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Synthesis of substituted 2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*]-[1,2]diazepine-8-carboxylates

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Dedicated to Professor Dr. Miha Tišler, Professor Emeritus of the University of Ljubljana, on the occasion of his 80th birthday

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

1. Introduction

There are many methods described in the literature for the synthesis of the pyrazole ring. Two of the most important methods for practical purposes are the reaction between hydrazines and β-difunctional compounds, and 1,3-dipolar cycloadditions. Other methods are alkylation at the 4-position of 1-substituted pyrazoles, and alkylation at the 5-position. Only a few reports describe introduction of an aryl or heteroaryl group into the pyrazole ring under Pd(0) catalysis.[1–8] *N*-Substituted pyrazole dicarboxylate and bicyclic derivatives such as pyrazolo-oxazine, pyrazolo-pyrazine, pyrazolo-oxazepine and pyrazolo-diazepine[9,10] and other fused pyrazoles[11,12] are prospective pharmaceuticals and agrochemicals.

In connection with our interest in alkyl 3-dimethylaminopropenoates and related enaminones as building blocks for the preparation of various heterocyclic systems and functionalised heterocycles, such as heteroaryl-substituted α-amino- and α-hydroxy acid derivatives, fused pyridinones, pyrimidones, pyranones and related systems,[13–15] including some naturally occurring alkaloids,[16–21] we reported recently some transformations of alkyl [(*Z*)-4-dimethylaminomethylidene-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl]acetate with *N*-nucleophiles into 2*H*-pyrazolo[4,3-*c*]pyridine-7-carboxylates[22,23] and (substituted pyrazol-3-yl)pyrimidinones and (pyrazol-3-yl)pyranones.[24]

While pyrazolo[3,4-*d*][1,2]diazepines have been obtained by cycloaddition of 2-diazopropane to 1,2-diazepine derivatives,[25–30] isomeric pyrazolo[4,3-*d*][1,2]diazepines are mentioned in the literature only once. In the heterocyclisation of 5-acetylenylpyrazole-4-carboxylic acid hydrazides under the influence of CuCl an unexpected formation of a diazepinone and dehydrodimerisation into the corresponding bis(pyrazolo[4,3-*d*][1,2]diazepinone) have been described.[31]

2. Results and discussion

Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)-methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}-propenoate (**1**) was prepared from ethyl (5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)acetate according to the procedure described in the literature.[23] In the reaction of **1** with hydrazine or monosubstituted hydrazines the corresponding 5-amino-substituted pyrazolo[4,3-*c*]pyridine-7-carboxylates were formed.[23]

When compound **1** was reacted with 1,2-disubstituted hydrazines **2** in acetonitrile cyclisation did not take place to give compound **3**. However, when the reaction was carried out in an alcohol, compounds **4** were formed (Scheme 1). The mechanism of the formation of **4** is unknown so far. However, since the cyclisation in non-hydroxylic solvent did not produce the pyrazolo[4,3-*d*][1,2]diazepine derivatives **3**, the addition of alcohol to the $C_7{=}C_8$ double bond in compound **3** seems to be very unlikely. The possible explanation is therefore that either an aminal **5** or enol ether **6** are formed as intermediates in the presence of an alcohol. In the

