4O_6$ (308.25): C 46.76; H 3.92; N 18.18. Found: C 46.48; H 3.94; N 17.98. IR (cm^{-1}):

3190, 1730, 1650, 1580, 1560, 1440, 1370, 1340, 1200, 1110, 1030, 790, 770, 590, 550, 530. ^{1}H NMR (DMSO-d_6): δ 1.18 (t, 3H, J = 7.1, OCH_2CH_3); 3.78 (s, 2H, CH_2); 4.09 (q, 2H, J = 7.1, OCH_2CH_3); 8.14 (s, 1H, =CH); 11.35 (br s, 1H, NH); 11.63 (br s, 1H, NH); 13.11 (br s, 1H, OH).

Ethyl (*Z*)-2-[4,5-dihydro-4-(6-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-ylmethylidene)-5-oxo-1*H*-pyrazol-3-yl]acetate (7b)

From **3** and 1,3-dimethylbarbituric acid (**5b**) (78 mg, 0.5 mmol). Yield: 80% (134 mg). mp 203–205°C (EtOH). *Anal*. Calcd for $C_{14}H_{16}N_4O_6$ (336.30): C 50.00; H 4.80; N 16.66. Found: C 50.19; H 4.99; N 16.57. IR (cm^{-1}): 3280, 1730, 1720, 1660, 1650, 1580, 1560, 1370, 1280, 1210, 1150, 930, 790, 760, 720, 630, 580, 490. ^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H, J = 7.1, OCH_2CH_3); 3.40 (s, 3H, NMe); 3.44 (s, 3H, NMe); 3.80 (s, 2H, CH_2); 4.21 (q, 2H, J = 7.1, OCH_2CH_3); 8.46 (s, 1H, =CH); 14.65 (br s, 1H, OH).

Ethyl (*Z*)-2-[4,5-dihydro-4-(3-hydroxy-1-oxo-1*H*-inden-2-ylmethylidene)-5-oxo-1*H*-pyrazol-3-yl]acetate (7c)

From **3** and 1,3-indanedione (**5c**) (73 mg, 0.5 mmol). Yield: 66% (108 mg). mp 189–193°C (EtOH/water). *Anal*. Calcd for $C_{17}H_{14}N_2O_5$ (326.30): C 62.57; H 4.32; N 8.59. Found: C 62.73; H 4.29; N 8.51. IR (cm^{-1}): 3320, 1730, 1710, 1650, 1610, 1590, 1520, 1360, 1340, 1210, 1180, 1120, 1030, 930, 820, 740, 600. ^{1}H NMR ($CDCl_3$): δ 1.30 (t, 3H, J = 7.1, OCH_2CH_3); 3.82 (s, 2H, CH_2); 4.23 (q, 2H, J = 7.1, OCH_2CH_3); 7.66 (s, 1H, =CH); 7.73–7.84 (m, 2H, Ph); 7.93–7.95 (m, 5H, Ph); 15.447 (br s, 1H, OH).

Ethyl (*Z*)-2-[4,5-dihydro-4-(5-hydroxy-1,3-diphenyl-1*H*-pyrazol-4-ylmethylidene)-5-oxo-1*H*-pyrazol-3-yl]acetate (7d)

From **3** and 1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (**18l**) (118 mg, 0.5 mmol). Yield: 61% (127 mg). mp 188–191°C (EtOH/water). *Anal*. Calcd for $C_{23}H_{20}N_4O_4$ (416.43): C 66.43; H 4.84; N 13.45. Found: C 66.67; H 5.03; N 13.17. IR (cm^{-1}): 3290, 1730, 1620, 1600, 1520, 1490, 1410, 1350, 1330, 1200, 1180, 1020, 960, 860, 750, 700, 690, 670, 580. ^{1}H NMR ($CDCl_3$): δ 1.19 (t, 3H, J = 7.1, OCH_2CH_3); 3.59 (s, 2H, CH_2); 4.13 (q, 2H, J = 7.1, OCH_2CH_3); 7.29–7.33 (m, 1H, Ph); 7.44–7.53 (m, 5H, Ph); 7.57 (s, 1H, =CH); 7.63–7.66 (m, 2H, Ph); 7.98–8.01 (m, 2H, Ph); 9.47 (br s, 1H, OH).

