HETEROCYCLES, Vol. 66, 2005, pp. 207 – 218. © The Japan Institute of Heterocyclic Chemistry
Received, 16th March 2005, Accepted, 26th April, 2005, Published online, 28th April, 2005. COM-05-S(K)1

SYNTHESIS AND TRANSFORMATIONS OF ETHYL (2*E*)-3-*N,N*-DIMETHYLAMINO-2-(5-ETHOXY-1-PHENYL-1*H*-PYRAZOL-3-YL)PROPENOATE

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Dedicated to Dr. Kenji Koga, Emeritus Professor of Tokyo University

Abstract – The reaction of amines (**4a-g**) with ethyl (2*E*)-3-*N,N*-dimethylamino-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)propenoate (**3**), prepared in two steps from ethyl (4,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazol-3-yl)acetate (**1**), gave ethyl (2*E*)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-3-(substituted amino)propenoates (**5a-g**). The reaction of compound (**3**) with 2-aminopyridine (**4h**), 3 amino-1*H*-pyrazole (**4i**), 2*H*-pyran-2-one (**6a**), and 5,5-dimethylcyclohexane-1,3-dione (**6b**) afforded 3-(pyrazol-3-yl)pyridopyrimidinone (**7a**), 6-(pyrazol-3-yl)pyridopyrimidinone (**7b**), 3-(pyrazol-3-yl)pyranopyrandione (**7c**), and 3-(pyrazol-3-yl)-chromenedione (**7d**), respectively.

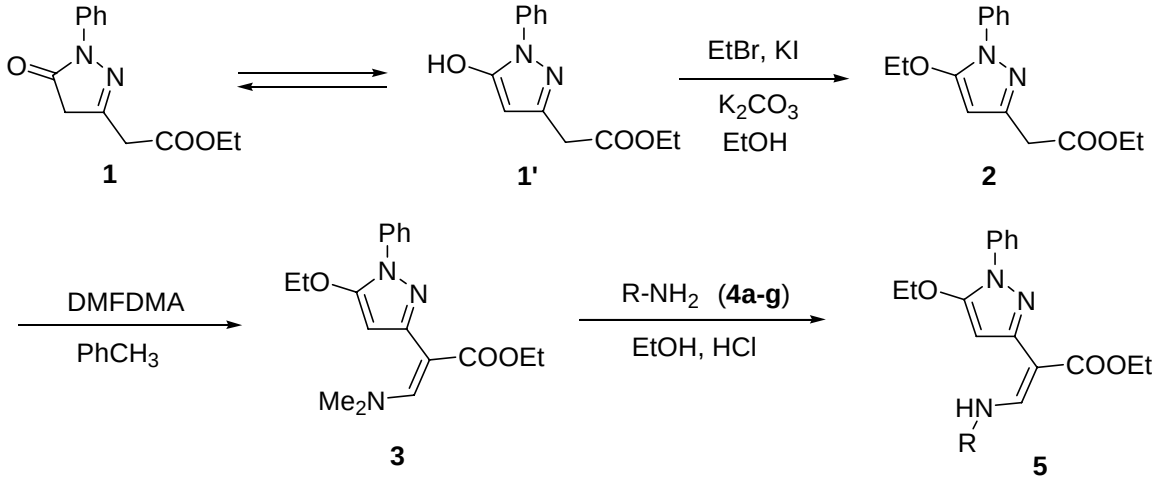
There are many methods for the synthesis of pyrazole ring construction described in the literature. Two most important methods for practical purposes are the reaction between hydrazines and β-difunctional compounds, and 1,3-dipolar cycloadditions. Both procedures are well documented.[1-6] Other methods are alkylation at 4-position of 1-substituted pyrazoles with alkyl halides which is achieved in the presence of aluminum trichloride, and alkylation at 5-position which can be achieved by lithiation followed by the reaction with *C*-electrophiles.[3] Only a few reports describe introduction of aryl or heteroaryl group into pyrazole ring under Pd(0) catalysis.[7,8] Recently, a novel and general approach of 5-aryl- and 5-heteroaryl-substituted 1-benzyloxypyrazoles by combining directed ortho- metallation/transmetallation and palladium catalyzed cross-coupling has been reported.[9]

Alkyl 3-dimethylaminopropenoates and related enaminones play an important role 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 pyridinones, pyrimidones, pyranones and related systems, which are the basic structures of many alkaloids and their synthetic derivatives exhibiting various biological activities.[10-12] Among others, application of various 3-dimethylamino-2-vinylaminopropenoates and dimethylaminomethylidene-substituted heterocycles as reagents for the preparation of aplysinopsins and its analogues,[13-16] and condensed indolyl pyrimidinones as meridianine analogues have been reported.[17]

Recently, we reported some transformations of alkyl [(*Z*)-4-dimethylaminomethylidene-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl]acetate with *N*- and *C*- nucleophiles into alkyl 4-(substituted amino)-methylidene- and (4-heteroarylmethylidene-4,5-dihydro-1*H*-pyrazol-3-yl)acetates followed by cyclization into 2*H*-pyrazolo[4,3-*c*]pyridine-7-carboxylates.[18,19]

In continuation of our research in this area, we now report on the preparation of ethyl (2*E*)-3-*N*,*N*-dimethylamino-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)propenoate (**3**) and its transformation with *N*- and *C*- nucleophiles into ethyl (2*E*)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-3-(substituted amino)propenoates (**5a-g**), fused pyrazol-3-ylpyrimidinones (**7a,b**) and fused pyrazol-3-ylpyranones (**7c,d**), respectively.

