The Synthesis, Structure and Properties of *N*-Acetylated Derivatives of Ethyl 3-Amino-1*H*-pyrazole-4-carboxylate

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Ethyl 3-amino-1*H*-pyrazole-4-carboxylate (1) was yielded through total synthesis and reacted with acetic anhydride to give the acetylated products 2—6. Compounds 1—6 were studied with HPLC, X-ray, FT-IR, ^{1}H-NMR, ^{13}C-NMR and MS. Acetylation was carried out in solvents of various polarity, namely; chloroform; dioxane; DMF; acetic anhydride, at room temperature and at boiling points; and in the presence and absence of DMAP. The acetylated products are mainly nitrogen atoms in the ring. The position of the ring proton in the solution was based on NOESY; multinuclear HMBC, HSQC spectra and calculations. For equivalent amounts (1—1.5 mol) of acetic anhydride at room temperature two products of monoacetylation are produced in the ring: 2 and 3, *ca.* 2 : 1 and at the same time only small amount of the third product of monoacetylated, 5 in DMF, as well the product diacetylated, 4. The greatest amount of the product 4 is produced during the reaction with chloroform. However, in this solvent and in dioxane no product 5 is produced. Compound 2 is, largely, formed in dimethylformamide, in the presence DMAP, 0.2 eq. In the presence of this catalytic base, for the first hour, there is a mixture 2 and 3 to the ratio *ca.* 95 : 5. With 8 eq of Ac_2O at reflux, after another hour, the compounds 3, 4 and 6 appear about equal amounts. After a longer time, the compound, which appears most in this mixture is triacetylated derivative 6. The structural and spectroscopic characteristics of compounds 1—6 have been given and the methods for their preparation have been provided.

Key words acetylation; hetareneamino acid; hydrogen bonding; FT-IR spectra; ^{1}H-NMR spectra; ^{13}C-NMR spectra

Azoleamino acids have the potential to form hetarene oligoamides, which belong both to those most promising small molecules controlling gene expression[1)] and, morever, are the constituents of natural; modified and artificial peptides which are useful for biological and non-biological purposes. Azoleamino acids possesses a few nitrogen atoms. Usefulness of azoleamino acids results from their flat, rigid system capable of acting as both a hydrogen bond acceptor and/or donor.[2)]

Of practical importance, in connection with medicinal chemistry program,[3—10)] is capability of azoleamino acids to be acetylated in selective way, and this reactivity has so far been poorly explored.[8,11—13)] We selected for investigation ethyl 3-amino-1*H*-pyrazole-4-carboxylate (**1**) to be acetylated with acetic anhydride. Catalytic effect of 4-dimethylaminepyridine (DMAP)[14,15)] a known nucleophilic catalyst, was also tested. The final part of this paper concerns the delineation of the synthesis (preparation) and the structure and properties of *N*-acetylated derivatives **2**—**6** of ethyl 3-amino-1*H*-pyrazole-4-carboxylate (**1**) (Fig. 1).

Results and Discussion

Selected examples of acetylation of **1** are given in Figs. 2A—F and Figs. 3A—C (Figs. 2, 3). Molecules of **1** have three points to be acetylated: the primary exocyclic NH_2 group and two annular nitrogen atoms. With equivalent (1—1.5 mol) of acetic anhydride at room temperature, the acetylation of two annular nitrogen atoms always ensues, regardless of the polarity of solvents. After 4 h, a mixture of monoacetylated products, ethyl 3-amino-1-acetyl-1*H*-pyrazole-4-carboxylate (**2**), and ethyl 1-acetyl-5-amino-1*H*-pyrazole-4-carboxylate (**3**), had been formed in the ratio *ca.* 2 : 1, and a small amount of diacetylated compound **4** (Figs. 2A—C). Isomer **2** appears as the kinetic product and isomer **3** as the thermodynamic one. In the separated stage, the isomerisation of **2** to **3** is performed by heating of compound **2** in chloroform to give 45% of **3**. The greatest quantity of **4** is produced in the reaction in chloroform (Fig. 2A). In DMF, a minute amount of exocyclic monoacetyl ethyl 5-(acetylamino)-1*H*-pyrazole-4-carboxylate (**5**) appears (Fig. 2C). In reaction with 8 eq of Ac_2O at room temperature, after 1 h, the amounts of **2**, **3** and **4** are about equal. After 4 h the amount of **2** has decreased, while **3** and **4** have increased (Fig. 2D). Upon further standing, after 2 d, compound **2** has disappeared while amounts of compounds **3** and **4** have not changed and the triacetylated compound **6** has appeared (Fig. 2E). After, however, several days compound **3** decreases and compound **4** increases, thus proving the progress of the reaction at the cost of **2** and the resistance of isomer **3** to further acetylation. The use of DMAP in dimethylformamide brings a larger reaction regioselectivity at the annular nitrogen atoms. After 1 h, in the presence of 0.2 eq of DMAP, the ratio of **2** to **3** was 95 : 5 (Fig. 2F) and **2** was isolated at a yield of 56%. But after some time, amounts of **2** and **3** equalize and **5** appears.

