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Reactions of ethyl 3-[(*E*)-(dimethylamino)methylidene]pyruvate (**3**) and 3-[(dimethylamino)methylidene]-2-oxosuccinate (**4**) with hydrazine monohydrochloride (**5a**) and (hetero)arylhydrazines (**5b–i**) afforded, regioselectively, 1-substituted ethyl 1*H*-pyrazole-5-carboxylates **9a–f** and diethyl 1*H*-pyrazole-3,4-dicarboxylates, **11a–i**, respectively. Upon treatment of **3** with pyridazinylhydrazines **5d–f**, the stable intermediates, 1-substituted ethyl 4,5-dihydro-5-hydroxy-1*H*-pyrazole-5-carboxylates **8d–f**, were isolated. Treatment of compounds **8d–f** in acetic acid under reflux furnished the pyrazoles **9d–f**. On the other hand, reaction of **3** with *N,N'*-dimethylhydrazine (**5l**) gave ethyl 1-methyl-1*H*-pyrazole-3-carboxylate (**14**). The structures of compounds **3**, **4**, **14** were determined by nmr (noesy and hmbc techniques), while the structures of compounds **8f**, **9f**, and **11e,f** were determined by X-ray diffraction.

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Pyrazoles are important class of heterocyclic compounds, which found a widespread use in various applications [1–3]. The pyrazole ring is a constituent of a variety of natural and synthetic products. Examples of pyrazole ring containing natural products are (*S*)-3-pyrazolylalanine [4], pyrazomycin [5], and 4,5-dihydro-3-phenyl-6*H*-pyrrolo[1,2-*b*]pyrazole [6], while lonazolac [7], fezolamin [8], difenamizole [9], and mepirizole [10] are examples of biologically active synthetic pyrazole derivatives (Figure 1).

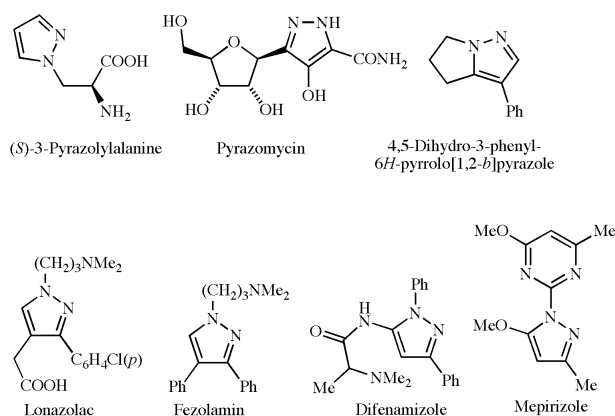


Figure 1

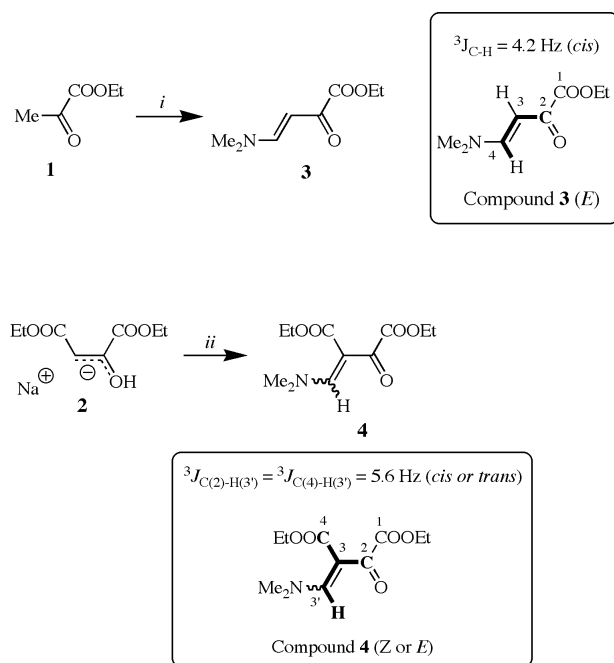
Pyrazoles are usually prepared by condensation between a hydrazine derivative and a 1,3-dicarbonyl compound or by 1,3-dipolar cycloaddition of diazoalkanes or nitrile imines to olefins or acetylenes. Although these two basic synthetic methods are simple and efficient, the use of unsymmetrically substituted precursors often leads to a mixture of regioisomeric pyrazole derivatives [1–3].

In the last decade, alkyl 2-substituted 3-(dimethylamino)propenoates proved to be easily available and efficient reagents for the preparation of various heterocyclic systems [11]. Since 3-(dimethylamino)propenoates are actually masked 1,3-dicarbonyl compounds, they can be transformed into substituted pyrazoles upon treatment with hydrazine derivatives. In most cases, these reactions proceed under acidic conditions regioselectively *via* initial substitution of the dimethylamino group followed by condensation to the carbonyl group. In this connection we have previously reported regioselective syntheses of pyrazole derivatives from alkyl 2-substituted 3-(dimethylamino)propenoates and their analogs [12–15]. In some cases, the intermediate hydrazones were also isolated [12].

In this paper, we report the preparation of ethyl 3-[(*E*)-(dimethylamino)methylidene]pyruvate (**3**), diethyl 3-[(dimethylamino)methylidene]-2-oxosuccinate (**4**), their transformations with hydrazine derivatives into 1-substituted 1*H*-pyrazole-5-carboxylates **9a–f**, **11a–i**, and the isolation of ethyl 4,5-dihydro-1-heteroaryl-5-hydroxy-1*H*-pyrazole-5-carboxylates **8d–f** as stable intermediates in the synthesis of 1-substituted 1*H*-pyrazole-5-carboxylates **9d–f** from the enaminone **3**.

The first starting compound, ethyl 3-[(*E*)-(dimethylamino)methylidene]pyruvate (**3**) was prepared from ethyl pyruvate (**1**) and dimethylformamide diethyl acetal (DMFDEA) in dichloromethane at room temperature. Similarly, diethyl 3-[(dimethylamino)methylidene]-2-oxosuccinate (**4**) was prepared from sodium salt of diethyl 2-oxosuccinate (**2**) by treatment with dimethylformamide dimethyl acetal (DMFDMA) in dichloromethane at room temperature followed by addition of 1 equivalent of acetic acid. The reagents **3** and **4** were not prepared in analytically pure form and were used for further transformation

Scheme 1

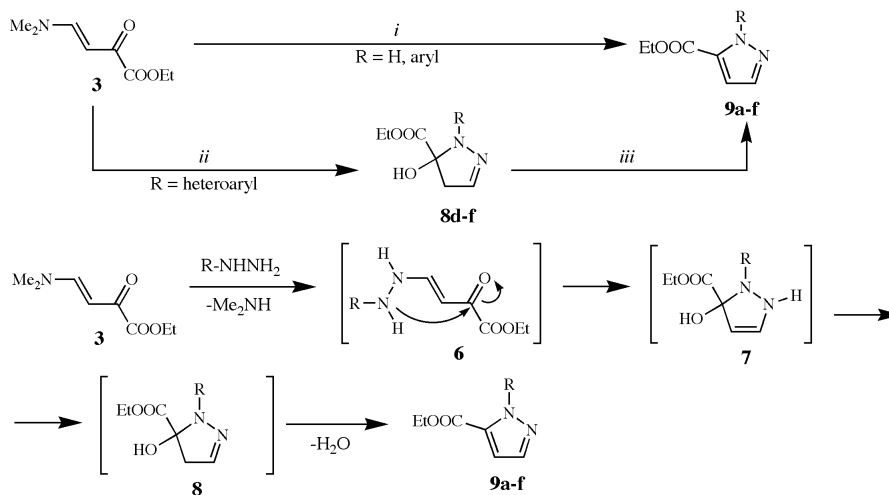


Reagents and Conditions: i) $\text{Me}_2\text{NCH}(\text{OEt})_2$, CH_2Cl_2 , r.t.;
 ii) $\text{Me}_2\text{NCH}(\text{OMe})_2$, EtOH, AcOH (1 equiv.), EtOH, r.t..

without purification. Both compounds **3** and **4** have already been prepared previously by Gompper and Sobotta, however, no experimental details were given in the literature [16,17]. The same authors have also previously reported the use of **3** for the preparation of some pyrazole derivatives [17].

Both enaminones, **3** and **4**, exhibit single sets of signals in ^1H - and ^{13}C -nmr spectra, indicating that these compounds **3** and **4** exist in CDCl_3 solution as single isomers. The configuration around the $\text{C}=\text{C}$ double bond in enaminone **3** was determined by 2D nmr (hmbc technique) on the basis of long range heteronuclear coupling constant, $^3J_{C-H}$. Usually, the magnitude of heteronuclear coupling constant, $^3J_{C-H}$, between the methine proton and the carbonyl carbon atom of the $\text{H}-\text{C}=\text{C}-\text{C}=\text{O}$ structural element is dependent on the configuration around the $\text{C}=\text{C}$ double bond: a) $^3J_{C-H} = 2\text{--}5 \text{ Hz}$ for the *cis*-oriented nuclei and b) $^3J_{C-H} = 5\text{--}10 \text{ Hz}$ for the *trans*-oriented nuclei [18,19]. In the case of compound **3**, the magnitude of coupling constant between the methine proton $\text{H}-\text{C}(4')$ and the carbonyl carbon atom $\text{O}=\text{C}(2)$, $^3J_{C-H} = 4.2 \text{ Hz}$, clearly indicating the (*E*)-configuration. In the case of compound **4**, however, the same magnitude of coupling constants, $^3J_{C(2)-H(3')} = ^3J_{C(4)-H(3')} = 5.6 \text{ Hz}$, between the methine proton $\text{H}-\text{C}(3')$ and two different carbonyl carbon atoms,

Scheme 2



Compound	R	Yield [%]	
		8	9
5a–9a	H	-	76
5b–9b	Ph	-	9
5c–9c	4-nitrophenyl	-	72
5d–8d	6-chloropyridazin-3-yl	78	-
9d	1,6-dihydro-6-oxopyridazin-3-yl	-	75
5e–9e	6-phenylpyridazin-3-yl	95	88
5f–9f	imidazo[1,2- <i>b</i>]pyridazin-6-yl	47	69

Reagents and Conditions: i) $\text{R}-\text{NHNH}_2 \times \text{HCl}$ (**5a,b**), MeOH or EtOH, $20\text{--}60^\circ\text{C}$ (**5a,b**→**9a,b**); ii) $\text{R}-\text{NHNH}_2$ (**5c–f**), EtOH, 37% HCl (aq., ~1 equiv.), room temperature (**5c**→**9c** and **5d–f**→**8d–f**); iii) AcOH, reflux (**8d–f**→**9d–f**).