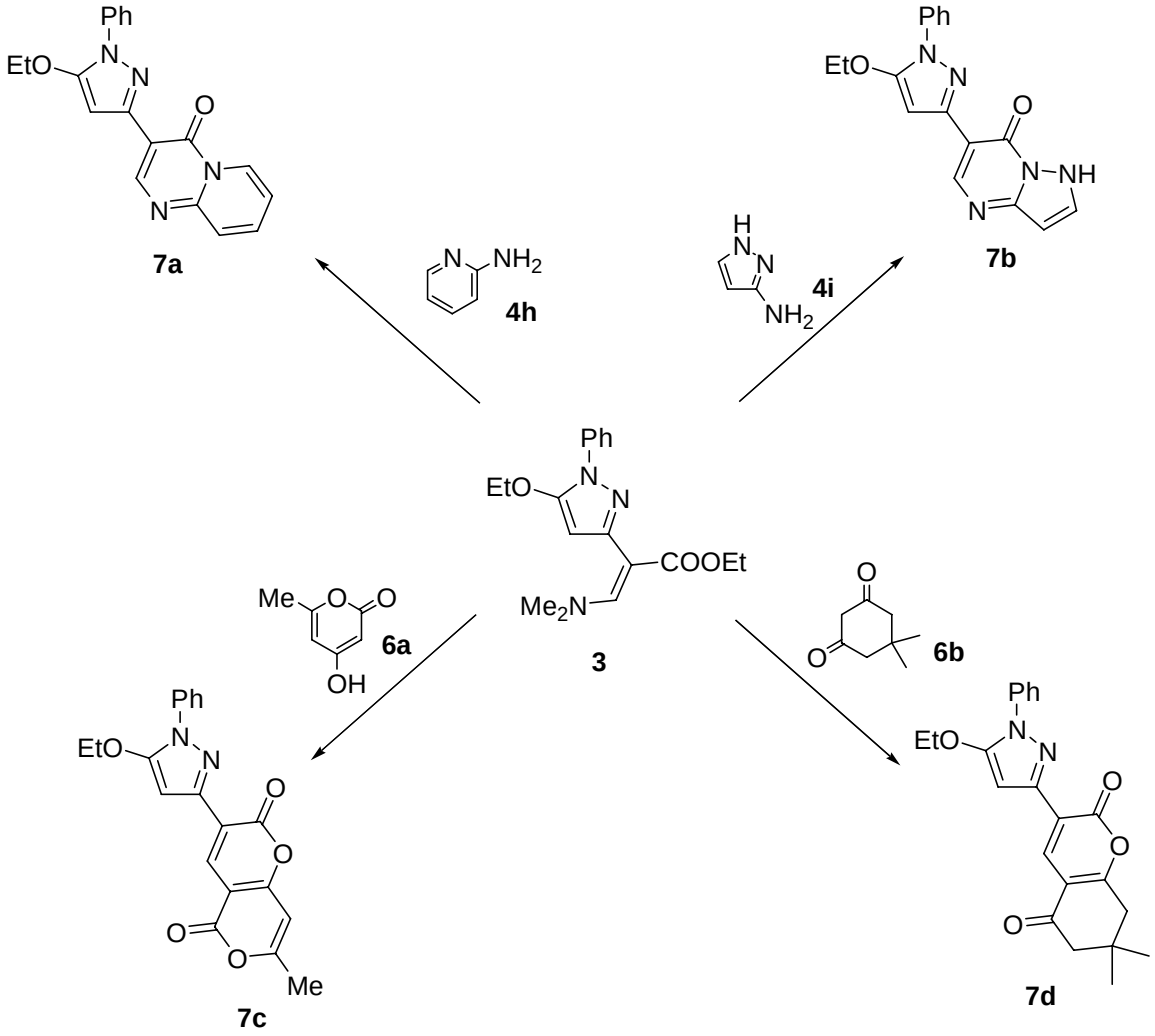


Reaction	**R**	Reaction	**R**
4a→5a	phenyl	**4e→5e**	-CH_2COOMe
4b→5b	4-methylphenyl	**4f→5f**	1*H*-indazol-3-yl
4c→5c	4-methoxyphenyl	**4g→5g**	5-methylisoxazol-3-yl
4d→5d	4-nitrophenyl		

Scheme 1.

Ethyl (2*E*)-3-dimethylamino-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)propenoate (**3**) was prepared in two steps from ethyl (4,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazol-3-yl)acetate[20] (**1**) by treatment with ethyl

bromide in ethanol under reflux to give ethyl 5-ethoxy-1-phenyl-1*H*-pyrazol-3-ylacetate (**2**), followed by treatment with *N*,*N*-dimethylformamide dimethylacetal (DMF DMA) in toluene under reflux. Compound (**3**) reacted with anilines (**4a-d**), methyl glycinate hydrochloride (**4e**), 3-amino-1*H*-indazole (**4f**), and 3-amino-5-methylisoxazole (**4g**) in ethanol in the presence of hydrochloric acid under reflux for 1–3 h to provide the corresponding ethyl (2*E*)-3-(arylamino)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)propenoates (**5a-d)**, ethyl (2*E*)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-3-(methoxycarbonylmethyl)aminopropenoate (**5e**), (2*E*)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-3-[(1*H*-indazol-3-yl)amino]propenoate (**5f**), and (2*E*)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-3-[(5-methylisoxazol-3-yl)amino]propenoate (**5g**). (Scheme 1)



Scheme 2.