Temperature has no influence on the amount of derivative **3**, but accelerates the formation of derivative **4** (Figs. 3A, B). With 8 eq of Ac_2O at reflux, after 1 h, compounds **3**, **4** and **6** are about equal in amount, (Fig. 3C). After further time, the compound, which is in greatest quantity in this mixture, is the triacetylated derivative **6** with two acetyl residues at the amino group. It is impossible for **6** to be isolated in a pure state.

Compound **2** has been subjected to test of its reactivity under various conditions. In a freezer, it is stable at least a year, but left standing in the solid state at room temperature

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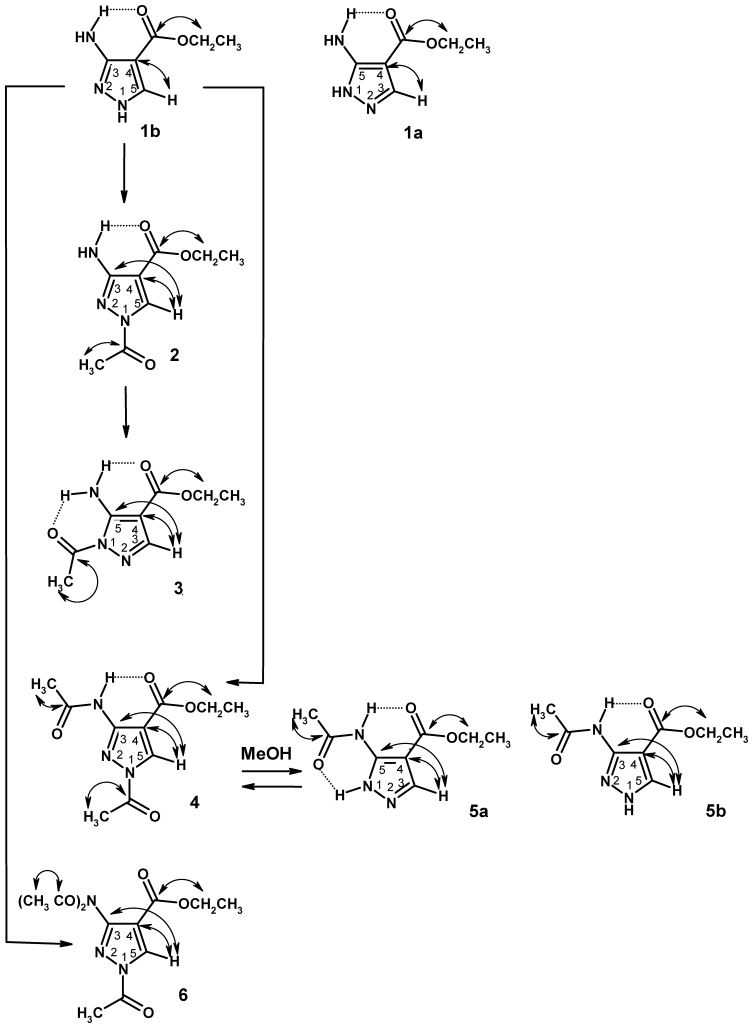


Fig. 1. Structure of Obtained Compounds **1**—**6** Together with Their Preparative and HMBC Conectivity

····, internal hydrogen bond.