Ethyl (*E*)-3-(dimethylamino)-2-{(Z)-4-[(dimethylamino)methylene]-4,5-dihydro-5-oxo-1*H*-pyrazol-3-yl}propenoate (8)

A mixture of ethyl (*Z*)-2-{4-[(dimethylamino)methylene]-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl}acetate (**3**) (225 mg, 1 mmol) DMFDMA (0.5 mL) and DMF (2 mL) was heated at reflux temperature for 1.5 h. Solvent was evaporated *in vacuo*, EtOH (~2 mL) was added to the residue and cooled to -30°C. After 12 h yellow crystals were filtered off. Yield: 70 % (197 mg). mp 212–215°C (toluene/EtOH). *Anal*. Calcd for $C_{13}H_{20}N_4O_3$ (280.32): C 55.70; H 7.19; N 19.99; Found: C 55.85; H 7.35; N 19.76. IR (cm^{-1}): 3100, 2950, 1690, 1670, 1600, 1530, 1430, 1390, 1310, 1210, 1130, 1070, 1060, 950, 820, 770, 690, 540. ^{1}H NMR ($CDCl_3$): δ 1.19 (t, 3H, *J* = 7.0, OCH_2CH_3); 2.86 (s, 6H, NMe_2); 3.24 (s, 3H, NMe); 3.89 (s, 3H, NMe); 4.13 (br s, 2H, OCH_2CH_3); 6.89 (s, 1H, =CH); 7.67 (s, 1H, =CH); 8.54 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 15.0; 43.6; 48.1; 59.8; 88.4; 100.5; 151.2; 153.0; 155.4; 165.6; 169.9. $^3J_{COOEt\text{-}H}$ = 5 Hz. $^3J_{C(4)\text{-}H}$ = 8 Hz.

Synthesis of ethyl 3,5-dihydro-3-oxo-2*H*-pyrazolo[4,3-*c*]pyridine-7-carboxylates (10a–c):

To a solution of ethyl (*E*)-3-(dimethylamino)-2-{(Z)-4-[(dimethylamino)methylidene]-5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**8**) (140mg, 0.5 mmol) in water (2 mL) was added water solution of amine (0.5 mmol in 1 mL) with hydrochloric acid (1 equiv.) and the solution left at rt for 12 h. Product was filtered off and recrystallised from appropriate solvent.

Ethyl 3,5-dihydro-5-methyl-3-oxo-2*H*-pyrazolo[4,3-*c*]pyridine-7-carboxylate (10a)

From **8** and methylamine hydrochloride (**9a**) (34 mg, 0.5 mmol). Yield: 29% (32 mg). mp 307–309°C (EtOH). *Anal*. Calcd for $C_{10}H_{11}N_3O_3$ (221.21): C 54.29; H 5.01; N 19.00. Found: C 54.06; H 5.10; N 18.85. IR (cm^{-1}): 3400, 3290, 2990, 1720, 1640, 1620, 1530, 1310, 1200, 1140, 1030, 980, 790, 750, 720, 660, 590, 550, 490. ^{1}H NMR (DMSO-d_6): δ 1.30 (t, 3H, *J* = 7.1, OCH_2CH_3); 3.83 (s, 3H, NMe); 4.30 (q, 2H, *J* = 7.1, OCH_2CH_3); 8.07 (d, 1H, *J* = 1.5, 4–H); 8.45 (d, 1H, *J* = 1.5, 6–H); 11.43 (br s, 1H, NH).

Ethyl 5-(cyanomethyl)-3,5-dihydro-3-oxo-2*H*-pyrazolo[4,3-*c*]pyridine-7-carboxylate (10b)

From **8** and aminoacetonitrile hydrochloride (**9b**) (46 mg, 0.5 mmol). Yield: 75% (92 mg). mp >350°C (EtOH). *Anal*. Calcd for $C_{11}H_{10}N_4O_3$ (246.22): C 53.66; H 4.09; N 22.75. Found: C 53.33; H 4.23; N 22.67. IR (cm^{-1}): 3100, 2990, 1920, 1730, 1660, 1500, 1390, 1310, 1200, 1130, 1020, 780, 750, 600, 580, 490. ^{1}H NMR (DMSO-d_6): δ 1.31 (t, 3H, *J* = 7.1, OCH_2CH_3); 4.32 (q, 2H, *J* = 7.1, OCH_2CH_3); 5.36 (s, 2H, CH_2); 8.25 (d, 1H, *J* = 1.6, 4–H); 8.56 (d, 1H, *J* = 1.6, 6–H); 11.57 (br s, 1H, NH).