On the other hand, when compound (**3**) was heated with 2-aminopyridine (**4h**) and 3-amino-1*H*-pyrazol (**4i**) in acetic acid, the corresponding 3-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**7a**) and 6-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)pyrazolo[1,5-*a*]pyrimidin-7(1*H*)-one (**7b**) were isolated in 70 % and 77 % yields, respectively. Similarly, the reaction of compound (**3**) with 4-hydroxy-6-

methyl-2*H*-pyran-2-one (**6a**) and 5,5-dimethylcyclohexane-1,3-dione (**6b**) acetic acid afforded 3-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-7-methyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione (**7c**) and 3-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-7,8-dihydro-7,7-dimethyl-2*H*-chromene-2,5-dione (**7d**) in 26 % and 82 % yields, respectively (Scheme 2).

Structure determination

The structures of all compounds were established on the basis of elemental analyses, IR, MS, and ^{1}H and ^{13}C NMR spectra. The orientation around the double bond in compounds (**3**) and (**5b**) were established on the basis of 2D-HMBC NMR spectral techniques. The magnitude of heteronuclear coupling constants, $^{3}J_{C\text{-}H}$, for the nuclei ***H***-C=C-***C***=O with *cis* configuration around the C=C double bond are smaller (2-6 Hz) than those for the *trans*-orientated ones (8-12 Hz).[10,11,21] Accordingly, the heteronuclear coupling constants for compound (**3**), $^{3}J_{C\text{-}H}$ = 5 Hz, and for compound (**5b**), $^{3}J_{C\text{-}H}$ = 4 Hz, clearly indicates the (*E*)-orientation. The structure of compound (**5e**) was confirmed also by X-Ray analysis. The ORTEP drawing of **5e** is shown in Figure 2.

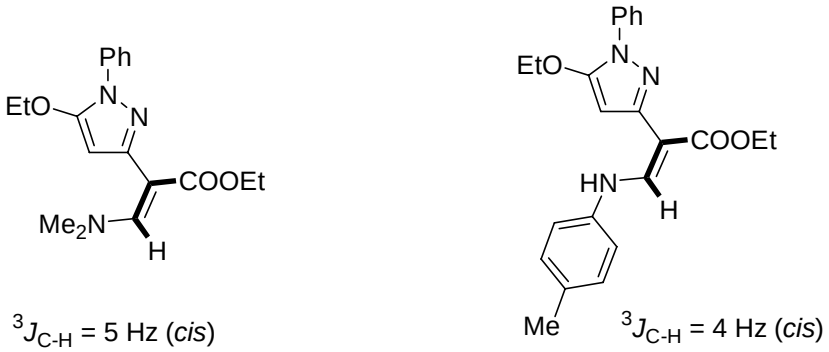


Figure 1. Determination of configuration around the C=C double bonds by NMR spectroscopy.

X-Ray structure analysis

Structure of compound (**5e**) was solved by X-Ray analysis.[22]

Fractional coordinates and equivalent displacement parameters (Å^2) for compound (**5e**). U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U_{eq}
O(31)	0.2172(4)	0.2228(3)	1.1783(2)	0.075(1)
O(32)	0.3925(3)	0.3079(2)	1.2432(2)	0.066(1)

O(33)	0.9918(3)	0.3697(3)	0.7622(2)	0.074(1)
O(34)	1.1372(3)	0.4684(2)	0.8344(2)	0.066(1)
O(5)	0.3148(3)	0.0608(2)	0.8032(2)	0.058(1)
N(1)	0.5385(4)	0.1595(2)	0.8033(2)	0.048(1)
N(2)	0.5883(3)	0.2187(2)	0.8716(2)	0.050(1)
N(3)	0.7504(4)	0.3412(3)	0.9581(2)	0.055(1)
C(11)	0.6344(4)	0.1595(3)	0.6909(3)	0.046(1)
C(12)	0.7434(5)	0.2399(3)	0.6446(3)	0.056(1)
C(13)	0.8434(5)	0.2403(4)	0.5365(3)	0.064(2)
C(14)	0.8338(5)	0.1621(4)	0.4735(3)	0.069(2)
C(15)	0.7252(6)	0.0825(4)	0.5199(3)	0.070(2)
C(16)	0.6270(5)	0.0801(3)	0.6284(3)	0.063(2)
C(3)	0.4664(4)	0.2129(3)	0.9674(3)	0.047(1)
C(31)	0.4836(4)	0.2700(3)	1.0570(3)	0.047(1)
C(32)	0.3523(5)	0.2629(3)	1.1618(3)	0.050(1)
C(33)	0.2709(5)	0.3015(4)	1.3513(3)	0.070(2)
C(34)	0.3156(6)	0.3734(4)	1.4200(3)	0.079(2)
C(35)	0.6205(4)	0.3273(3)	1.0469(3)	0.048(1)
C(36)	0.8936(4)	0.4011(3)	0.9537(3)	0.056(1)
C(37)	1.0089(4)	0.4101(3)	0.8391(3)	0.053(1)
C(38)	1.2670(6)	0.4797(4)	0.7300(3)	0.082(2)
C(4)	0.3361(4)	0.1510(3)	0.9607(3)	0.050(1)
C(5)	0.3855(4)	0.1196(3)	0.8575(3)	0.049(1)
C(51)	0.1485(5)	0.0256(3)	0.8618(3)	0.058(1)
C(52)	0.0956(5)	-0.0393(4)	0.7885(3)	0.066(2)