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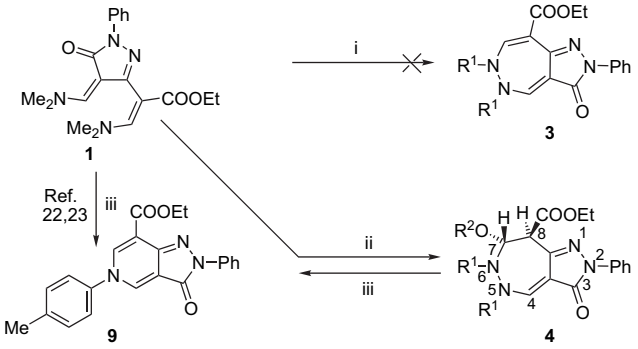
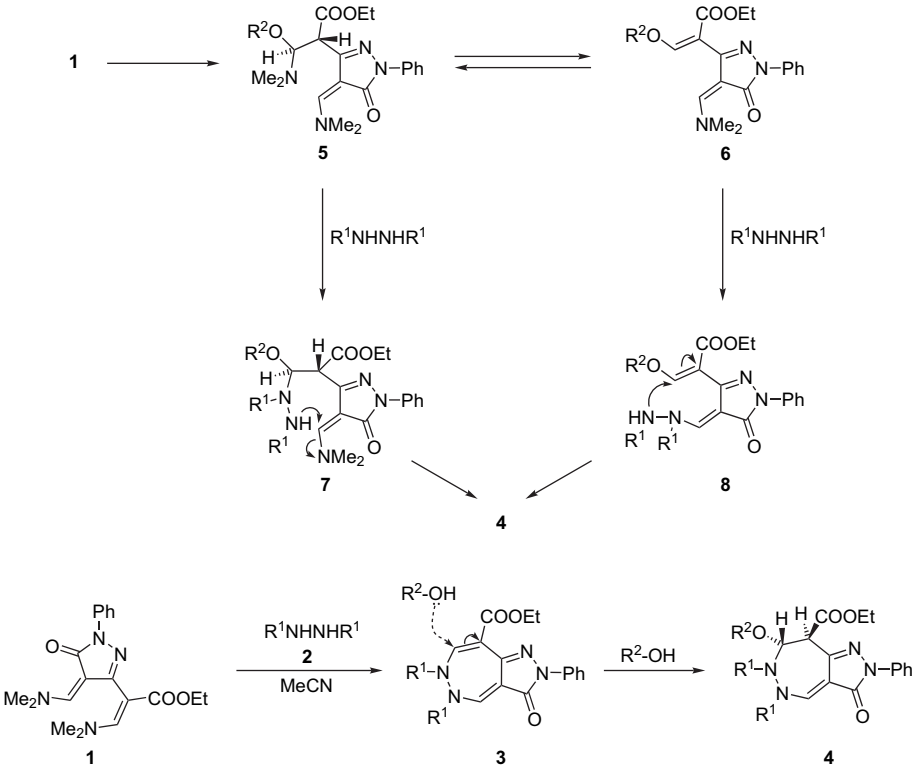


Compound	R^1	R^2	Reaction time [h]	Yield [%]
4a	Me	Me	1.5	74
4b	Me	Et	1.5	81
4c	Me	*n*-Pr	4	83
4d	Me	*i*-Pr	4	41
4e	Me	*n*-Bu	2	67
4f	Me	*t*-Bu	3	89
4g	Me	Allyl	7.5	59
4h	Et	Me	7	51
4i	Et	Et	7	61
4j	Et	*n*-Pr	7	40
4k	Et	*i*-Pr	7	47

Scheme 1. Reagents and reaction conditions: (i) R^1NHNHR^1 (**2a** R^1=Me; **2b** R^1=Et), MeCN, reflux; (ii) R^1NHNHR^1 (**2a** R^1=Me; **2b** R^1=Et), R^2OH, reflux; (iii) 4-Me-C_6H_4-NH_2×HCl, MeOH, reflux.



Scheme 2.

reaction with 1,2-disubstituted hydrazine the corresponding intermediates **7** or **8** are formed, which cyclise to give the final products **4** (Scheme 2).

Compound **4a** was transformed using 4-methylaniline into 2*H*-pyrazolo[4,3-*c*]pyridine-7-carboxylate derivative **9** identical with the compound prepared previously.[22,23]

3. Structure determination

The structures of all new compounds were determined by spectroscopic methods (IR, ^{1}H NMR; in the case of **4b** also by ^{13}C and HMBC) and by elemental analyses. Physical and spectral data for compound **5** were in agreement with the literature data.[22,23] Compounds **4** were obtained as pure