O=C(2) (ketone) and O=C(4) (ester), was measured by 2D nmr (hmbc technique). Therefore, we were so far not able to determine the configuration around the double bond in the enaminone **4** (Scheme 1).

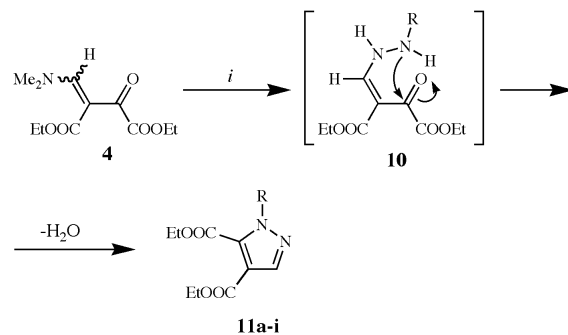
Treatment of **3** with hydrazine monohydrochloride (**5a**), phenylhydrazine hydrochloride (**5b**) and 4-nitrophenylhydrazine hydrochloride (**5c**) in methanol or ethanol gave the corresponding pyrazole-5-carboxylates **9a–c**. On the other hand, similar treatment with pyridazinylhydrazines **5d–f** afforded ethyl 4,5-dihydro-1-heteroaryl-5-hydroxy-1H-pyrazole-5-carboxylates **8d–f** as stable intermediates in 47–95% yields. Intermediates **8d–f** were then transformed into the corresponding pyrazoles **9d–f** upon dehydration in refluxing acetic acid. Regioselective acid-catalyzed formation of pyrazoles **9a–f** could be explained by initial substitution of the dimethylamino group in the reagent **3** to give the enehydrazines **6** which cyclize, *via* dihydropyrazoles **7** and **8**, into the 1-substituted ethyl 1H-pyrazole-5-carboxylates **9** (Scheme 2).

Acid-catalyzed cyclocondensations of the reagent **4**, were performed with hydrazine derivatives **5a–i** in ethanol at room temperature to give the corresponding 1-substituted diethyl 1H-pyrazole-4,5-dicarboxylates **11a–i**. Also in this case, the reaction mechanism could be explained by initial substitution of the dimethylamino group in **4** to give the enehydrazine intermediate **10**, followed by condensation to the carbonyl group to furnish the pyrazole derivative **11** (Scheme 3).

In the reaction of **3** with 1,2-dimethylhydrazine dihydrochloride (**5i**) in acetic acid under reflux ethyl 1-methyl-1H-pyrazole-3-carboxylate (**14**) was obtained in 43% yield. This result was surprising, since the reaction of a 1,2-disubstituted hydrazine with a 1,3-dicarbonyl compound usually does not lead to the formation of an aromatic pyrazole

derivative. The reaction mechanism for the formation of **14** could be explained by substitution of the dimethylamino group to give the enehydrazine **12**, followed by addition of the second NH group to the carbonyl group to give the dihydropyrazole intermediate **13**. Aromatisation of 1,2-dimethylpyrazoline **13** is, at least formally, feasible *via* elimination of methanol which leads to regioisomeric pyrazole **14** (Path A) or **15** (Path B). The structure of the

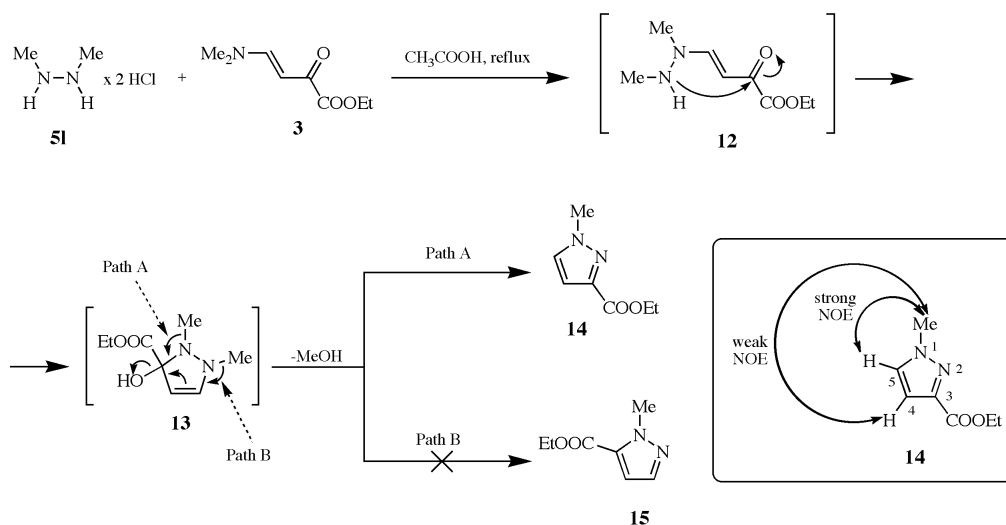
Scheme 3



Compound	R	Yield of 11 [%]
5a, 11a	H	56
5b, 11b	phenyl	86
5c, 11c	4-nitrophenyl	36
5d, 11d	6-chloropyridazin-3-yl	29
5e, 11e	6-phenylpyridazin-3-yl	37
5f, 11f	imidazo[1,2- <i>b</i>]pyridazin-6-yl	48
5g, 11g	1,2,4-triazolo[4,3- <i>b</i>]pyridazin-6-yl	44
5h, 11h	tetrazolo[1,5- <i>b</i>]pyridazin-6-yl	70
5i, 11i	pyrimidin-2-yl	89

Reagents and Conditions: i) R-NHNH₂ (**5a–i**), EtOH, 37% HCl (aq., ~1 equiv.), 20–60°C.

Scheme 4



product was determined by nmr: the ^1H -nmr and ^{13}C -nmr data were in agreement with the literature data for ethyl 1*H*-pyrazole-3-carboxylate (**14**) [20]. In the NOESY spectrum, a strong NOE between the $\text{H}_3\text{C}-\text{N}(1)$ and $\text{H}-\text{C}(5)$, as well as a weak NOE between the $\text{H}_3\text{C}-\text{N}(1)$ and $\text{H}-\text{C}(4)$ was observed. This observation supports the regioisomer **14** as the product with the heteroaromatic protons 5-H at the *ortho* position (strong NOE) and 4-H and the *meta* position (weak NOE) with respect to the $\text{N}-\text{CH}_3$ group. In the case of regioisomer **15**, presumably, two weak NOE should have been expected, since both heteroaromatic protons are located at the *meta*-position with respect to the $\text{N}-\text{CH}_3$ group (Scheme 4).

The structures of compounds **3**, **4**, **8**, **9**, **11**, and **14** were determined by spectroscopic methods (nmr, ir, ms, hrms) and/or by analyses for C, H, and N. Spectral data for pyrazoles **9**, **11**, and **14** are in agreement with the literature data for related pyrazole derivatives [1,3]. Total assignment of ^1H and ^{13}C signals for compounds **3** and **4** was performed by 2D nmr using hmqc and hmbc techniques. The structures of compounds **3**, **4**, **8b,e**, **11a,b**, and **14**, which were not isolated in analytically pure form, were confirmed by ^{13}C nmr and hrms. The structures of compounds **8f**, **9f**, and **11e,f** were determined by X-ray diffraction (Figures 2–5).

In conclusion, the propenoates **3** and **4** proved to be easily available reagents for the regioselective preparation of 1-substituted 1*H*-pyrazole-5-carboxylates **9** and 1*H*-pyrazole-4,5-dicarboxylates **11**. In the case of reaction of **3** with heteroarylhydrazines, also the stable intermediates, ethyl 4,5-dihydro-1-heteroaryl-5-hydroxy-1*H*-pyrazole-5-carboxylates **8** can be obtained under mild conditions.

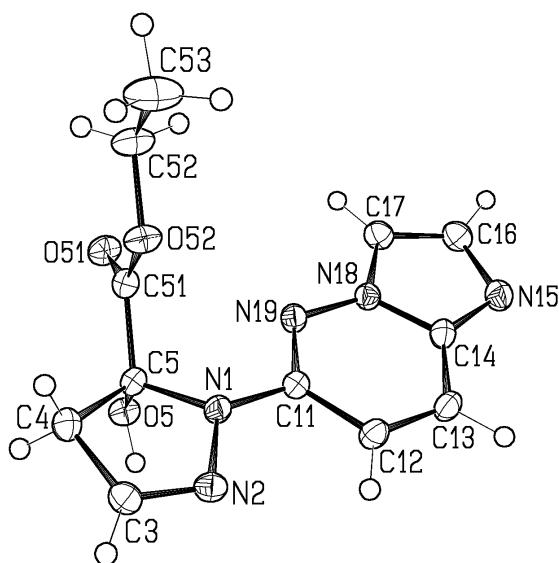


Table 1

Crystal Data, Data Collection, and Structure Refinement for Compounds **8f**, **9f**, **11e**, and **11f**