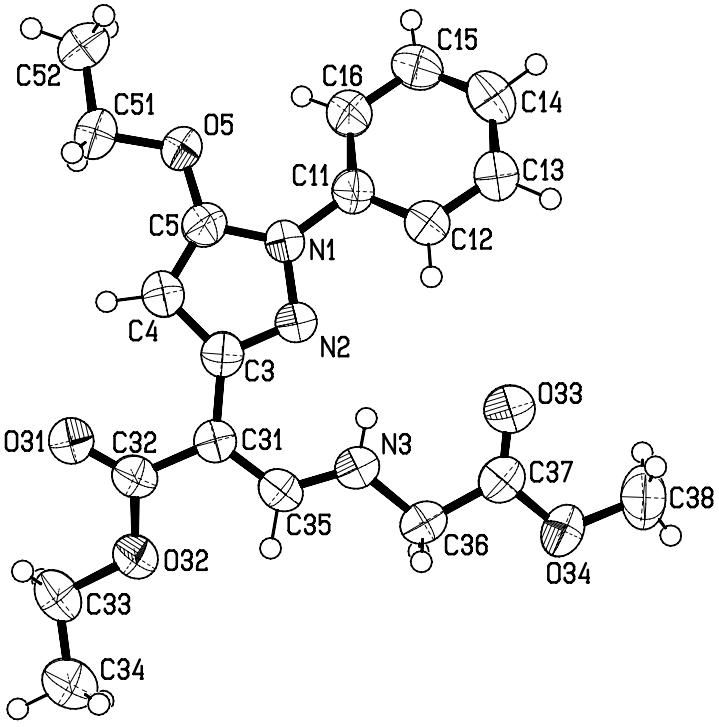


Figure 2. Ortep view of compound (**5e**) at the 50% probability level. H atoms are drawn as ellipsoids of arbitrary radii.

Bond Distances (Å^2) and Bond Angles (°) for compound (**5e**) with e.s.d.'s in parentheses

O(32)-C(32)	1.351(5)	C(11)-C(16)	1.376(6)
O(32)-C(33)	1.449(4)	C(11)-C(12)	1.380(5)
O(33)-C(37)	1.194(5)	C(12)-C(13)	1.383(5)
O(34)-C(37)	1.331(5)	C(13)-C(14)	1.375(7)
O(34)-C(38)	1.450(4)	C(14)-C(15)	1.370(6)
O(5)-C(5)	1.339(5)	C(15)-C(16)	1.379(5)
O(5)-C(51)	1.441(4)	C(3)-C(4)	1.413(6)
N(1)-C(5)	1.366(4)	C(3)-C(31)	1.463(5)
N(1)-N(2)	1.376(5)	C(31)-C(35)	1.366(5)
N(1)-C(11)	1.416(4)	C(31)-C(32)	1.458(4)
N(2)-C(3)	1.341(4)	C(33)-C(34)	1.478(7)
N(3)-C(35)	1.325(4)	C(36)-C(37)	1.489(5)
N(3)-C(36)	1.443(5)	C(4)-C(5)	1.352(5)
C(11)-C(16)	1.376(6)	C(51)-C(52)	1.487(7)

C(37)-O(34)-C(38)	117.1(3)	C(35)-C(31)-C(32)	118.9(3)
C(5)-O(5)-C(51)	115.7(3)	C(35)-C(31)-C(3)	122.3(3)
C(5)-N(1)-N(2)	109.4(3)	C(32)-C(31)-C(3)	118.7(3)
C(5)-N(1)-C(11)	131.5(3)	O(31)-C(32)-O(32)	120.7(3)
N(2)-N(1)-C(11)	118.7(3)	O(31)-C(32)-C(31)	125.7(4)
C(3)-N(2)-N(1)	106.0(3)	O(32)-C(32)-C(31)	113.6(3)
C(35)-N(3)-C(36)	123.7(3)	O(32)-C(33)-C(34)	108.9(4)
C(16)-C(11)-C(12)	119.3(3)	N(3)-C(35)-C(31)	126.5(3)
C(16)-C(11)-N(1)	122.5(3)	N(3)-C(36)-C(37)	110.7(3)
C(12)-C(11)-N(1)	118.2(3)	O(33)-C(37)-O(34)	124.2(3)
C(11)-C(12)-C(13)	120.0(4)	O(33)-C(37)-C(36)	125.4(4)
C(14)-C(13)-C(12)	120.7(4)	O(34)-C(37)-C(36)	110.4(3)
C(15)-C(14)-C(13)	119.0(3)	C(5)-C(4)-C(3)	105.4(3)
C(14)-C(15)-C(16)	120.8(4)	O(5)-C(5)-C(4)	133.1(3)
C(11)-C(16)-C(15)	120.2(4)	O(5)-C(5)-N(1)	118.1(3)
N(2)-C(3)-C(4)	110.3(3)	C(4)-C(5)-N(1)	108.9(3)
N(2)-C(3)-C(31)	118.6(3)	O(5)-C(51)-C(52)	107.1(3)
C(4)-C(3)-C(31)	131.1(3)		

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 (5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)acetate (2)[23]