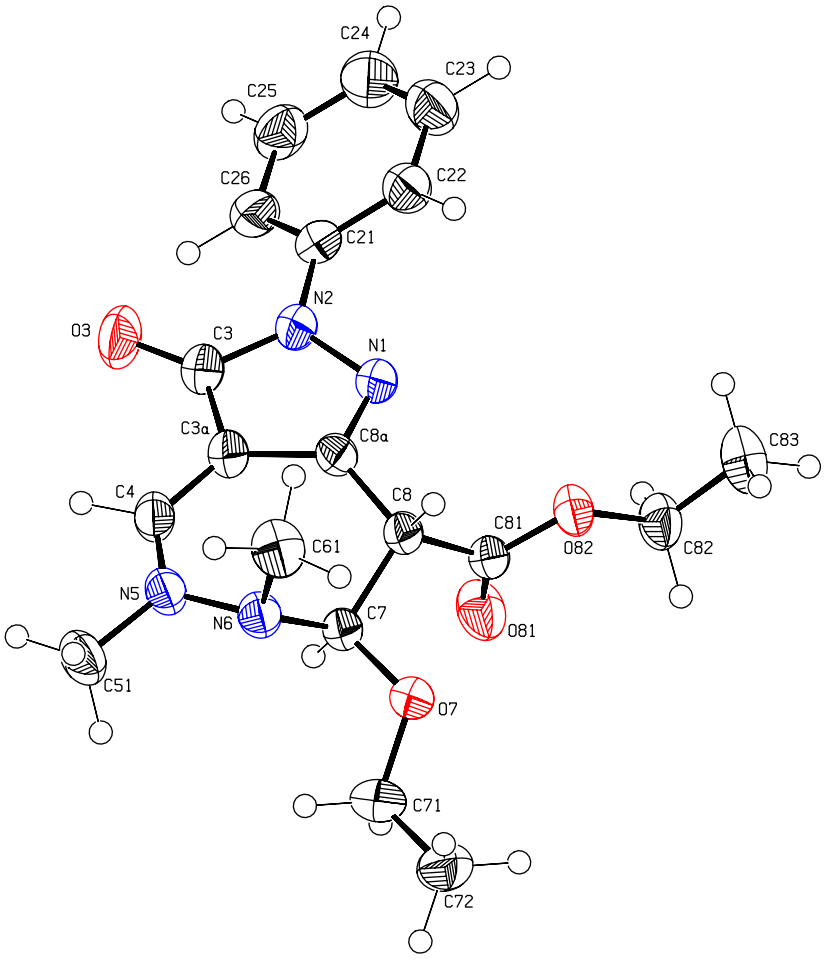


Figure 1.

diastereomers. The *anti*-orientation of the 7-alkoxy and 8-ester groups in compound **4** was established on the basis of the vicinal coupling constant, $J_{7\text{-H},8\text{-H}} \approx 10$ Hz. The position of the 7-alkoxy group was established from the HMBC spectrum for compound **4b**. The structure of compound **4b** was confirmed by X-ray diffraction analysis (Fig. 1).

4. Conclusion

Substituted 2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylates **4** were obtained from ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**), via substitution of both dimethylamino groups with 1,2-dialkylhydrazines **2**, and subsequent addition of alcohol to $C_7{=}C_8$ double bond. Reaction of pyrazolo[4,3-*d*][1,2]diazepine-8-carboxylates **4** with an amine resulted in conversion into pyrazolo[4,3-*c*]pyridine-7-carboxylate **9**.

5. Experimental

5.1. General

Melting points were determined on a Kofler micro hot stage. The ^{1}H NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H, and 75.5 MHz for ^{13}C nucleus, using $CDCl_3$ as solvents and TMS as the internal standard. IR spectra were recorded on a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyser 2400 II. 1,2-Dimethylhydrazine hydrochloride (**2a**), 1,2-diethylhydrazine hydrochloride (**2b**), and 4-methylaniline hydrochloride are commercially available (Fluka AG). Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) was prepared according to the literature procedure.[23]

5.2. General procedure for the preparation of ethyl (7*R**,8*S**)-5,6-dimethyl-7-alkoxy-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylates 4a–g

Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)-methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-dimethylhydrazine hydrochloride (**2a**) (44 mg, 0.5 mmol) in alcohol (2 mL) were heated at the reflux temperature for 7 h. After cooling to −30 °C, the product precipitates, or water (2 mL) is added and the product gradually precipitates. The crystals were filtered off and crystallised from alcohol/water mixture.