	Compound 8f	Compound 9f	Compound 11e	Compound 11f
Formula	C ₁₂ H ₁₃ N ₅ O ₃	C ₁₂ H ₁₁ N ₅ O ₂	C ₁₉ H ₁₈ N ₄ O ₄	C ₁₅ H ₁₅ N ₅ O ₄
Rel. formula weight	275.27	257.25	366.37	329.32
Crystal System	monoclinic	monoclinic	triclinic	triclinic
Space group	P2 ₁ /n, No. 14	P2 ₁ /c, No. 14	P-1, No. 2	P-1, No. 2
a (Å)	5.9644(1)	15.1665(4)	7.7152(2)	7.8266(1)
b (Å)	13.4690(3)	4.1916(1)	10.2421(2)	8.4823(2)
c (Å)	15.7822(3)	19.3604(5)	11.6747(3)	12.1252(3)
α (°)	90.00	90.00	87.973(1)	92.519(1)
β (°)	94.948(1)	102.332(1)	85.209(1)	98.939(1)
γ (°)	90.00	90.00	87.509(1)	105.281(1)
V (Å ³)	1263.13(4)	1202.38(5)	917.97(4)	764.02(3)
Z	4	4	2	2
ρ (Mg m ⁻³)	1.447	1.421	1.325	1.431
μ (mm ⁻¹)	0.108	0.102	0.095	0.107
Temperature (K)	150	150	293	293
Color of crystal	yellow	yellow	colorless	yellow
Shape of crystal	prism	needle	prism	prism
Dimensions (mm)	0.30×0.20×0.20	0.52×0.10×0.05	0.30×0.18×0.13	0.30×0.20×0.18
θ _{max} (°)	27.5	27.1	27.5	27.5
No. of integr. refl.	17712	17952	16247	13297
No. of indep. refl.	2891	2659	4136	3426
R _{int}	0.036	0.096	0.043	0.032
No. of observed refl.	2349	2011	2726	2720
Threshold criterion	F ² > 2.0σ(F ²)	F ² > 2.0σ(F ²)	F ² > 2.0σ(F ²)	F ² > 2.0σ(F ²)
Final R and R _w	0.067, 0.067	0.046, 0.050	0.055, 0.066	0.041, 0.046
Δρ _{max} , Δρ _{min} (e Å ⁻³)	0.99, -0.90	0.30, -0.29	0.33, -0.27	0.21, -0.24
(Δσ) _{max}	0.0004	0.0004	0.0099	0.003

Table 2

Fractional Coordinates and Equivalent Temperature Factors (Å²) for compound **8f**. 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(5)	0.4054(4)	0.9424(2)	0.5890(2)	0.0223(8)
O(51)	0.3052(5)	0.8318(2)	0.4529(2)	0.0259(8)
O(52)	0.6012(5)	0.7309(2)	0.4849(2)	0.0243(8)
N(1)	0.6159(5)	0.8073(2)	0.6517(2)	0.0198(8)
N(2)	0.8118(5)	0.8379(2)	0.6996(2)	0.0208(9)
N(15)	0.0160(6)	0.5504(3)	0.7664(2)	0.0248(9)
N(18)	0.1500(5)	0.6541(2)	0.6728(2)	0.0189(8)
N(19)	0.2887(5)	0.7198(2)	0.6371(2)	0.0201(8)
C(3)	0.9151(6)	0.8967(3)	0.6529(2)	0.022(1)
C(4)	0.8018(6)	0.9126(3)	0.5654(2)	0.022(1)
C(5)	0.5642(6)	0.8699(3)	0.5755(2)	0.0185(9)
C(11)	0.4677(6)	0.7448(3)	0.6870(2)	0.0181(9)
C(12)	0.5186(6)	0.7089(3)	0.7725(2)	0.022(1)
C(13)	0.3751(6)	0.6438(3)	0.8050(2)	0.023(1)
C(14)	0.1822(6)	0.6137(3)	0.7531(2)	0.021(1)
C(16)	-0.1231(7)	0.5524(3)	0.6926(3)	0.026(1)
C(17)	-0.0447(6)	0.6157(3)	0.6340(3)	0.024(1)
C(51)	0.4695(6)	0.8093(3)	0.4982(2)	0.020(1)
C(52)	0.5295(7)	0.6710(3)	0.4108(3)	0.030(1)
C(53)	0.698(1)	0.5898(4)	0.4045(4)	0.044(2)

EXPERIMENTAL

All starting materials were commercially available (in most cases from Fluka). Melting points were taken with a Kofler micro

hot stage. The ¹H nmr (300 MHz) and ¹³C nmr (75.5 MHz) spectra were obtained with a Bruker Avance DPX 300 (300 MHz) spectrometer with deuteriochloroform and dimethyl sulfoxide-*d*₆ as solvents and tetramethylsilane as internal standard. Ir spectra were recorded with Perkin-Elmer Spectrum BX FTIR and Perkin-Elmer 1310 spectrophotometers. The microanalyses for C, H, and N were obtained with a Perkin-Elmer CHN Analyser 2400. Tlc: alu foils coated with silica gel 60 F 254 (0.2 mm, Merck). Column chromatography: silica gel (Fluka, silica gel 60, 0.04–0.063 mm).

The following compounds were prepared according to the procedures described in the literature: 6-chloro-3-hydrazinopyridazine (**5d**) [21], 3-hydrazino-6-phenylpyridazine (**5e**) [22], 6-hydrazinoimidazo[1,2-*b*]pyridazine (**5f**) [23], 6-hydrazino-1,2,4-triazolo[4,3-*b*]pyridazine (**5g**), 6-hydrazinotetrazolo[1,5-*b*]pyridazine (**5h**) [24], and 2-hydrazinopyrimidine (**5i**) [25].

Ethyl (*E*)-4-Dimethylamino-2-oxobut-3-enoate (**3**).

A mixture of ethyl pyruvate (**1**) (1.16 g, 10 mmoles), dichloromethane (20 ml), and *N,N*-dimethylformamide diethyl acetal (1.4 ml, 10 mmoles) was stirred at room temperature for 2 h. Volatile components were evaporated *in vacuo*, the residue was dissolved in *n*-hexane (5 ml), and the solution was left in a refrigerator (approx. –20 °C) for 24 h. The precipitate was collected by filtration to give **3**. Yield: 1.06 g (62%), yellow crystals; mp 36–39°, lit [16] mp 38°. Ir (cm⁻¹): 1724, 1644 (C=O). ¹H nmr (deuteriochloroform): δ 1.36 (3H, t, *J* = 7.1 Hz, CH₃CH₂); 2.94 and 3.18 (6H, 2s, 1:1, NMe₂); 4.30 (2H, q, *J* = 7.1 Hz, CH₂CH₃); 5.81 (1H, br d, *J* = 12.4 Hz, 3-H); 7.82 (1H, d, *J* = 12.4 Hz, 4-H). ¹³C nmr (deuteriochloroform): δ 14.5 (OCH₂CH₃); 37.9 (NCH₃); 45.8 (NCH₃); 62.0 (OCH₂CH₃); 92.0 (3-C); 156.4 (4-C); 164.9 (1-C), 178.4 (2-C).

Table 3

Fractional Coordinates and Equivalent Temperature Factors ($\text{\AA}^2$) for compound **9f**. 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(51)	0.62376(9)	0.3115(4)	0.49556(7)	0.0341(5)
O(52)	0.58705(9)	0.1143(4)	0.38546(7)	0.0318(5)
N(1)	0.8160(1)	0.2659(4)	0.46387(8)	0.0244(5)
N(2)	0.8823(1)	0.3781(5)	0.43295(9)	0.0308(5)
N(15)	0.8754(1)	-0.3011(4)	0.72077(8)	0.0274(5)
N(18)	0.8014(1)	-0.2123(4)	0.60954(8)	0.0225(5)
N(19)	0.7809(1)	-0.0892(4)	0.54311(8)	0.0235(5)
C(3)	0.8391(2)	0.4913(6)	0.3710(1)	0.0362(7)
C(4)	0.7452(1)	0.4514(6)	0.3606(1)	0.0328(6)
C(5)	0.7321(1)	0.3060(5)	0.4210(1)	0.0255(6)
C(11)	0.8406(1)	0.1136(5)	0.53048(9)	0.0230(5)
C(12)	0.9239(1)	0.1942(5)	0.5769(1)	0.0262(6)
C(13)	0.9422(1)	0.0622(5)	0.6426(1)	0.0268(6)
C(14)	0.8781(1)	-0.1457(5)	0.66094(9)	0.0236(5)
C(16)	0.7957(1)	-0.4656(5)	0.7060(1)	0.0298(6)
C(17)	0.7484(1)	-0.4170(5)	0.6381(1)	0.0263(6)
C(51)	0.6438(1)	0.2431(5)	0.4410(1)	0.0257(6)
C(52)	0.4961(1)	0.0536(7)	0.3959(1)	0.0335(7)
C(53)	0.4413(2)	-0.0586(8)	0.3258(1)	0.0404(8)

Table 4

Fractional Coordinates and Equivalent Temperature Factors ($\text{\AA}^2$) for compound **11e**. 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(41)	0.7739(4)	0.3418(3)	-0.0299(2)	0.086(1)
O(42)	0.6584(3)	0.4629(2)	0.1155(2)	0.0695(8)
O(51)	0.5713(3)	0.3775(2)	0.3831(2)	0.0671(8)
O(52)	0.3308(3)	0.4211(2)	0.2903(2)	0.0610(7)
N(1)	0.4642(3)	0.1190(2)	0.2549(2)	0.0437(6)
N(2)	0.5185(3)	0.0371(2)	0.1677(2)	0.0525(7)
N(1')	0.2161(3)	0.1175(2)	0.5249(2)	0.0540(7)
N(2')	0.3029(3)	0.1563(2)	0.4260(2)	0.0531(7)
C(3)	0.5981(4)	0.1136(3)	0.0884(2)	0.0543(9)
C(4)	0.5977(3)	0.2443(3)	0.1224(2)	0.0498(8)
C(5)	0.5092(3)	0.2444(2)	0.2300(2)	0.0439(7)
C(41)	0.6859(4)	0.3520(3)	0.0596(2)	0.0574(9)
C(42)	0.7406(6)	0.5796(4)	0.0665(4)	0.080(1)
C(43)	0.6755(9)	0.6884(4)	0.1427(5)	0.103(2)
C(51)	0.4755(4)	0.3545(2)	0.3118(2)	0.0497(8)
C(52)	0.2784(7)	0.5262(4)	0.3689(4)	0.090(2)
C(53)	0.1061(9)	0.5766(6)	0.3406(6)	0.122(2)
C(3')	0.3747(3)	0.0677(2)	0.3557(2)	0.0429(7)
C(4')	0.3697(4)	-0.0658(3)	0.3777(2)	0.0522(8)
C(5')	0.2825(4)	-0.1044(3)	0.4794(2)	0.0533(9)
C(6')	0.2050(3)	-0.0096(3)	0.5518(2)	0.0448(7)
C(61')	0.1059(3)	-0.0419(3)	0.6633(2)	0.0481(8)
C(62')	0.0478(4)	0.0573(3)	0.7376(2)	0.059(1)
C(63')	-0.0464(4)	0.0292(4)	0.8409(3)	0.071(1)
C(64')	-0.0849(4)	-0.0978(4)	0.8718(3)	0.071(1)
C(65')	-0.0290(4)	-0.1964(4)	0.7998(3)	0.069(1)
C(66')	0.0664(4)	-0.1696(3)	0.6955(3)	0.060(1)