Ethyl (4,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazol-3-yl)acetate (2.46 g, 10 mmol), ethyl bromide (1 mL, 13 mmol), potassium iodide (1.66 g, 10 mmol), and potassium carbonate (1.38 g, 10 mmol) in ethanol (30 mL) were heated at the reflux temperature for 3 h. Solid residue was filtered off, solvent was evaporated *in vacuo*. Oily residue was dissolved in ether (40 mL), and solution was shaken with 10 % NaOH (40 mL), and then with water (50 mL). Organic phase was dried with anhydrous sodium sulfate. Solvent was evaporated *in vacuo* to give oily residue, which was further purified by column chromatography on silica gel (EtOAc : hexane, 1 : 1). The compound was used without any additional purification in further experiments. Colorless oil; yield: 42 % (1.151 g); ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H, *J* = 7.2, OCH_2CH_3); 1.42 (t, 3H, *J* = 7.0, OCH_2CH_3); 3.66 (s, 2H, CH_2); 4.11–4.22 (m, 4H, 2× OCH_2CH_3); 5.68 (s, 1H, 4-H); 7.19–7.25 (m, 1H, Ph); 7.35–7.42 (m, 2H, Ph); 7.68–7.72 (m, 2H, Ph).

Ethyl (2*E*)-3-(*N*,*N*-dimethylamino)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)propenoate (3)

Ethyl (5-ethyl-1-phenyl-1*H*-pyrazol-3-yl)acetate (**2**) and DMFDMA (2.16 mL, 15 mmol) in toluene (20 mL) were heated at the reflux temperature for 3 h. Solvent was evaporated *in vacuo*. Oily residue was purified by column chromatography on silica gel (EtOAc : hexane, 1 : 2) to give white crystals. Yield: 42 % (1.157 g); mp 86–104°C (Ethanol). *Anal*. Calcd for $C_{18}H_{23}N_3O_3$: C 65.63; H 7.04; N 12.76. Found, C 65.78; H 7.13; N 12.98. MS: *m/z* (M^+, 329; MH^+, 330). IR (cm^{-1}): 1670, 1620, 1560, 1390, 1290, 1210, 1060, 770. ^{1}H NMR ($CDCl_3$): δ 1.26 (t, 3H, *J* = 7.2, OCH_2CH_3); 1,47 (t, 3H, *J* = 7.0, OCH_2CH_3); 2.87 (s, 6H, NMe_2); 4.15–4.22 (m, 4H, 2 × OCH_2CH_3); 5.71 (s, 1H, 4-H); 7.20–7.25 (m, 1H, Ph); 7.38–7.43 (m, 2H, Ph); 7.65 (s, 1H, =CH); 7.75–7.81 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$): δ 15.0; 15.1; 59.0; 68.1; 90.6; 91.4; 122.0; 125.9; 129.0; 139.5; 147.6; 148.5; 151.4; 154.6; 170.1.

General Procedures for the Preparation of Ethyl (2*E*)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-3-(substituted amino)propenoates (5a-g), fused pyrimidinones (7a,b) and fused pyranones (7c,d):

General Procedure A: **3** (165 mg, 0.5 mmol) and **4** (0.5 mmol) were dissolved in ethanol (5 mL) and hydrochloric acid (3 drops, 33%, 1 mmol), and the solution heated at reflux temperature. The product was filtered off, and recrystallized from ethanol.

General Procedure B: **3** (165 mg, 0.5 mmol) and nucleophile (**4** or **6**) (0.5 mmol) were dissolved in acetic acid (3 mL), and the solution heated at reflux temperature. After cooling, the product was filtered off, and recrystallized from ethanol.

Ethyl (2*E*)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-3-phenylaminopropenoate (5a). This compound was prepared from **3** (165 mg, 0.5 mmol) and aniline hydrochloride (**4a**) (65 mg, 0.5 mmol). (Procedure

A, 1 h reflux); grey needles; yield: 89% (168 mg); mp 142–144°C. *Anal*. Calcd for $C_{22}H_{23}N_3O_3$: C 70.01; H 6.14; N 11.13. Found, C 70.27; H 6.26; N 10.85. MS: *m/z* (M^+, 378; MH^+, 377). IR (cm^{-1}): 1690, 1640, 1560, 1510, 1400, 1260, 1060, 780. ^{1}H NMR ($CDCl_3$): δ 1.39 (t, 3H, *J* = 7.1, OCH_2CH_3); 1.48 (t, 3H, *J* = 7.0, OCH_2CH_3); 4.23–4.34 (m, 4H, 2 × OCH_2CH_3); 6.47 (s, 1H, 4-H); 7.01–7.11 (m, 3H, Ph); 7.24–7.37 (m, 3H, Ph); 7.44–7.49 (m, 2H, Ph); 7.76–7.79 (m, 2H, Ph); 8.36 (d, 1H, *J* = 12.9, =CH); 11.38 (br d, 1H, *J* = 12.7; NH). ^{13}C NMR ($CDCl_3$): δ 15.3; 60.2; 68.9; 87.6; 95.7; 116.8; 121.8; 123.9; 126.9; 130.1; 130.7; 139.0; 140.7; 141.1; 149.5; 154.6; 167.2.