5.2.1. Ethyl (7*R,8*S**)-7-methoxy-5,6-dimethyl-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4a).** Ethyl (2*E*)-3-(dimethylamino)-

2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-dimethylhydrazine hydrochloride (**2a**) (44 mg, 0.5 mmol) in methanol (3 mL) were heated at the reflux temperature for 1.5 h. After cooling, the product precipitates, and the crystals were collected by filtration and crystallised from methanol. Yield: 88 mg (74%) of yellow crystals. Mp: 225–229 °C. IR (KBr) ν_{max}: 2980, 1730, 1670, 1610, 1490, 1650, 1320, 1100, 830, 750, 650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (3H, t, J=7.1 Hz, OCH_2CH_3), 2.65 (3H, s, NMe), 3.41 (3H, s, NMe), 3.44 (3H, s, OMe), 4.10 (1H, d, J=10.1 Hz, 7-H), 4.24 (1H, dq, J=10.8, 7.1 Hz, OCH_2CH_3), 4.35 (1H, dq, J=10.8, 7.1 Hz, OCH_2CH_3), 4.62 (1H, d, J=10.1 Hz, 8-H), 7.09–7.14 (1H, m, Ph), 7.32–7.38 (2H, m, Ph), 7.62 (1H, s, 4-H), 7.94–7.98 (2H, m, Ph). Anal. Calcd for $C_{18}H_{22}N_4O_4$ (358.39): C 60.32; H 6.19; N 15.63. Found: C 60.12; H 6.37; N 15.58.

5.2.2. Ethyl (7*R,8*S**)-7-ethoxy-5,6-dimethyl-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4b).** Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-dimethylhydrazine hydrochloride (**2a**) (44 mg, 0.5 mmol) in ethanol (3 mL) were heated under reflux temperature for 1.5 h. After cooling, the product precipitates, and the crystals were collected by filtration and crystallised from methanol. Yield: 100 mg (81%) of yellow crystals. Mp: 196–199 °C. IR (KBr) ν_{max}: 2980, 1730, 1680, 1610, 1350, 1190, 1100, 840, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.33 (3H, t, J=7.1 Hz, OCH_2CH_3), 2.65 (3H, s, NMe), 3.40 (3H, s, NMe), 3.48 (1H, dd, J=9.6, 7.1 Hz, OCH_2CH_3), 3.81 (1H, dd, J=9.5, 7.1 Hz, OCH_2CH_3), 4.10 (1H, d, J=10.1 Hz, 7-H), 4.25 (1H, dq, J=10.8, 7.1 Hz, OCH_2CH_3), 4.32 (1H, dq, J=9.6, 7.1 Hz, OCH_2CH_3), 4.72 (1H, d, J=10.1 Hz, 8-H), 7.08–7.14 (1H, m, Ph), 7.32–7.37 (2H, m, Ph), 7.62 (1H, s, 4-H), 7.95–7.98 (2H, m, Ph). ^{13}C NMR ($CDCl_3$): 14.7, 15.0, 29.6, 44.7, 50.2, 61.7, 64.3, 90.7, 100.3, 119.2, 124.6, 128.9, 139.7, 143.0, 148.9, 165.4, 165.4, 169.5. Anal. Calcd for $C_{19}H_{24}N_4O_4$ (372.42): C 61.28; H 6.49; N 15.04. Found: C 61.30; H 6.58; N 15.06.