Table 5

Fractional Coordinates and Equivalent Temperature Factors ($\text{\AA}^2$) for compound **11f**. 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(41)	0.2972(2)	0.5465(2)	0.1653(1)	0.0640(6)
O(42)	0.5747(2)	0.5157(2)	0.1710(1)	0.0485(4)
O(51)	-0.0417(2)	0.3265(2)	0.2758(1)	0.0533(5)
O(52)	-0.0436(2)	0.1590(2)	0.1260(1)	0.0439(4)
N(1)	0.2451(2)	0.0901(2)	0.3129(1)	0.0358(4)
N(2)	0.4253(2)	0.1007(2)	0.3325(1)	0.0410(5)
N(1')	-0.0347(2)	-0.0257(2)	0.3529(1)	0.0351(4)
N(6')	-0.1481(2)	-0.1552(2)	0.3895(1)	0.0332(4)
N(7')	-0.2488(2)	-0.3976(2)	0.4560(1)	0.0444(5)
C(3)	0.5018(2)	0.2390(2)	0.2931(1)	0.0394(5)
C(4)	0.3748(2)	0.3199(2)	0.2480(1)	0.0366(5)
C(5)	0.2109(2)	0.2218(2)	0.2628(1)	0.0340(5)
C(41)	0.4067(2)	0.4726(2)	0.1916(1)	0.0408(5)
C(42)	0.6293(3)	0.6664(2)	0.1176(2)	0.0525(7)
C(43)	0.8177(3)	0.6846(3)	0.1004(2)	0.0669(9)
C(51)	0.0265(2)	0.2431(2)	0.2254(1)	0.0360(5)
C(52)	-0.2202(3)	0.1714(4)	0.0753(2)	0.0675(9)
C(53)	-0.2663(3)	0.0882(4)	-0.0390(2)	0.0655(9)
C(2')	0.1247(2)	-0.0439(2)	0.3510(1)	0.0354(5)
C(3')	0.1830(2)	-0.1825(2)	0.3820(2)	0.0528(7)
C(4')	0.0669(2)	-0.3093(2)	0.4192(2)	0.0530(7)
C(5')	-0.1076(2)	-0.2976(2)	0.4240(1)	0.0385(5)
C(8')	-0.3797(2)	-0.3180(2)	0.4410(2)	0.0425(6)
C(9')	-0.3222(2)	-0.1687(2)	0.4004(2)	0.0407(6)

Table 6

Bond Distances ($\text{\AA}$) and Bond Angles ($^\circ$) with e.s.d.'s in parentheses for compound **8f**.

O(5)-C(5)	1.390(4)	N(18)-C(14)	1.376(5)
O(51)-C(51)	1.201(4)	N(18)-C(17)	1.367(5)
O(52)-C(51)	1.344(5)	N(19)-C(11)	1.314(4)
O(52)-C(52)	1.455(5)	C(3)-C(4)	1.499(5)
N(1)-N(2)	1.397(4)	C(4)-C(5)	1.550(5)
N(1)-C(5)	1.479(5)	C(5)-C(51)	1.534(5)
N(1)-C(11)	1.373(5)	C(11)-C(12)	1.442(5)
N(2)-C(3)	1.276(5)	C(12)-C(13)	1.356(5)
N(15)-C(14)	1.338(5)	C(13)-C(14)	1.414(5)
N(15)-C(16)	1.371(5)	C(16)-C(17)	1.370(6)
N(18)-N(19)	1.366(4)	C(52)-C(53)	1.495(7)
C(51)-O(52)-C(52)	115.2(3)	N(1)-C(5)-C(51)	112.3(3)
N(2)-N(1)-C(5)	112.2(3)	C(4)-C(5)-C(51)	113.1(3)
N(2)-N(1)-C(11)	119.9(3)	N(1)-C(11)-N(19)	115.6(3)
C(5)-N(1)-C(11)	125.6(3)	N(1)-C(11)-C(12)	119.6(3)
N(1)-N(2)-C(3)	107.0(3)	N(19)-C(11)-C(12)	124.7(3)
C(14)-N(15)-C(16)	104.9(3)	C(11)-C(12)-C(13)	118.8(3)
N(19)-N(18)-C(14)	126.5(3)	C(12)-C(13)-C(14)	118.4(3)
N(19)-N(18)-C(17)	125.5(3)	N(15)-C(14)-N(18)	110.5(3)
C(14)-N(18)-C(17)	108.0(3)	N(15)-C(14)-C(13)	132.0(3)
N(18)-N(19)-C(11)	114.1(3)	N(18)-C(14)-C(13)	117.5(3)
N(2)-C(3)-C(4)	114.8(3)	N(15)-C(16)-C(17)	111.7(3)
C(3)-C(4)-C(5)	101.3(3)	N(18)-C(17)-C(16)	105.0(3)
O(5)-C(5)-N(1)	111.9(3)	O(51)-C(51)-O(52)	124.3(3)
O(5)-C(5)-C(4)	113.4(3)	O(51)-C(51)-C(5)	124.4(3)
O(5)-C(5)-C(51)	106.6(3)	O(52)-C(51)-C(5)	111.2(3)
N(1)-C(5)-C(4)	99.6(3)	O(52)-C(52)-C(53)	107.8(4)

Table 7

Bond Distances (Å) and Bond Angles (°) with e.s.d.'s in parentheses for compound **9f**

O(51)-C(51)	1.196(3)	N(18)-C(17)	1.371(3)
O(52)-C(51)	1.339(2)	N(19)-C(11)	1.302(3)
O(52)-C(52)	1.459(3)	C(3)-C(4)	1.405(3)
N(1)-N(2)	1.359(3)	C(4)-C(5)	1.369(3)
N(1)-C(5)	1.374(2)	C(5)-C(51)	1.493(3)
N(1)-C(11)	1.416(2)	C(11)-C(12)	1.426(2)
N(2)-C(3)	1.326(3)	C(12)-C(13)	1.362(3)
N(15)-C(14)	1.337(3)	C(13)-C(14)	1.405(3)
N(15)-C(16)	1.368(3)	C(16)-C(17)	1.371(3)
N(18)-N(19)	1.359(2)	C(52)-C(53)	1.507(3)
N(18)-C(14)	1.389(2)		
C(51)-O(52)-C(52)	115.1(2)	N(1)-C(11)-N(19)	114.0(1)
N(2)-N(1)-C(5)	111.6(2)	N(1)-C(11)-C(12)	119.5(2)
N(2)-N(1)-C(11)	118.8(1)	N(19)-C(11)-C(12)	126.5(2)
C(5)-N(1)-C(11)	129.4(2)	C(11)-C(12)-C(13)	117.9(2)
N(1)-N(2)-C(3)	104.7(2)	C(12)-C(13)-C(14)	118.3(2)
C(14)-N(15)-C(16)	104.7(1)	N(15)-C(14)-N(18)	110.3(2)
N(19)-N(18)-C(14)	126.1(2)	N(15)-C(14)-C(13)	132.2(2)
N(19)-N(18)-C(17)	125.8(1)	N(18)-C(14)-C(13)	117.6(2)
C(14)-N(18)-C(17)	108.1(1)	N(15)-C(16)-C(17)	112.5(2)
N(18)-N(19)-C(11)	113.5(1)	N(18)-C(17)-C(16)	104.4(2)
N(2)-C(3)-C(4)	112.1(2)	O(51)-C(51)-O(52)	124.4(2)
C(3)-C(4)-C(5)	105.0(2)	O(51)-C(51)-C(5)	126.8(2)
N(1)-C(5)-C(4)	106.6(2)	O(52)-C(51)-C(5)	108.8(2)
N(1)-C(5)-C(51)	126.0(2)	O(52)-C(52)-C(53)	106.6(2)
C(4)-C(5)-C(51)	127.0(2)		

Table 8

Bond Distances (Å) and Bond Angles (°) with e.s.d.'s in parentheses for compound **11e**