Ethyl (2*E*)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-3-[(4-methylphenyl)amino]propenoate (5b). This compound was prepared from **3** (165 mg, 0.5 mmol) and 4-methylaniline hydrochloride (**4b**) (72 mg, 0.5 mmol). (Procedure A, 2.5 h reflux); white crystals; yield: 84% (165 mg); mp 123–125°C. *Anal*. Calcd for $C_{23}H_{25}N_3O_3$: C 70.75; H 6.44; N 10.73. Found, C 70.68; H 6.62; N 10.49. MS: *m/z* (M^+, 391; MH^+, 392). IR (cm^{-1}): 1680, 1650, 1560, 1510, 1330, 1260, 1070, 780, 760. ^{1}H NMR ($CDCl_3$): δ 1.38 (t, 3H, *J* = 7.2, OCH_2CH_3); 1.48 (t, 3H, *J* = 7.0, OCH_2CH_3); 2.32 (s, 3H, CH_3); 4.22–4.34 (m, 4H, 2 × OCH_2CH_3); 6.46 (s, 1H, 4-H); 7.00 (d, 2H, *J* = 8.5; Ph'); 7.14 (d, 2H, *J* = 8.5; Ph'); 7.24–7.29 (m, 1H, Ph); 7.43–7.48 (m, 2H, Ph); 7.76–7.79 (m, 2H, Ph); 8.33 (d, 1H, *J* = 12.9, =CH); 11.32 (br d, 1H, *J* = 12.9; NH). ^{13}C NMR ($CDCl_3$): δ 14.6; 14.7; 20.7; 59.6; 67.9; 86.6; 94.6; 116.2; 121.2; 125.6; 128.9; 130.1; 132.5; 138.5: 138.9; 141.0; 149.4; 154.2; 167.7.

Ethyl (2*E*)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-3-[(4-methoxyphenyl)amino]propenoate (5c). This compound was prepared from **3** (165 mg, 0.5 mmol) and 4-methoxyaniline (**4c**) (62 mg, 0.5 mmol). (Procedure A, 3 h reflux); white needles; yield: 38% (78 mg); mp 91–94°C. *Anal*. Calcd for $C_{23}H_{25}N_3O_4$: C 67.80; H 6.18; N 10.31. Found, C 67.55; H 6.40; N 10.21. MS: *m/z* (M^+, 407; MH^+, 408). IR (cm^{-1}): 1690, 1640, 1560, 1520, 1240, 780. ^{1}H NMR ($CDCl_3$): δ 1.37 (t, 3H, *J* = 7.0, OCH_2CH_3); 1.48 (t, 3H, *J* = 7.2, OCH_2CH_3); 3.80 (s, 3H, OCH_3); 4.22–4.33 (m, 4H, 2 × OCH_2CH_3); 6.46 (s, 1H, 4-H); 6.90 (d, 2H, *J* = 9.0; Ph'); 7.05 (d, 2H, *J* = 9.0; Ph'); 7.24–7.28 (m, 1H, Ph); 7.43–7.48 (m, 2H, Ph); 7.75–7.78 (m, 2H, Ph); 8.28 (d, 1H, *J* = 12.9, =CH); 11.29 (br d, 1H, *J* = 12.9; NH). ^{13}C NMR ($CDCl_3$): δ 15.3; 56.2; 60.0; 68.9; 87.4; 94.4; 116.0; 118.4; 121.8; 126.8; 130.1; 134.6; 139.1; 141.8; 149.8; 154.6; 156.4; 167.2.

Ethyl (2*E*)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-3-[(4-nitrophenyl)amino]propenoate (5d). This compound was prepared from **3** (165 mg, 0.5 mmol) and 4-nitroaniline (**4d**) (69 mg, 0.5 mmol). (Procedure A, 2 h reflux); yellow needles; yield: 91% (193 mg); mp 154–156°C. *Anal*. Calcd for $C_{22}H_{22}N_4O_5$: C 62.55; H 5.25; N 13.26. Found, C 62.53; H 5.32; N 13.45. MS: *m/z* (M^+, 422; MH^+, 423). IR (cm^{-1}): 1680, 1640, 1590, 1560, 1510, 1330, 1260, 1110, 840, 780, 750, 690. ^{1}H NMR (DMSO-d_6): δ

1.33 (t, 3H, *J* = 7.0, OCH_2CH_3); 1.41 (t, 3H, *J* = 7.2, OCH_2CH_3); 4.22–4.33 (m, 4H, 2 × OCH_2CH_3); 6.42 (s, 1H, 4-H); 7.33–7.39 (m, 1H, Ph); 7.39 (d, 2H, *J* = 9.4, Ph'); 7.53–7.58 (m, 2H, Ph); 7.78–7.81 (m, 2H, Ph); 8.23 (d, 2H, *J* = 9.4, Ph'); 8.31 (d, 1H, *J* = 12.4, =CH); 11.42 (br d, 1H, *J* = 12.4; NH).

Ethyl (2*E*)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-3-[(2-methoxy-2-oxoethyl)amino]propenoate (5e). This compound was prepared from **3** (165 mg, 0.5 mmol) and methyl glycinate hydrochloride (**4e**) (63 mg, 0.5 mmol). (Procedure A, 3.5 h reflux); white crystals; yield: 66% (133 mg); mp 92–94°C. *Anal*. Calcd for $C_{19}H_{23}N_3O_5$: C 61.11; H 6.21; N 11.25. Found, C 61.42; H 6.21; N 11.11. MS: *m/z* (M^+, 373; MH^+, 374). IR (cm^{-1}): 1750, 1680, 1620, 1560, 1510, 1390, 1260, 1220, 1060, 760. ^{1}H NMR ($CDCl_3$): δ 1.33 (t, 3H, *J* = 7.2, OCH_2CH_3); 1.46 (t, 3H, *J* = 7.0, OCH_2CH_3); 3.80 (s, 3H, OCH_3); 4.13 (d, 2H, *J* = 5.7, CH_2); 4.20–4.25 (m, 4H, 2 × OCH_2CH_3); 6.41 (s, 1H, 4-H); 7.19–7.25 (m, 1H, Ph); 7.39–7.45 (m, 2H, Ph); 7.72 (d, 1H, *J* = 12.8, =CH); 7.77–7.81 (m, 2H, Ph); 9.43–9.51 (m, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 15.0; 15.1; 50.3; 52.8; 59.8; 68.3; 86.7; 93.3; 121.6; 125.8; 129.1; 139.4; 149.4; 150.0; 154.5; 168.0; 170.3.