5.2.3. Ethyl (7*R,8*S**)-7-*n*-propoxy-5,6-dimethyl-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4c).** Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-dimethylhydrazine hydrochloride (**2a**) (44 mg, 0.5 mmol) in *n*-propanol (3 mL) were heated at the reflux temperature for 4 h. After cooling, the product precipitates, and the crystals were collected by filtration and crystallised from *n*-propanol/water mixture. Yield: 107 mg (83%) of yellow crystals. Mp: 155–157 °C. IR (KBr) ν_{max}: 1720, 1660, 1610, 1360, 1330, 1190, 1100, 840, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (3H, t, J=7.3 Hz, $CH_2CH_2CH_3$), 1.32 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.58 (2H, deg tq, J=7.3 Hz, $CH_2CH_2CH_3$), 2.66 (3H, s, NMe), 3.36 (1H, dt, J=9.3, 6.5 Hz, $CH_2CH_2CH_3$), 3.44 (3H, s, NMe), 3.72 (1H, dt, J=9.3, 6.5 Hz, $CH_2CH_2CH_3$), 4.11 (1H, d, J=10.1 Hz, 7-H), 4.25 (1H, dq, J=10.8, 7.1 Hz, OCH_2CH_3), 4.31 (1H, dq, J=10.7, 7.1 Hz, OCH_2CH_3), 4.70 (1H, d, J=10.1 Hz, 8-H), 7.09–7.14 (1H, m, Ph), 7.32–7.38 (2H, m, Ph), 7.66 (1H, s, 4-H), 7.94–7.97 (2H, m, Ph). Anal. Calcd for $C_{20}H_{26}N_4O_4$ (386.44): C 62.16; H 6.78; N 14.50. Found: C 62.42; H 7.01; N 14.56.

5.2.4. Ethyl (7*R,8*S**)-7-*i*-propoxy-5,6-dimethyl-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4d).** Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-dimethylhydrazine hydrochloride (**2a**) (44 mg, 0.5 mmol) in 2-propanol (3 mL) were heated at the reflux temperature for 4 h. After cooling, water (~2 mL) was added. The precipitate was filtered off and crystallised from 2-propanol/water mixture. Yield: 53 mg (41%) yellow crystals. Mp: 192–194 °C. IR (KBr) ν_{max}: 1750, 1680, 1630, 1350, 1240, 1090, 1060, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (3H, d, J=6.1 Hz, CH_3CHCH_3), 1.19 (3H, d, J=6.3 Hz, CH_3CHCH_3), 1.32 (3H, t, J=7.1 Hz, OCH_2CH_3), 2.66 (3H, s, NMe), 3.42 (3H, s, NMe), 3.92 (1H, septet, J=6.3 Hz, CH_3CHCH_3), 4.09 (1H, d, J=10.1 Hz, 7-H), 4.27 (2H, q, J=7.1 Hz, OCH_2CH_3), 4.80 (1H, d, J=10.1 Hz, 8-H), 7.08–7.14 (1H, m, Ph), 7.31–7.38 (2H, m, Ph), 7.62 (1H, s, 4-H), 7.94–7.98 (2H, m, Ph). Anal. Calcd for $C_{20}H_{26}N_4O_4$ (386.44): C 62.16; H 6.78; N 14.50. Found: C 62.36; H 6.98; N 14.53.

5.2.5. Ethyl (7*R,8*S**)-7-*n*-butoxy-5,6-dimethyl-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4e).** Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-dimethylhydrazine hydrochloride (**2a**) (44 mg, 0.5 mmol) in 1-butanol (2 mL) were heated at the reflux temperature for 2 h. Solvent was removed in vacuo and the residue was crystallised from ethanol/water mixture. Yield: 90 mg (67%) of yellow crystals. Mp: 153–154 °C. IR (KBr) ν_{max}: 1730, 1670, 1610, 1360, 1110, 750 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (3H, t, J=7.3 Hz, $CH_2CH_2CH_2CH_3$), 1.32 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.32–1.42 (2H, m, $CH_2CH_2CH_2CH_3$), 1.54 (2H, quintet, J=7.3 Hz, $CH_2CH_2CH_2CH_3$), 2.65 (3H, s, NMe), 3.39 (1H, dt, J=9.4, 6.3 Hz, $CH_2CH_2CH_2CH_3$), 3.45 (3H, s, NMe), 3.76 (1H, dt, J=9.4, 6.4 Hz, $CH_2CH_2CH_2CH_3$), 4.11 (1H, d, J=10.1 Hz, 7-H), 4.24 (1H, dq, J=10.8, 7.1 Hz, OCH_2CH_3), 4.30 (1H, dq, J=10.8, 7.2 Hz, OCH_2CH_3), 4.70 (1H, d, J=10.1 Hz, 8-H), 7.09–7.14 (1H, m, Ph), 7.32–7.37 (2H, m, Ph), 7.68 (1H, s, 4-H), 7.93–7.97 (2H, m, Ph). Anal. Calcd for $C_{21}H_{28}N_4O_4$ (400.47): C 62.98; H 7.05; N 13.99. Found: C 62.77; H 7.17; N 13.91.