O(41)-C(41)	1.202(4)	C(4)-C(41)	1.463(4)
O(42)-C(41)	1.331(4)	C(5)-C(51)	1.504(4)
O(42)-C(42)	1.454(5)	C(42)-C(43)	1.494(7)
O(51)-C(51)	1.194(4)	C(52)-C(53)	1.464(8)
O(52)-C(51)	1.321(3)	C(3')-C(4')	1.384(4)
O(52)-C(52)	1.461(5)	C(4')-C(5')	1.369(4)
N(1)-N(2)	1.369(3)	C(5')-C(6')	1.393(4)
N(1)-C(5)	1.360(3)	C(6')-C(61')	1.488(3)
N(1)-C(3')	1.411(3)	C(61')-C(62')	1.394(4)
N(2)-C(3)	1.320(4)	C(61')-C(66')	1.388(4)
N(1')-N(2')	1.342(3)	C(62')-C(63')	1.383(4)
N(1')-C(6')	1.333(3)	C(63')-C(64')	1.375(6)
N(2')-C(3')	1.318(3)	C(64')-C(65')	1.369(5)
C(3)-C(4)	1.409(4)	C(65')-C(66')	1.394(4)
C(4)-C(5)	1.379(3)		
C(41)-O(42)-C(42)	118.4(3)	O(51)-C(51)-C(5)	123.2(2)
C(51)-O(52)-C(52)	115.4(3)	O(52)-C(51)-C(5)	110.3(2)
N(2)-N(1)-C(5)	112.2(2)	O(52)-C(52)-C(53)	107.2(4)
N(2)-N(1)-C(3')	119.4(2)	N(1)-C(3')-N(2')	114.8(2)
C(5)-N(1)-C(3')	128.4(2)	N(1)-C(3')-C(4')	121.1(2)
N(1)-N(2)-C(3)	104.4(2)	N(2')-C(3')-C(4')	124.1(2)
N(2')-N(1')-C(6')	119.9(2)	C(3')-C(4')-C(5')	116.0(2)
N(1')-N(2')-C(3')	119.4(2)	C(4')-C(5')-C(6')	119.1(2)
N(2)-C(3)-C(4)	112.2(2)	N(1')-C(6')-C(5')	121.4(2)
C(3)-C(4)-C(5)	104.9(2)	N(1')-C(6')-C(61')	115.6(2)
C(3)-C(4)-C(41)	126.5(2)	C(5')-C(6')-C(61')	123.0(2)
C(5)-C(4)-C(41)	128.5(2)	C(6')-C(61')-C(62')	120.1(2)
N(1)-C(5)-C(4)	106.4(2)	C(6')-C(61')-C(66')	121.6(2)
N(1)-C(5)-C(51)	124.2(2)	C(62')-C(61')-C(66')	118.3(2)
C(4)-C(5)-C(51)	129.3(2)	C(61')-C(62')-C(63')	120.9(3)
O(41)-C(41)-O(42)	124.2(3)	C(62')-C(63')-C(64')	120.3(3)
O(41)-C(41)-C(4)	124.8(3)	C(63')-C(64')-C(65')	119.6(3)
O(42)-C(41)-C(4)	111.1(2)	C(64')-C(65')-C(66')	120.7(4)
O(42)-C(42)-C(43)	105.9(4)	C(61')-C(66')-C(65')	120.2(3)
O(51)-C(51)-O(52)	126.5(3)		

Table 9

Bond Distances (Å) and Bond Angles (°) with e.s.d.'s in parentheses for compound **11f**.

O(41)-C(41)	1.201(3)	N(6')-C(9')	1.365(2)
O(42)-C(41)	1.335(2)	N(7')-C(5')	1.327(2)
O(42)-C(42)	1.451(2)	N(7')-C(8')	1.363(3)
O(51)-C(51)	1.192(2)	C(3)-C(4)	1.408(2)
O(52)-C(51)	1.333(2)	C(4)-C(5)	1.375(2)
O(52)-C(52)	1.456(3)	C(4)-C(41)	1.473(2)
N(1)-N(2)	1.372(2)	C(5)-C(51)	1.504(2)
N(1)-C(5)	1.361(2)	C(42)-C(43)	1.489(4)
N(1)-C(2')	1.418(2)	C(52)-C(53)	1.474(4)
N(2)-C(3)	1.316(2)	C(2')-C(3')	1.414(3)
N(1')-N(6')	1.357(2)	C(3')-C(4')	1.357(3)
N(1')-C(2')	1.301(2)	C(4')-C(5')	1.405(3)
N(6')-C(5')	1.393(2)	C(8')-C(9')	1.368(3)
C(41)-O(42)-C(42)	117.0(2)	O(41)-C(41)-O(42)	124.5(2)
C(51)-O(52)-C(52)	116.1(2)	O(41)-C(41)-C(4)	125.4(2)
N(2)-N(1)-C(5)	111.9(1)	O(42)-C(41)-C(4)	110.1(2)
N(2)-N(1)-C(2')	118.6(1)	O(42)-C(42)-C(43)	106.9(2)
C(5)-N(1)-C(2')	129.4(1)	O(51)-C(51)-O(52)	126.2(2)
N(1)-N(2)-C(3)	104.7(1)	O(51)-C(51)-C(5)	124.8(1)
N(6')-N(1')-C(2')	113.7(1)	O(52)-C(51)-C(5)	109.0(1)
N(1')-N(6')-C(5')	126.4(1)	O(52)-C(52)-C(53)	108.6(2)
N(1')-N(6')-C(9')	126.2(1)	N(1)-C(2')-N(1')	114.5(1)
C(5')-N(6')-C(9')	107.5(1)	N(1)-C(2')-C(3')	119.6(1)
C(5')-N(7')-C(8')	105.0(1)	N(1')-C(2')-C(3')	125.9(1)
N(2)-C(3)-C(4)	111.9(1)	C(2')-C(3')-C(4')	119.0(2)
C(3)-C(4)-C(5)	105.4(1)	C(3')-C(4')-C(5')	118.2(2)
C(3)-C(4)-C(41)	128.0(1)	N(6')-C(5')-N(7')	110.4(2)
C(5)-C(4)-C(41)	126.6(2)	N(6')-C(5')-C(4')	116.8(1)
N(1)-C(5)-C(4)	106.2(1)	N(7')-C(5')-C(4')	132.7(2)
N(1)-C(5)-C(51)	124.9(1)	N(7')-C(8')-C(9')	112.2(2)
C(4)-C(5)-C(51)	128.8(1)	N(6')-C(9')-C(8')	104.9(2)

Anal. Calcd. for $C_8H_{13}NO_3$ (171.19): C, 56.13; H, 7.65; N, 8.18. Found: C, 54.57; H, 8.63; N, 7.55. *Hrms* Calcd. for $C_8H_{13}NO_3$: 171.089543. Found: 171.089700.

Diethyl 3-[(Dimethylamino)methylidene]-2-oxosuccinate (**4**).

A mixture of sodium salt of diethyl 2-oxosuccinate (**2**) (2.12 g, 10 mmol), anhydrous ethanol (5 ml), and *N,N*-dimethylformamide dimethyl acetal (2.66 ml, 20 mmol) was stirred at room temperature for 30 min. Then acetic acid (100%, 1.2 ml, 20 mmol) was added in 6 portions (0.2 ml each) in 30 minute intervals and the mixture was stirred at room temperature for 24 h. Volatile components were evaporated *in vacuo* and the oily residue was purified by column chromatography (ethyl acetate/*n*-hexane, 1:2). Fractions containing the product were combined and evaporated *in vacuo* to give **4** which was used for further transformations without purification. Yield: 1.15 g (47%); oil. *Ir* (cm^{-1}): 1732, 1691, 1641 (C=O). *Ms* (*m/z*): 243 (M^+ , EI); 244 (MH^+ , FAB). 1H nmr (deuteriochloroform): δ 1.26 and 1.36 (6H, 2t, 1:1, $J = 7.2$ Hz, 2 x CH_3CH_2); 3.04 and 3.35 (6H, 2s, 1:1, NMe_2); 4.17 and 4.30 (4H, 2q, 1:1, $J = 7.2$ Hz, 2 x CH_2CH_3); 7.84 (1H, s, $CHNMe_2$). ^{13}C nmr (deuteriochloroform): δ 14.4 (OCH_2CH_3), 14.6 (OCH_2CH_3), 43.5 (NCH_3), 48.7 (NCH_3), 60.6 (OCH_2CH_3), 61.7 (OCH_2CH_3), 97.9 (3-C); 160.4 (3'-C), 166.3 (COOEt), 167.0 (COOEt), 183.7 (C=O).

Anal. Calcd. for $C_{11}H_{17}NO_5$ (243.26): C, 54.31; H, 7.04; N, 5.76. Found: C, 52.36; H, 7.24; N, 5.43. *Hrms* Calcd. for $C_{11}H_{17}NO_5$: 243.110673. Found: 243.111240.

Ethyl 1-(6-Chloropyridazin-3-yl)-4,5-dihydro-5-hydroxy-1H-pyrazole-5-carboxylate (**8d**).

Hydrochloric acid (37%, 4 drops, ~1.3 mmol) was added to a solution of **3** (0.514 g, 3 mmol) and 6-chloro-3-hydrazinopyridazine (**5d**) (0.433 g, 3 mmol) in ethanol (15 ml) and the mixture was stirred at room temperature for 24 h. Volatile components were evaporated *in vacuo*, the residue was dissolved in chloroform (100 ml), and the chloroform solution was washed with aqueous sodium hydrogensulfate (1M, 2 x 50 ml) and water (2 x 50 ml). The organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. The solid residue was crystallized from methanol to give **8d**. Yield: 0.639 g (78%); mp 95–96° (from methanol). *Ir* (cm^{-1}): 3393 (O–H), 1748 (C=O). 1H nmr (deuteriochloroform): δ 1.28 (3H, t, $J = 7.1$ Hz, CH_3CH_2); 3.24 (1H, dd, $J = 1.6, 18.7$ Hz, 4–Ha); 3.41 (1H, dd, $J = 1.6, 18.7$ Hz, 4–Hb); 4.32 (2H, q, $J = 7.1$ Hz, CH_2CH_3); 5.18 (1H, s, OH); 7.03 (1H, t, $J = 1.6$ Hz, 3–H); 7.36 (1H, d, $J = 9.3$ Hz, 5'–H); 7.56 (1H, d, $J = 9.3$ Hz, 4'–H).

Anal. Calcd. for $C_{10}H_{11}ClN_4O_3$ (270.67): C, 44.37; H, 4.10; N, 20.70. Found: C, 44.60; H, 4.35; N, 20.91.

Ethyl 4,5-Dihydro-5-hydroxy-1-(6-phenylpyridazin-3-yl)-1H-pyrazole-5-carboxylate (**8e**).