Ethyl (2*E*)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-3-[(1*H*-indazol-3-yl)amino]propenoate (5f). This compound was prepared from **3** (165 mg, 0.5 mmol) and 4-nitroaniline (**4f**) (67 mg, 0.5 mmol). (Procedure B, 2 h); yellow needles; yield: 78% (163 mg); mp 175–194°C. *Anal*. Calcd for $C_{23}H_{23}N_5O_3$: C 66.17; H 5.55; N 16.78. Found, C 66.50; H 5.53; N 16.90. MS: *m/z* (M^+, 417; MH^+, 418). IR (cm^{-1}): 1700, 1640, 1590, 1560, 1510, 1390, 1070, 780, 690. ^{1}H NMR ($CDCl_3$): δ 1.39 (t, 3H, *J* = 7.2, OCH_2CH_3); 1.49 (t, 3H, *J* = 7.0, OCH_2CH_3); 4.25–4.35 (m, 4H, 2 × OCH_2CH_3); 6.56 (s, 1H, 4-H); 7.11–7.16 (m, 1H, Ph'); 7.28–7.34 (m, 1H, Ph); 7.39–7.41 (m, 2H, Ph'); 7.47–7.52 (m, 2H, Ph); 7.67–7.70 (m, 1H, Ph'); 7.84–7.88 (m, 2H, Ph); 8.76 (d, 1H, *J* = 12.4, =CH); 9.31 (br s, 1H, 1'-NH); 11.88 (d, 1H, *J* = 12.4; NH).

Ethyl (2*E*)-2-(5-ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-3-[(5-methylisoxazol-3-yl)amino]propenoate (5g). This compound was prepared from **3** (165 mg, 0.5 mmol) and 3-amino-5-methylisoxazole (**4g**) (49 mg, 0.5 mmol). (Procedure B, 2 h reflux); white needles; yield: 37% (75 mg); mp 123–125°C. *Anal*. Calcd for $C_{20}H_{22}N_4O_4$ C 62.82; H 5.80; N 14.65. Found, C 62.73; H 5.99; N 14.49. MS: *m/z* (M^+, 382; MH^+, 383). IR (cm^{-1}): 2980, 1700, 1650, 1550, 1470, 1260, 1070, 790, 760, 680. ^{1}H NMR ($CDCl_3$): δ 1.37 (t, 3H, *J* = 7.2, OCH_2CH_3); 1.47 (t, 3H, *J* = 7.0, OCH_2CH_3); 2.39 (d, 3H, *J* = 0.8; CH_3); 4.21–4.33 (m, 4H, 2 × OCH_2CH_3); 5.86 (d, 1H, *J* = 0.8; 4'-H); 6.46 (s, 1H, 4-H); 6.67 (s, 1H, 4'-H); 7.25–7.30 (m, 1H, Ph); 7.43–7.48 (m, 2H, Ph); 7.70–7.74 (m, 2H, Ph); 8.19 (d, 1H, *J* = 12.4, =CH); 11.23 (d, 1H, *J* = 12.4, NH). ^{13}C NMR ($CDCl_3$): δ 13.1; 14.9; 15.1; 60.4; 68.4; 87.4; 93.7; 98.9; 121.9; 126.4; 129.3; 139.0; 140.1; 148.9; 154.6; 160.8; 167.4; 170.8.

3-(5-Ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7a). This compound was prepared from **3** (165 mg, 0.5 mmol) and 2-aminopyridine (**4h**) (47 mg, 0.5 mmol). (Procedure B, 2 h reflux); yellow needles; yield: 70% (116 mg); mp 175–176°C. *Anal*. Calcd for $C_{19}H_{16}N_4O_2$: C 68.66; H 4.85; N 16.86. Found, C 68.48; H 5.00; N 17.05. MS: *m/z* (M^+, 332; MH^+, 333). IR (cm^{-1}): 1690, 1590, 1490, 1380, 1050, 770, 760, 680. ^{1}H NMR ($CDCl_3$): δ 1.49 (t, 3H, *J* = 7.0, OCH_2CH_3); 4.30 (q, 2H, *J* = 7.0, OCH_2CH_3); 6.67 (s, 1H, 4'-H); 7.21–7.31 (m, 2H, Ph, 7-H); 7.42–7.49 (m, 2H, Ph); 7.75–7.78 (m, 2H, 8-H, 9-H); 7.83–7.86 (m, 2H, Ph); 9.21–9.24 (m, 1H, 6-H); 9.28 (s, 1H, 2-H).