5.2.6. Ethyl (7*R,8*S**)-7-*tert*-butoxy-5,6-dimethyl-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4f).** Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-dimethylhydrazine hydrochloride (**2a**) (44 mg, 0.5 mmol) in *tert*-butanol (3 mL) were heated at the reflux temperature for 3 h. Solvent was removed in vacuo and the residue was crystallised from ethanol/water mixture. Yield: 119 mg (89%) of yellow crystals. Mp: 166–168 °C. IR (KBr) ν_{max}: 1740, 1680, 1620, 1500, 1350, 1240, 1070, 840, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (9H, s, *t*-Bu),

1.32 (3H, t, J=7.1 Hz, OCH_2CH_3), 2.66 (3H, s, NMe), 3.42 (3H, s, NMe), 4.12 (1H, d, J=9.8 Hz, 7-H), 4.23 (1H, dq, J=10.8, 7.1 Hz, OCH_2CH_3), 4.28 (1H, dq, J=10.8, 7.1 Hz, OCH_2CH_3), 5.06 (1H, d, J=9.8 Hz, 8-H), 7.08–7.14 (1H, m, Ph), 7.31–7.38 (2H, m, Ph), 7.61 (1H, s, 4-H), 7.93–7.98 (2H, m, Ph). Anal. Calcd for $C_{21}H_{28}N_4O_4$ (400.47): C 62.98; H 7.05; N 13.99. Found: C 62.99; H 7.26; N 13.96.

5.2.7. Ethyl (7*R,8*S**)-7-allyloxy-5,6-dimethyl-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4g).** Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-dimethylhydrazine hydrochloride (**2a**) (44 mg, 0.5 mmol) in allyl alcohol (2 mL) were heated at the reflux temperature for 7.5 h. Water (2 mL) was added, the product gradually crystallises. Crystals were filtered off and crystallised from allyl alcohol/water mixture. Yield: 113 mg (59%). Mp: 175–178 °C. IR (KBr) ν_{max}: 1730, 1680, 1610, 1590, 1490, 1350, 1330, 1180, 1100, 830, 760, 520 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (3H, t, J=7.1 Hz, OCH_2CH_3), 2.66 (3H, s, NMe), 3.41 (3H, s, NMe), 4.04 (1H, deg dddd, J=12.8, 6.6, 1.3 Hz, $CH_2CH{=}CH_2$), 4.14 (1H, d, J=10.1 Hz, 7-H), 4.19–4.37 (3H, m, $CH_2CH{=}CH_2$, OCH_2CH_3), 4.79 (1H, d, J=10.1 Hz, 8-H), 5.20–5.31 (2H, m, $CH_2CH{=}CH_2$), 5.86 (1H, dddd, J=17.0, 10.4, 6.5, 5.0 Hz, $CH_2CH{=}CH_2$), 7.09–7.14 (1H, m, Ph), 7.32–7.37 (2H, m, Ph), 7.61 (1H, s, 4-H), 7.94–7.97 (2H, m, Ph). Anal. Calcd for $C_{20}H_{24}N_4O_4$ (384.43): C 62.49; H 6.26; N 14.57. Found: C 62.75; H 6.41; N 14.74.

5.3. General procedure for the preparation of ethyl (7*R**,8*S**)-5,6-diethyl-7-alkoxy-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylates 4h–k

Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)-methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-diethylhydrazine hydrochloride (**2b**) (44 mg, 0.5 mmol) in alcohol (2 mL) were heated at the reflux temperature for 7 h. After cooling to −30 °C, the product precipitates, or water (2 mL) is added and the product gradually precipitates. The crystals were filtered off and crystallised from alcohol/water mixture.