Hydrochloric acid (37%, 2 drops, ~0.7 mmol) was added to a solution of **3** (0.171 g, 1 mmol) and 3-hydrazino-6-phenylpyridazine (**5e**) (0.186 g, 1 mmol) in methanol (4 ml) and the mixture was stirred at room temperature for 24 h. Volatile components were evaporated *in vacuo*, the residue was dissolved in chloroform (100 ml), and the chloroform solution was washed with aqueous sodium hydrogensulfate (1M, 2 x 100 ml) and water (2 x 100 ml). The organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. The solid residue was crystallized from methanol to give **8e**. Yield: 0.297 g (95%); mp 149–151° (from methanol). *Ir* (cm^{-1}):

3420 (O–H), 1753 (C=O). 1H nmr (deuteriochloroform): δ 1.25 (3H, t, $J = 7.1$ Hz, CH_3CH_2); 3.24 (1H, dd, $J = 1.6, 18.7$ Hz, 4–Ha); 3.41 (1H, dd, $J = 1.6, 18.7$ Hz, 4–Hb); 4.32 (2H, q, $J = 7.1$ Hz, CH_2CH_3); 5.41 (1H, br s, OH); 7.01 (1H, t, $J = 1.6$ Hz, 3–H); 7.43–7.51 (3H, m, 3H of Ph); 7.64 (1H, d, $J = 9.3$ Hz, 4'–H); 7.79 (1H, d, $J = 9.3$ Hz, 5'–H); 7.95–7.98 (2H, m, 2H of Ph). ^{13}C nmr (deuteriochloroform): δ 14.4, 48.1, 63.3, 88.9, 116.1, 126.7, 126.9, 129.3, 129.6, 136.9, 142.0, 154.3, 155.6, 171.2.

Anal. Calcd. for $C_{16}H_{16}N_4O_3$ (312.32): C, 61.53; H, 5.16; N, 17.94. Found: C, 63.81; H, 5.44; N, 16.41. *Hrms* Calcd. for $C_{16}H_{16}N_4O_3$: 312.122241. Found: 312.123540.

Ethyl 4,5-Dihydro-5-hydroxy-1-(imidazo[1,2-*b*]pyridazin-6-yl)-1H-pyrazole-5-carboxylate (**8f**).

A mixture of **3** (0.513 g, 3 mmol) and 6-hydrazinoimidazo[1,2-*b*]pyridazine (**5f**) (0.445 g, 3 mmol), and acetic acid (100%, 5 ml) was stirred at room temperature for 24 h. Volatile components were evaporated *in vacuo*, the residue was dissolved in chloroform (50 ml), and the chloroform solution was washed with saturated aqueous sodium hydrogencarbonate (2 x 50 ml) and water (2 x 50 ml). The organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. The oily residue was purified by column chromatography (chloroform/methanol, 20:1). Fractions containing the product were combined and evaporated *in vacuo* to give **8f**. Yield: 0.389 g (47%); mp 177–180°. *Ir* (cm^{-1}): 3462 (O–H), 1761 (C=O). 1H nmr (deuteriochloroform): δ 1.21 (3H, t, $J = 7.1$ Hz, CH_3CH_2); 3.19 (1H, dd, $J = 1.6, 18.6$ Hz, 4–Ha); 3.40 (1H, dd, $J = 1.6, 18.6$ Hz, 4–Hb); 4.30 (2H, q, $J = 7.1$ Hz, CH_2CH_3); 5.05 (1H, br s, OH); 6.97 (1H, t, $J = 1.6$ Hz, 3–H); 7.37 (1H, d, $J = 9.8$ Hz, 7'–H); 7.57 (1H, d, $J = 1.1$ Hz, 3'–H); 7.61 (1H, br s, 2'–H); 7.82 (1H, dd, $J = 0.8, 9.8$ Hz, 8'–H). ^{13}C nmr (dimethyl sulfoxide- d_6): δ 14.4, 48.4, 63.3, 88.6, 110.7, 116.3, 127.3, 132.5, 137.3, 141.3, 150.6, 171.3.

Anal. Calcd. for $C_{12}H_{13}N_5O_3$ (275.26): C, 52.36; H, 4.76; N, 25.44. Found: C, 52.60; H, 4.68; N, 25.75.

Ethyl 1H-Pyrazole-5(3)-carboxylate (**9a**).

A mixture of **3** (0.342 g, 2 mmol), hydrazine monohydrochloride (**5a**) (0.137 g, 2 mmol), and methanol (2 ml) was stirred at 60° for 6 h. Volatile components were evaporated *in vacuo*, the residue was dissolved in chloroform (50 ml), and the chloroform solution was washed with aqueous sodium hydrogensulfate (1M, 2 x 50 ml) and with water (2 x 50 ml). Organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. The solid residue was crystallized from chloroform to give **9a**. Yield: 0.213 g (76%); mp 158–160° (from chloroform), lit [26] mp 158.0–158.5°. *Ir* (cm^{-1}): 3250 (N–H), 1699 (C=O). 1H nmr (deuteriochloroform): δ 1.41 (3H, t, $J = 7.1$ Hz, CH_3CH_2); 4.42 (2H, q, $J = 7.1$ Hz, CH_2CH_3); 6.86 (1H, d, $J = 2.3$ Hz, 4–H); 7.76 (1H, d, $J = 2.3$ Hz, 3–H). ^{13}C nmr (dimethyl sulfoxide- d_6): δ 15.1, 60.8, 108.2, 130.8, 143.8, 163.0.

Anal. Calcd. for $C_6H_8N_2O_2$ (140.14): C, 51.42; H, 5.75; N, 19.99. Found: C, 51.18; H, 6.02; N, 19.60.

Ethyl 1-Phenyl-1H-pyrazole-5-carboxylate (**9b**).

A solution of phenylhydrazine monohydrochloride (**5b**) (0.723 g, 5 mmol) in methanol (10 ml) was added to a solution of **3** (0.856 g, 5 mmol) in methanol (5 ml) and the mixture was stirred at room temperature for 12 h. Volatile components were evaporated *in vacuo*, the residue was dissolved in chloroform

(100 ml), and the chloroform solution was washed with saturated aqueous sodium hydrogencarbonate (2 x 100 ml), aqueous sodium hydrogensulfate (1M, 2 x 100 ml), and water (2 x 100 ml). Organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. The oily residue was purified by column chromatography (chloroform/methanol, 50:1). Fractions containing the product were combined and evaporated *in vacuo*. The oily residue was purified again by column chromatography (diethyl ether/*n*-hexane, 5:1). Fractions containing the product were combined and evaporated *in vacuo* to give **9b**. Yield: 0.101 g (9%); oil. Ir (cm⁻¹): 1731 (C=O). ¹H nmr (deuteriochloroform): δ 1.23 (3H, t, *J* = 7.2 Hz, CH₃CH₂); 4.23 (2H, q, *J* = 7.2 Hz, CH₂CH₃); 7.02 (1H, d, *J* = 2.3 Hz, 4-H); 7.39–7.49 (5H, m, Ph); 7.68 (1H, d, *J* = 2.3 Hz, 3-H). ¹³C nmr (deuteriochloroform): δ 14.4, 61.5, 112.9, 126.4, 128.9, 129.0, 133.9, 140.0, 140.8, 159.6.

Anal. Calcd. for C₁₂H₁₂N₂O₂ (216.24): C, 66.65; H, 5.59; N, 12.96. Found: C, 65.82; H, 5.85; N, 12.28. *Hrms* Calcd. for C₁₂H₁₂N₂O₂: 216.089878. Found: 216.090550.

Ethyl 1-(4-Nitrophenyl)-1H-pyrazole-5-carboxylate (**9c**).

A solution of **3** (0.172 g, 1 mmole) in ethanol (3 ml) was added to a solution of 4-nitrophenylhydrazine (**5c**) (0.154 g, 1 mmole) in a mixture of ethanol (3 ml) and hydrochloric acid (37%, 4 drops, ~1.3 mmole) and the mixture was stirred at room temperature for 24 h. Volatile components were evaporated *in vacuo*, the residue was dissolved in chloroform (100 ml), and the chloroform solution was washed with aqueous sodium hydrogensulfate (1M, 2 x 100 ml), saturated aqueous sodium hydrogencarbonate (2 x 100 ml), and water (2 x 100 ml). The organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. The solid residue was crystallized from ethanol to give **9c**. Yield: 0.189 g (72%); mp 114–117° (from ethanol). Ir (cm⁻¹): 1727 (C=O). ¹H nmr (deuteriochloroform): δ 1.31 (3H, t, *J* = 7.2 Hz, CH₃CH₂); 4.30 (2H, q, *J* = 7.2 Hz, CH₂CH₃); 7.09 (1H, d, *J* = 1.9 Hz, 4-H); 7.66 (2H, dt, *J* = 2.0, 9.0 Hz, 2H of C₆H₄); 7.76 (1H, d, *J* = 1.9 Hz, 3-H); 8.33 (2H, dt, *J* = 2.0, 9.0 Hz, 2H of C₆H₄).

Anal. Calcd. for C₁₂H₁₁N₃O₄ (261.23): C, 55.17; H, 4.24; N, 16.09. Found: C, 55.09; H, 4.27; N, 15.78. *Hrms* Calcd. for C₁₂H₁₁N₃O₄: 261.074956. Found: 261.075950.

Ethyl 1-(1,6-Dihydro-6-oxopyridazin-3-yl)-1H-pyrazole-5-carboxylate (**9d**).

A mixture of **8d** (0.091 g, 0.3 mmole) and acetic acid (100%, 2 ml) was heated under reflux for 3 h and cooled to room temperature. Then water (50 ml) was added and the product was extracted with dichloromethane (3 x 50 ml). Organic phases were combined, dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo* to give **9d**. Yield: 0.060 g (75%); mp 131–132.5°. Ir (cm⁻¹): 1713, 1692 (C=O). ¹H nmr (deuteriochloroform): δ 1.33 (3H, t, *J* = 7.1 Hz, CH₃CH₂); 4.33 (2H, q, *J* = 7.1 Hz, CH₂CH₃); 6.98 (1H, d, *J* = 1.9 Hz, 4-H); 7.08 (1H, d, *J* = 10.0 Hz, 4'-H); 7.58 (1H, d, *J* = 10.0 Hz, 5'-H); 7.73 (1H, d, *J* = 1.9 Hz, 3-H); 10.92 (1H, br s, NH). ¹³C nmr (dimethyl sulfoxide-d₆): δ 14.5, 62.2, 113.3, 131.7, 132.0, 134.9, 141.5, 142.4, 159.4, 161.6.