Ethyl 3,5-dihydro-3-oxo-5-(quinolin-3-yl)- 2*H*-pyrazolo[4,3-*c*]pyridine-7-carboxylate (10c)

From **8** and 3-aminoquinoline (**9c**) (72 mg, 0.5 mmol). Yield: 78% (130 mg). mp 302–304°C (suspended in toluene). *Anal*. Calcd for $C_{18}H_{14}N_4O_3$ (334.33): C 64.66; H 4.22; N 16.76. Found: C 64.39; H 4.14; N 16.64. IR (cm^{-1}): 3640, 3120, 1720, 1660, 1630, 1530, 1330, 1310, 1200, 1130, 1040, 920, 790, 770, 630, 550, 490. ^{1}H NMR (DMSO-d_6): δ 1.32 (t, 3H, J = 7.1, OCH_2CH_3); 4.34 (q, 2H, J = 7.1, OCH_2CH_3); 7.72–7.78 (m, 1H, quinoline); 7.86–7.91 (m, 1H, quinoline); 8.09–8.16 (m, 2H, quinoline); 8.39 (d, 1H, J = 1.6, 4–H); 8.79 (d, 1H, J = 2.6, 4-H-quinoline); 8.88 (d, 1H, J = 1.6, 6–H); 9.22 (d, 1H, J = 2.6, 2-H-quinoline); 11.64 (br s, 1H, NH).

Ethyl (7*S,8*R**)-2,3,5,6,7,8-hexahydro-7-methoxy-5,6-dimethyl-3-oxo-pyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (12a)**

A mixture of ethyl (*E*)-3-(dimethylamino)-2-{(Z)-4-[(dimethylamino)methylidene]-4,5-dihydro-5-oxo-1*H*-pyrazol-3-yl}propenoate (**8**) (140mg, 0.5 mmol) and *N*,*N*'-dimethylhydrazine hydrochloride (**11**) (44 mg, 0.5 mmol) in MeOH (2 mL) was heated at reflux temperature for 5.5 h. After cooling to rt product precipitates from reaction mixture. White crystals were filtered off and recrystallised from MeOH. Yield: 29% (41 mg). mp 216–218°C. *Anal.* Calcd for $C_{12}H_{18}N_4O_4$ (282.30): C 51.06; H 6.43; N 19.85. Found: C 51.07; H 6.49; N 20.01. IR (cm^{-1}): 3150, 2990, 1730, 1670, 1600, 1380, 1310, 1180, 1110, 1030, 830, 760, 600, 540. ^{1}H NMR (DMSO-d_6): δ 1.18 (t, 3H, J = 7.1, OCH_2CH_3); 2.51 (s, 3H, NMe); 3.29 (s, 3H, NMe); 3.41 (s, 3H, OMe); 3.91 (d, 1H, J = 10.2, 7–H); 4.05 (dq, 1H, J = 10.9, 7.1, OCH_2CH_3); 4.15 (dq, 1H, J = 10.9, 7.1, OCH_2CH_3); 4.51 (d, 1H, J = 10.2, 8–H); 7.68 (s, 1H, 4–H); 10.77 (s, 1H, NH).

Ethyl (7*S,8*R**)-7-Ethoxy-2,3,5,6,7,8-hexahydro-5,6-dimethyl-3-oxo-pyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (12b)**

A mixture of ethyl (*E*)-3-(dimethylamino)-2-{(Z)-4-[(dimethylamino)methylidene]-4,5-dihydro-5-oxo-1*H*-pyrazol-3-yl}acrylate (**8**) (140mg, 0.5 mmol) and *N*,*N*'-dimethylhydrazine hydrochloride (**11**) (44 mg, 0.5 mmol) in EtOH (2 mL) was heated at reflux temperature for 5.5 h. After cooling to rt product precipitates from reaction mixture. White crystals were filtered off and recrystallised from EtOH. Yield: 28% (42 mg). mp 214–217°C. *Anal.* Calcd for $C_{13}H_{20}N_4O_4$ (296.32): C 52.69; H 6.80; N 18.91. Found: C 52.91; H 7.06; N 18.89. IR (cm^{-1}): 3150, 2990, 1740, 1670, 1600, 1380, 1180, 1110, 1020, 830, 760, 600. ^{1}H NMR (DMSO-d_6): δ 1.07 (t, 3H, J = 7.1, OCH_2CH_3); 1.18 (t, 3H, J = 7.1, OCH_2CH_3); 2.52 (s, 3H, NMe); 3.39 (s, 3H, NMe); 3.37–3.47 (m, 1H, OCH_2CH_3); 3.74 (dq, 1H, J = 17.2, 7.1, OCH_2CH_3); 3.91 (d,

1H, J = 10.2, 7–H); 4.07 (dq, 1H, J = 11.0, 7.2, OCH_2CH$_3$); 4.13 (dq, 1H, J = 11.0, 7.2, OCH_2CH$_3$); 4.62 (d, 1H, J = 10.2, 8–H); 7.67 (s, 1H, 4–H); 10.76 (s, 1H, NH).