6-(5-Ethoxy-1-phenyl-1*H*-pyrazol-3-yl)pyrazolo[1,5-*a*]pyrimidin-7(1*H*)-one (7b). This compound was prepared from **3** (165 mg, 0.5 mmol) and 3-amino-1*H*-pyrazole (**4i**) (42 mg, 0.5 mmol). (Procedure B, 5 h reflux); white needles; yield: 77% (123 mg); mp 291–293°C. *Anal*. Calcd for $C_{17}H_{15}N_5O_2$ C 63.54; H 4.71; N 21.79. Found, C 63.61; H 4.88; N 21.55. MS: *m/z* (M^+, 321; MH^+, 322). IR (cm^{-1}): 1660, 1630, 1590, 1550, 1500, 1260, 1050, 770, 570. ^{1}H NMR (DMSO-d_6): δ 1.41 (t, 3H, *J* = 7.0, OCH_2CH_3); 4.29 (q, 2H, *J* = 7.0; OCH_2CH_3); 6.26 (d, 1H, *J* = 2.0, 3-H); 6.52 (s, 1H, 4'-H); 7.28–7.34 (m, 1H, Ph); 7.47–7.52 (m, 2H, Ph); 7.75–7.79 (m, 2H, Ph); 7.92 (d, 1H, *J* = 2.0, 2-H); 8.51 (s, 1H, 5-H); 12.8 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 15.3; 68.9; 87.8; 90.3; 102.1; 122.3; 126.9; 129.8; 137.2; 139.3; 141.8; 144.0; 145.6; 155.0; 156.0.

3-(5-Ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-7-methyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione (7c). This compound was prepared from **3** (165 mg, 0.5 mmol) and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**6a**) (63 mg, 0.5 mmol). (Procedure B, 4 h reflux); white needles; yield: 26% (47 mg); mp 270–272°C. *Anal*. Calcd for $C_{20}H_{16}N_2O_5$ C 65.93; H 4.43; N 7.69. Found, C 65.95; H 4.60; N 7.46. MS: *m/z* (M^+, 364; MH^+, 365). IR (cm^{-1}): 1740, 1600, 1560, 1030, 770, 690. ^{1}H NMR (DMSO-d_6): δ 1.39 (t, 3H, *J* = 7.0, OCH_2CH_3); 2.36 (s, 3H, CH_3); 2.39 (s, 2H, CH_2); 4.29 (q, 2H, *J* = 7.0; OCH_2CH_3); 6.72 (2 × s, 2 × 1H, 4'-H, 8-H); 7.33–7.38 (m, 1H, Ph); 7.49–7.54 (m, 2H, Ph); 7.75–7.78 (m, 2H, Ph); 8.37 (s, 1H, 4-H).

3-(5-Ethoxy-1-phenyl-1*H*-pyrazol-3-yl)-7,8-dihydro-7,7-dimethyl-2*H*,6*H*-chromene-2,5-dione (7d). This compound was prepared from **3** (165 mg, 0.5 mmol) and 5,5-dimethyl-1,3-cyclohexadione (**6b**) (70 mg, 0.5 mmol). (Procedure B, 8 h reflux); white needles; yield: 82% (155 mg); mp 226–229°C. *Anal*. Calcd for $C_{22}H_{22}N_2O_4$ C 69.83; H 5.86; N 7.40. Found, C 69.79; H 6.01; N 7.17. MS: *m/z* (M^+, 378; MH^+, 379). IR (cm^{-1}): 1710, 1690, 1670, 1600, 1510, 1370, 1230, 1170, 1050, 790, 700, 570. ^{1}H NMR (DMSO-d_6): δ 0.83 (s, 6H, 2 × Me); 1.36 (t, 3H, *J* = 7.1, OCH_2CH_3); 2.36 (s, 2H, CH_2); 2.39 (s, 2H, CH_2); 4.38 (q, 2H, *J* = 7.1; OCH_2CH_3); 5.95 (s, 1H, 4'-H); 7.29–7.32 (m, 2H, Ph); 7.45–7.54 (m, 3H, Ph); 8.37 (s, 1H, 4-H). ^{13}C NMR (DMSO-d_6): δ 15.0; 28.3; 33.3; 49.9; 62.2; 86.5; 114.3; 114.6; 125.9; 129.2;

130.2; 133.4; 139.6; 150.5; 152.8; 164.0; 170.3; 193.7.

ACKNOWLEDGEMENTS

The financial support from the Ministry of Higher Education, Science and Technology, Slovenia through grants P0-0502-0103, P1-0179, and J1-6689-0103-04 is gratefully acknowledged.
The diffraction data for compound (**5e**) were collected on the Kappa CCD Nonius diffractometer in the Laboratory of Inorganic Chemistry, Faculty of Chemistry and Chemical Technology, University of Ljubljana, Slovenia. We acknowledge with thanks the financial contribution of the Ministry of Higher Education, Science and Technology, Republic of Slovenia through grants X-2000 and PS-511-103, which thus made purchase of the apparatus possible.

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22. A single crystal (0.16×0.12×0.08 mm) grown from ethanol was used for unit-cell determination and data collection on a Nonius KAPPA CCD diffractometer, with graphite-monochromated Mo*K*α radiation (λ=0.7106 Å). Crystal data of **5e**: $C_{19}H_{23}N_3O_5$; *M*=373.411; triclinic, space group *P*-1 (#2), *Z*=2 with *a*=7.4886 (2) Å, *b*=11.8269 (3) Å, *c*=11.9923 (4) Å; α=73.355 (1)°, β=80.264 (1)°, γ=71.993 (1)°; *V*=963.98 (5) Å^3, and D_x=1.286 g/cm^3. All calculations were performed using the Xtal3.4[24] system. The structure was solved by direct method (SIR92).[25] The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were refined isotropically. The final *R*- and R_w- factors after full-matrix least-squares refinements were 0.047 and 0.042, respectively, for 1672 (I>2.50σ(I)) observed reflections.
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