Anal. Calcd. for C₁₀H₁₀N₄O₃ (234.21): C, 51.28; H, 4.30; N, 23.92. Found: C, 51.57; H, 4.51; N, 23.32. *Hrms* Calcd. for C₁₀H₁₀N₄O₃: 234.075290. Found: 234.075350.

Ethyl 1-(6-Phenylpyridazin-3-yl)-1H-pyrazole-5-carboxylate (**9e**).

A mixture of **8e** (0.115 g, 0.4 mmole) and acetic acid (100%, 6 ml) was heated under reflux for 1 h and cooled to room temperature. Then water (50 ml) was added and the product was extracted with dichloromethane (3 x 50 ml). Organic phases were combined, dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. The solid residue was purified by column chromatography (ethyl acetate/*n*-hexane, 1:2). Fractions containing the product were combined and evaporated *in vacuo* to give **9e**. Yield: 0.115 g (88%); mp 80–82°. Ir (cm⁻¹): 1732 (C=O). ¹H nmr (deuteriochloroform): δ 1.29 (3H, t, *J* = 7.1 Hz, CH₃CH₂); 4.35 (2H, q, *J* = 7.1 Hz, CH₂CH₃); 7.00 (1H, d, *J* = 1.8 Hz, 4-H); 7.52–7.56 (3H, m, 3H-Ph); 7.80 (1H, d, *J* = 1.8 Hz, 4'-H); 7.96 (1H, d, *J* = 9.0 Hz, 4'-H); 8.05 (1H, d, *J* = 9.0 Hz, 5'-H); 8.10–8.13 (2H, m, 2H-Ph). ¹³C nmr (deuteriochloroform): δ 14.4, 62.2, 113.1, 123.1, 126.3, 127.7, 129.5, 130.8, 135.6, 135.9, 142.0, 154.7, 159.5, 160.3.

Anal. Calcd. for C₁₆H₁₄N₄O₂ (294.31): C, 65.30; H, 4.79; N, 19.04. Found: C, 64.87; H, 4.88; N, 18.80. *Hrms* Calcd. for C₁₆H₁₄N₄O₂: 294.111676. Found: 294.112550.

Ethyl 1-(Imidazo[1,2-*b*]pyridazin-6-yl)-1H-pyrazole-5-carboxylate (**9f**).

A mixture of **8f** (0.250 g, 0.9 mmole) and acetic acid (100%, 3 ml) was heated under reflux for 8 h and cooled to room temperature. Then water (10 ml) was added and the product was extracted with dichloromethane (4 x 10 ml). Organic phases were combined, dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. The solid residue was crystallized from a mixture of diethyl ether and *n*-hexane to give **9f**. Yield: 0.161 g (69%); mp 64.5–66° (from diethyl ether/*n*-hexane). Ir (cm⁻¹): 1746 (C=O). ¹H nmr (deuteriochloroform): δ 1.26 (3H, t, *J* = 7.1 Hz, CH₃CH₂); 4.31 (2H, q, *J* = 7.1 Hz, CH₂CH₃); 7.03 (1H, d, *J* = 1.8 Hz, 4-H); 7.41 (1H, d, *J* = 9.5 Hz, 7'-H); 7.80 (1H, d, *J* = 1.8 Hz, 3-H); 7.85 (1H, d, *J* = 1.2 Hz, 3'-H); 7.95 (1H, br s, 2'-H); 8.10 (1H, d, *J* = 9.5 Hz, 8'-H). ¹³C nmr (deuteriochloroform): δ 14.4, 62.1, 113.4, 115.6, 117.6, 127.2, 135.3, 136.0, 138.8, 141.8, 148.4, 159.6.

Anal. Calcd. for C₁₂H₁₁N₅O₂ (257.25): C, 56.03; H, 4.31; N, 27.22. Found: C, 55.95; H, 4.43; N, 26.96.

Diethyl 1-Substituted 1H-Pyrazole-4,5-dicarboxylates **11a–d**, **f–i**.

General Procedure.

A mixture of **4** (0.243 g, 1 mmole), hydrazine derivative **5** (1 mmole), ethanol (10 ml), and hydrochloric acid (37%, 0.1 ml, ~1 mmole) was stirred at 20–60° for 2–24 h. Volatile components were evaporated *in vacuo*, the residue was dissolved in dichloromethane (100 ml), and the dichloromethane solution was washed with aqueous sodium hydrogensulfate (1M, 100 ml), saturated aqueous sodium hydrogencarbonate (2 x 100 ml), and water (100 ml). The organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo* to give **11a–d**, **f–i**.

Diethyl 1H-Pyrazole-4,5-dicarboxylate (**11a**).

This compound was prepared from **4** and hydrazine monohydrochloride (**5a**) (0.069 g, 1 mmole); stirring at 60° for 2 h. Yield: 0.120 g (56%); mp 69–71°, lit [27] mp 69–70°. Ir (cm⁻¹): 3156,

3123 (N–H), 1737, 1731 (C=O). ^1H nmr (deuteriochloroform): δ 1.37 and 1.42 (6H, 2t, 1:1, $J = 7.2$ Hz, $2 \times \text{CH}_3\text{CH}_2$); 4.34 and 4.45 (4H, 2q, 1:1, $J = 7.2$ Hz, $2 \times \text{CH}_2\text{CH}_3$); 8.09 (1H, s, 3–H); 11.31 (1H, br s, 1–H). ^{13}C nmr (deuteriochloroform): δ 14.2, 14.3, 60.9, 61.9, 115.1, 136.2, 141.4, 161.6, 162.0.

Diethyl 1-Phenyl-1H-pyrazole-4,5-dicarboxylate (**11b**).

This compound was prepared from **4** and phenylhydrazine monohydrochloride (**5a**) (0.145 g, 1 mmole); stirring at room temperature for 6 h. Yield: 0.247 g (86%); oil. Ir (cm^{-1}): 1741, 1722 (C=O). ^1H nmr (deuteriochloroform): δ 1.23 and 1.35 (6H, 2t, 1:1, $J = 7.2$ Hz, $2 \times \text{CH}_3\text{CH}_2$); 4.33 and 4.34 (4H, 2q, 1:1, $J = 7.2$ Hz, $2 \times \text{CH}_2\text{CH}_3$); 7.39–7.53 (5H, m, Ph); 8.05 (1H, s, 3–H). ^{13}C nmr (deuteriochloroform): δ 14.1, 14.6, 61.2, 63.1, 124.4, 129.4, 129.7, 137.4, 139.4, 141.7, 161.2, 162.1. Ir and nmr data are in agreement with the literature [28] data.

Hrms Calcd. for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_4$: 288.111007. Found: 288.111960.

Diethyl 1-(4-Nitrophenyl)-1H-pyrazole-4,5-dicarboxylate (**11c**).

This compound was prepared from **4** and 4-nitrophenylhydrazine (**5c**) (0.153 g, 1 mmole); stirring at room temperature for 24 h. Yield: 0.120 g (36%); mp 70–73° (from ethanol), lit [28] mp 73–75°. Ir (cm^{-1}): 1741, 1720 (C=O). ^1H nmr (deuteriochloroform): δ 1.32 and 1.36 (6H, 2t, 1:1, $J = 7.2$ Hz, $2 \times \text{CH}_3\text{CH}_2$); 4.35 and 4.40 (4H, 2q, 1:1, $J = 7.2$ Hz, $2 \times \text{CH}_2\text{CH}_3$); 7.23 (2H, dt, $J = 2.5, 9.0$ Hz, 2H of Ar); 8.09 (1H, s, 3–H); 8.35 (2H, dt, $J = 2.5, 9.0$ Hz, 2H of Ar). ^{13}C nmr (deuteriochloroform): δ 14.2, 14.6, 61.5, 63.6, 117.6, 124.5, 125.3, 137.4, 142.7, 144.0, 147.7, 160.9, 161.7.

Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_6$ (333.30): C, 54.05; H, 4.54; N, 12.61. Found: C, 53.93; H, 4.53; N, 12.75.

Diethyl 1-(6-Chloropyridazin-3-yl)-1H-pyrazole-4,5-dicarboxylate (**11d**).

This compound was prepared from **4** and 6-chloro-3-hydrazinopyridazine (**5d**) (0.145 g, 1 mmole); stirring at room temperature for 8 h. Yield: 0.093 g (29%); mp 95–99° (from ethanol). Ir (cm^{-1}): 1748, 1719 (C=O). ^1H nmr (deuteriochloroform): δ 1.36 and 1.43 (6H, 2t, 1:1, $J = 7.2$ Hz, CH_3CH_2); 4.35 and 4.55 (4H, 2q, 1:1, $J = 7.2$ Hz, CH_2CH_3); 7.68 (1H, d, $J = 9.0$ Hz, 5'–H); 8.12 (1H, s, 3–H); 8.17 (1H, d, $J = 9.4$ Hz, 4'–H). ^{13}C nmr (deuteriochloroform): δ 14.2, 14.5, 61.5, 63.5, 117.4, 121.8, 131.2, 137.4, 143.5, 153.7, 156.2, 161.2, 161.5.

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{ClN}_4\text{O}_4$ (324.72): C, 48.08; H, 4.04; N, 17.25. Found: C, 48.36; H, 3.99; N, 17.26.

Diethyl 1-(Imidazo[1,2-*b*]pyridazin-6-yl)-1H-pyrazole-4,5-dicarboxylate (**11f**).