5.3.1. Ethyl (7*R,8*S**)-5,6-diethyl-7-methoxy-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4h).** In methanol. Yield: 65 mg (51%) of yellow crystals. Mp: 144–147 °C (methanol/water); IR (KBr) ν_{max}: 3440, 2980, 1730, 1680, 1600, 1480, 1350, 1320, 1120, 820, 760, 690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.34 (3H, t, J=7.1 Hz, NCH_2CH_3), 1.48 (3H, t, J=7.2 Hz, OCH_2CH_3), 3.08 (2H, dq, J=2.4, 7.2 Hz, OCH_2CH_3), 3.50 (3H, s, OMe), 3.63–3.77 (2H, m, NCH_2CH_3), 4.12 (1H, d, J=10.2 Hz, 7-H), 4.24 (1H, qd, J=7.1, 10.8 Hz, OCH_2CH_3), 4.35 (1H, qd, J=7.1, 10.8 Hz, OCH_2CH_3), 4.63 (1H, d, J=10.2 Hz, 8-H), 7.08–7.14 (1H, m, Ph), 7.32–7.38 (2H, m, Ph), 7.69 (1H, s, 4-H), 7.94–7.98 (2H, m, Ph). Anal. Calcd for $C_{20}H_{26}N_4O_4$ (386.44): C 62.16; H 6.78; N 14.50. Found: C 62.07; H 6.73; N 14.56.

5.3.2. Ethyl (7*R,8*S**)-5,6-diethyl-7-ethoxy-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4i).** In ethanol. Yield: 82 mg (61%) of yellow crystals. Mp: 144–146 °C (ethanol/water). IR (KBr) ν_{max}: 3440, 2980, 1730, 1680, 1600, 1480, 1350, 1320, 1080, 820, 760, 690, 580 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (3H, t, J=7.3 Hz, NCH_2CH_3), 1.21 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.33 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.46 (3H, t, J=7.2 Hz, OCH_2CH_3), 3.09 (2H, q, J=7.2 Hz, NCH_2CH_3), 3.54 (1H, dq, J=9.3, 7.0 Hz, NCH_2CH_3), 3.61–3.75 (2H, m, NCH_2CH_3), 3.96 (1H, dq, J=9.3, 7.1 Hz, OCH_2CH_3), 4.12 (1H, d, J=10.1 Hz, 7-H), 4.25 (1H, dq, J=10.8, 7.1 Hz, OCH_2CH_3), 7.32 (1H, dq, J=10.8, 7.1 Hz, OCH_2CH_3), 4.72 (1H, d, J=10.2 Hz, 8-H), 7.08–7.14 (1H, m, Ph), 7.31–7.38 (2H, m, Ph), 7.68 (1H, s, 4-H), 7.94–7.98 (2H, m, Ph). Anal. Calcd for $C_{21}H_{28}N_4O_4$ (400.47): C 62.98; H 7.05; N 13.99. Found: C 63.05; H 7.21; N 14.12.

5.3.3. Ethyl (7*R,8*S**)-5,6-diethyl-3-oxo-2-phenyl-7-propoxy-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4j).** In *n*-propanol. Yield: 55 mg (40%). Mp: 118–121 °C (*n*-propanol/water). IR (KBr) ν_{max}: 3440, 3000, 1730, 1670, 1590, 1350, 1320, 1180, 1120, 1080, 1020, 820, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (3H, t, J=7.4 Hz, $OCH_2CH_2CH_3$), 1.18 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.33 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.46 (3H, t, J=7.2 Hz, OCH_2CH_3), 1.60 (2H, deg tq, J=7.4 Hz, $OCH_2CH_2CH_3$), 3.09 (2H, q, J=7.2 Hz, NCH_2CH_3), 3.41 (1H, dt, J=9.0, 6.4 Hz, $OCH_2CH_2CH_3$), 3.64 (1H, dt, J=20.8, 7.1 Hz, NCH_2CH_3), 3.71 (1H, dt, J=20.8, 7.1 Hz, NCH_2CH_3), 3.87 (1H, dt, J=9.0, 6.4 Hz, $OCH_2CH_2CH_3$), 4.13 (1H, d, J=10.1 Hz, 7-H), 4.25 (1H, dq, J=11.1, 7.2 Hz, OCH_2CH_3), 4.31 (1H, dq, J=11.1, 7.2 Hz, OCH_2CH_3), 4.71 (1H, d, J=10.1 Hz, 8-H), 7.08–7.14 (1H, m, Ph), 7.32–7.37 (2H, m, Ph), 7.69 (1H, s, 4-H), 7.95–7.98 (2H, m, Ph). Anal. Calcd for $C_{22}H_{30}N_4O_4$ (414.50): C 63.75; H 7.30; N 13.52. Found: C 63.76; H 7.49; N 13.85.