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REFERENCES

1 B. Stanovnik and J. Svete, *Synlett*, 2000, 1077.

2 B. Stanovnik and J. Svete, *Chem. Rev.*, 2004, **104**, 2433.

3 B. Stanovnik and J. Svete, *Targets in Heterocyclic Systems*, 2000, Vol. **4**, p. 105.

4 L. Selič, R. Jakše, K. Lampič, L. Golič, S. Golič Grdadolnik, and B. Stanovnik, *Helv. Chim. Acta*, 2000, **83**, 2802.

5 L. Selič and B. Stanovnik, *Tetrahedron*, 2001, **57**, 3159.

6 R. Jakše, V. Krošelj, S. Rečnik, G. Soršak, J. Svete, B. Stanovnik, and S. Golič Grdadolnik, *Z. Naturforsch.*, 2002, **57b**, 453.

7 L. Selič, S. Rečnik, and B. Stanovnik, *Heterocycles*, 2002, **58**, 577.

8 R. Jakše, J. Svete, and B. Stanovnik, A. Golobič, *Tetrahedron*, 2004, **60**, 4601.

9 Z. Časar, D. Bevk, J. Svete, and B. Stanovnik, *Tetrahedron*, 2005, **61**, 7508.

10 J. Wagger, D. Bevk, A. Meden, J. Svete, and B. Stanovnik, *Helv. Chim. Acta*, 2006, **89**, 240.

11 B. Stanovnik and J. Svete, *Mini-Reviews Org. Chem.*, 2005, **2**, 211, and references cited therein.

12 P. Čebašek, J. Wagger, D. Bevk, R. Jakše, J. Svete, and B. Stanovnik, *J. Comb. Chem.*, 2004, **6**, 356.

13 P. Čebašek, D. Bevk, S. Pirc, B. Stanovnik, and J. Svete, *J. Comb. Chem.*, 2006, **8**, 95.

14 Č. Malavašič, B. Brulc, P. Čebašek, G. Dachmann, N. Heine, D. Bevk, U. Grošelj, A. Meden, B. Stanovnik, and J. Svete, *J. Comb. Chem.*, 2007; in press.

15 D. Bevk, R. Jakše, J. Svete, A. Golobič, L. Golič, and B. Stanovnik, *Heterocycles*, 2003, **61**, 197.

16 D. Bevk, R. Jakše, A. Golobič, L. Golič, A. Meden, J. Svete, and B. Stanovnik, *Heterocycles*, 2004, **63**, 609.

17 D. Bevk, L. Golič, A. Golobič, J. Svete, and B. Stanovnik, *Heterocycles*, 2005, **66**, 207.

18 G. Taurand and J. Streith, *Tetrahedron Lett.*, 1972, 3575.

19 G. Kiehl, J. Streith, and G. Taurand, *Tetrahedron*, 1974, **30**, 2851.

20 P. Gesche, F. Klinger, J. Streith, and H. Strub, *Tetrahedron Lett.*, 1980, **21**, 4507.

21 P. Gesche, F. Klinger, W. Müller, J. Streith, H. Strub, and R. Sustmann, *Chem. Ber.*, 1985, **118**, 4682.

22 B. Stanovnik, *Tetrahedron*, 1991, **47**, 2925.

23 B. Jelen, A. Štimac, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.*, 1991, **28**, 369.

24 S. F. Vasilevsky, E. V. Mshvidobadze, V. I. Mamatyuk, G. V. Romanenko, and J. Elguero, *Tetrahedron Lett.*, 2005, **46**, 4457.

25 D. Bevk, U. Grošelj, A. Meden, J. Svete, and B. Stanovnik, *Tetrahedron*, 2006, **62**, 8126.

26 C. Bülow and H. Göller, *Ber.*, 1911, **44**, 2835.