This compound was prepared from **4** and 6-hydrazinoimidazo[1,2-*b*]pyridazine (**5f**) (0.149 g, 1 mmole); stirring at room temperature for 24 h. Yield: 0.160 g (49%); mp 91–94° (from ethanol). Ir (cm^{-1}): 1761, 1724 (C=O). ^1H nmr (deuteriochloroform): δ 1.37 and 1.43 (6H, 2t, 1:1, $J = 7.2$ Hz, $2 \times \text{CH}_3\text{CH}_2$); 4.35 and 4.53 (4H, 2q, 1:1, $J = 7.2$ Hz, $2 \times \text{CH}_2\text{CH}_3$); 7.83 (2H, br s, 2'–H and 3'–H); 7.83 (1H, d, $J = 9.8$ Hz, 7'–H); 8.10 (1H, s, 3–H); 8.11 (1H, d, $J = 9.8$ Hz, 8'–H). ^{13}C nmr (deuteriochloroform): δ 14.4, 14.6, 61.5, 63.2, 111.9, 117.2, 117.3, 128.3, 135.6, 136.9, 138.1, 142.8, 147.4, 161.2, 161.5.

Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{N}_5\text{O}_4$ (329.31): C, 54.71; H, 4.59; N, 21.27. Found: C, 55.01; H, 4.39; N, 21.44.

Diethyl 1-(1,2,4-Triazolo[4,3-*b*]pyridazin-6-yl)-1H-pyrazole-4,5-dicarboxylate (**11g**).

This compound was prepared from **4** and 6-hydrazino-1,2,4-triazolo[4,3-*b*]pyridazine (**5g**) (0.150 g, 1 mmole); stirring at room temperature for 10 h. Yield: 0.145 g (44%); mp 124–125° (from ethanol). Ir (cm^{-1}): 1745, 1731 (C=O). ^1H nmr (deuteriochloroform): δ 1.38 and 1.46 (6H, 2t, 1:1, $J = 7.2$ Hz, $2 \times \text{CH}_3\text{CH}_2$); 4.36 and 4.55 (4H, 2q, 1:1, $J = 7.2$ Hz, CH_2CH_3); 8.02 (1H, d, $J = 10.2$ Hz, 7'–H); 8.14 (1H, s, 3–H); 8.30 (1H, dd, $J = 0.8, 10.2$ Hz, 8'–H); 8.96 (1H, d, $J = 0.8$ Hz, 3'–H). ^{13}C nmr (deuteriochloroform): δ 14.4, 14.5, 61.7, 63.5, 116.2, 118.1, 127.6, 138.8, 143.4, 143.5, 149.0, 160.8, 161.2.

Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_6\text{O}_4$ (330.30): C, 50.91; H, 4.27; N, 25.44. Found: C, 50.95; H, 4.41; N, 25.68. *Hrms* Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_6\text{O}_4$: 330.107653. Found: 330.107050.

Diethyl 1-(Tetrazolo[1,5-*b*]pyridazin-6-yl)-1H-pyrazole-4,5-dicarboxylate (**11h**).

This compound was prepared from **4** and 6-hydrazinotetrazolo[1,5-*b*]pyridazine (**5h**) (0.151 g, 1 mmole); stirring at room temperature for 24 h. Yield: 0.250 g (70%); mp 141–143° (from ethanol). Ir (cm^{-1}): 1744, 1728 (C=O). ^1H nmr (deuteriochloroform): δ 1.38 and 1.53 (6H, 2t, 1:1, $J = 7.2$ Hz, $2 \times \text{CH}_3\text{CH}_2$); 4.37 and 4.65 (4H, 2q, 1:1, $J = 7.2$ Hz, $2 \times \text{CH}_2\text{CH}_3$); 8.19 (1H, s, 3–H); 8.41 (1H, d, $J = 9.8$ Hz, 7'–H); 8.55 (1H, d, $J = 9.8$ Hz, 8'–H). ^{13}C nmr (deuteriochloroform): δ 14.0, 14.2, 61.6, 63.8, 118.2, 119.6, 127.2, 137.6, 142.3, 143.9, 149.3, 160.3, 160.6.

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{N}_7\text{O}_4$ (331.29): C, 47.13; H, 3.96; N, 29.60. Found: C, 46.80; H, 4.24; N, 29.57.

Diethyl 1-(Pyrimidin-2-yl)-1H-pyrazole-4,5-dicarboxylate (**11i**).

This compound was prepared from **4** and 2-hydrazinopyrimidine (**5i**) (0.110 g, 1 mmole); stirring at room temperature for 4 h. Yield: 0.258 g (89%); mp 73–75° (from ethanol). Ir (cm^{-1}): 1730, 1721 (C=O). ^1H nmr (deuteriochloroform): δ 1.36 and 1.42 (6H, 2t, 1:1, $J = 7.2$ Hz, $2 \times \text{CH}_3\text{CH}_2$); 4.34 and 4.51 (4H, 2q, 1:1, $J = 7.2$ Hz, $2 \times \text{CH}_2\text{CH}_3$); 7.31 (1H, t, $J = 4.9$ Hz, 5'–H); 8.14 (1H, s, 3–H); 8.77 (2H, d, $J = 4.9$ Hz, 4'–H, 6'–H). ^{13}C nmr (deuteriochloroform): δ 13.9, 14.2, 61.0, 62.7, 116.6, 120.0, 138.2, 142.9, 155.2, 158.8, 161.3, 161.4.

Anal. Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_4$ (290.27): C, 53.79; H, 4.86; N, 19.30. Found: C, 53.95; H, 5.04; N, 19.45.

Diethyl 1-(6-Phenylpyridazin-3-yl)-1H-pyrazole-4,5-dicarboxylate (**11e**).

A mixture of **4** (0.243 g, 1 mmole), 3-hydrazino-6-phenylpyridazine (**5e**) (0.186 g, 1 mmole), ethanol (5 ml), and hydrochloric acid (37%, 0.1 ml, ~1 mmole) was stirred at room temperature for 24 h. The precipitate was collected by filtration and washed with ethanol to give **11e**. Yield: 0.134 g (37%); mp 110–112° (from ethanol). Ir (cm^{-1}): 1742, 1724 (C=O). ^1H nmr (deuteriochloroform): δ 1.37 and 1.45 (6H, 2t, 1:1, $J = 7.2$ Hz, $2 \times \text{CH}_3\text{CH}_2$); 4.36 and 4.59 (4H, 2q, 1:1, $J = 7.2$ Hz, $2 \times \text{CH}_2\text{CH}_3$); 7.51–7.58 (3H, m, 3H of Ph); 8.02 (1H, d, $J = 9.4$ Hz, 5'–H); 8.05–8.09 (2H, m, 2H of Ph); 8.14 (1H, s, 3–H); 8.21 (1H, d, $J = 9.0$ Hz, 4'–H). ^{13}C nmr (deuteriochloroform): δ 14.3, 14.6, 61.4, 63.4, 117.0, 119.8, 127.0, 127.6, 129.5, 130.8, 135.8, 137.1, 143.2, 153.3, 159.7, 161.5, 161.7.

Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_4$ (366.37): C, 62.29; H, 4.95; N, 15.29. Found: C, 62.36; H, 4.86; N, 15.52.

Ethyl 1-Methyl-1H-pyrazole-3-carboxylate (**14**).

A mixture of **3** (0.343 g, 2 mmol), 1,2-dimethylhydrazine dihydrochloride (0.266 g, 2 mmol) and acetic acid (100%, 2 ml) was heated under reflux for 4 h. Volatile components were evaporated *in vacuo*, chloroform (50 ml) was added to the residue, and the chloroform solution was washed with saturated aqueous sodium hydrogencarbonate (2 x 100 ml) and water (2 x 100 ml). The organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. The oily residue was purified by column chromatography (ethyl acetate/n-hexane, 1:1). Fractions containing the product were combined and evaporated *in vacuo* to give **14**. Yield: 0.133 g (43%); oil. IR (cm⁻¹): 1720 (C=O). ¹H NMR (deuteriochloroform): δ 1.40 (3H, t, *J* = 7.2 Hz, CH₃CH₂); 4.00 (3H, s, 1-Me); 4.40 (2H, q, *J* = 7.2 Hz, CH₂CH₃); 6.80 (1H, d, *J* = 2.3 Hz, 4-H); 7.41 (1H, d, *J* = 2.3 Hz, 3-H). ¹³C NMR (deuteriochloroform): δ 14.7 (CH₃CH₂), 40.0 (N-CH₃), 61.2 (CH₂CH₃), 109.5 (4-C), 131.7 (5-C), 144.0 (3-C), 162.7 (C=O).

Anal. Calcd. for C₇H₁₀N₂O₂ (154.17): C, 54.54; H, 6.54; N, 18.17. Found: C, 53.54; H, 6.81; N, 15.64. Hrms Calcd. for C₇H₁₀N₂O₂: 154.074228. Found: 154.075020.

X-Ray Crystallographic Study.

Diffraction data for compounds **8f**, **9f**, **11e** and **11f** were collected on a Nonius Kappa CCD diffractometer with graphite monochromated MoK α radiation. The data were processed using DENZO [29] program. Due to low value of the linear absorption coefficient for all four compounds, no absorption correction was applied. Structures were solved by direct methods using SIR97 [30]. We employed full-matrix least-squares refinement on F magnitudes with anisotropic displacement factors for all non-hydrogen atoms using Xtal3.4 [31]. The positions of hydrogen atoms were obtained from the difference Fourier maps. They were refined together with their isotropic displacement factors. In the final cycle of the refinement we used 2684, 2426, 3610 and 3164 reflections (included were those unobserved reflections for which F_C was greater than F_O) and 234, 217, 315 and 278 parameters for **8f**, **9f**, **11e** and **11f**, respectively. The resulting crystal data and details concerning data collection and refinement for all four compounds are quoted in Table 1. Final atomic coordinates and equivalent isotropic displacement parameters with their e.s.d.'s are reported in Tables 2–5. Bond lengths and bond angles for non-hydrogen atoms are listed in Tables 6, 7, 8 and 9 for **8f**, **9f**, **11e** and **11f**, respectively. ORTEP [32] drawings of the content of asymmetric units of all four compounds showing the atom-labeling scheme are presented in Figures 2–5.

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