5.3.4. Ethyl (7*R,8*S**)-5,6-diethyl-7-*i*-propoxy-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4k).** In *i*-propanol. Yield: 65 mg (47%) of yellow crystals. Mp: 184–186 °C (*i*-propanol/water). IR (KBr) ν_{max}: 3460, 2980, 1740, 1670, 1600, 1490, 1360, 1180, 1120, 1070, 1020, 830, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (3H, d, J=6.1 Hz, $OCH(CH_3)_2$), 1.18 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.22 (3H, d, J=6.3 Hz, $CH(CH_3)_2$), 1.32 (3H, t, J=7.1 Hz, NCH_2CH_3), 1.46 (3H, t, J=7.2 Hz, OCH_2CH_3), 3.10 (2H, q, J=7.2 Hz, NCH_2CH_3), 3.64 (1H, dq, J=20.9, 7.2 Hz, OCH_2CH_3), 3.72 (1H, dq, J=21.0, 7.2 Hz, OCH_2CH_3), 4.10 (1H, d, J=10.1 Hz, 7-H), 4.10 (1H, septet, J=6.1 Hz, $OCH(CH_3)_2$), 4.27 (2H, q, J=7.1 Hz, NCH_2CH_3), 4.80 (1H, d, J=10.1 Hz, 8-H), 7.08–7.14 (1H, m, Ph), 7.31–7.38 (2H, m, Ph), 7.69 (1H, s, 4-H), 7.94–7.98 (2H, m, Ph). Anal. Calcd for $C_{22}H_{30}N_4O_4$ (414.50): C 63.75; H 7.30; N 13.52. Found: C 63.66; H 7.47; N 13.56.

5.4. Ethyl 5-(4-methylphenyl)-3-oxo-2-phenyl-3,5-dihydro-2*H*-pyrazolo[4,3-*c*]pyridin-7-carboxylate (9)

Ethyl (7*R**,8*S**)-7-methoxy-5,6-dimethyl-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-

carboxylate (**4a**) (31 mg, 0.09 mmol) in 4-methylaniline hydrochloride (12 mg, 0.09 mmol) in methanol (3 mL) was heated at the reflux temperature for 12 h. After cooling to −30 °C, precipitate was filtered off. Product is identical to the product prepared from **1** and 4-methylaniline hydrochloride.[22,23] Yield: 12 mg (36%) of red crystals. Mp 233–235 °C (lit.[22,23] 233–235 °C) IR (KBr) ν_{max}: 1730, 1670, 1650, 1490, 1310, 1150, 790, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.48 (3H, t, J=7.2 Hz, OCH_2CH_3), 2.46 (3H, s, Me), 4.49 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.18–7.24 (1H, m, Ph), 7.32–7.47 (6H, m, 2Ph), 8.19 (1H, d, J=1.9 Hz, 4-H), 8.24–8.27 (2H, m, Ph), 8.35 (1H, d, J=1.5 Hz, 6-H).

5.5. X-ray structure determination

Single crystal X-ray diffraction data of compound **4b** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[32] DENZO and SCALEPACK[33] were used for indexing and scaling of the data. The structure was solved by means of SIR97.[34] Refinement was done using Xtal3.4[35] program package and the crystallographic plot was prepared by ORTEP III.[36] Crystal structure was refined on F values using the full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms were geometrically calculated and their positional and isotropic atomic displacement parameters were not refined. Absorption correction was not necessary. Regina[37] weighting scheme was used.

The crystallographic data for compound **4b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary material with the deposition number: CCDC 298823. These data can be obtained, free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

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