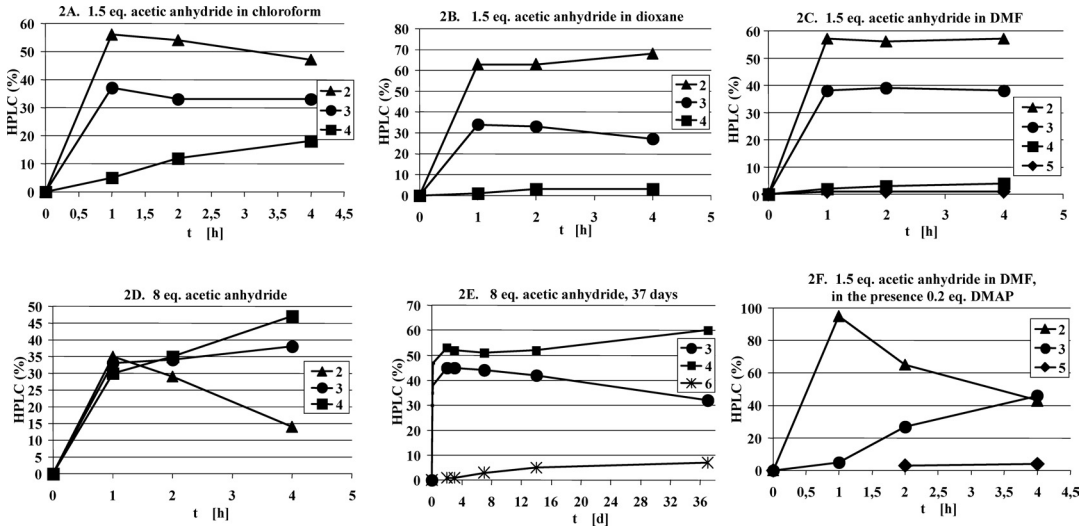


Fig. 2. Acetylation of **1** with Ac_2O at Room Temperature

(Table 1) it starts to rearrange itself into **3** and **5** and after six weeks quantities of **3** and **5** are about 8—9%. However, in a saturated chloroform solution of **2**, after 6 h, the amount of **3** reaches 63%. In a diluted solution, the rearrangement is much slower. Thus, it may be assumed that the conversion of **2** to **3** is an intermolecular trans-aminoacetylation. This can be called dissociation-recombination process as in analogical reaction with acyloindazoles.[16] In compounds **2** and **4**, the

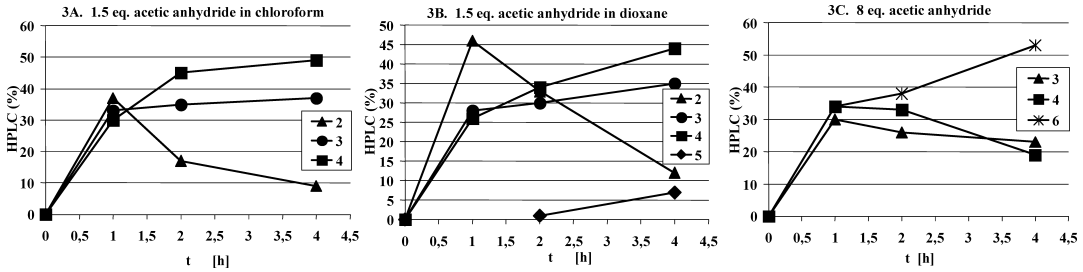


Fig. 3. Acetylation of **1** with Ac_2O at Reflux

Table 1. The Transformation of Isolated **2** Under Various Conditions at Room Temperature (Percentage by HPLC)

		2 h	6 h	12 d	28 d	42 d
A	**1**					1
	5			1	3	8
	2	99		95	90	81
	3			3	5	9
B	**1**			2	2	
	5			1		
	2	99	34	13	11	
	3	1	63	84	83	
C	**1**			1	2	
	5				2	
	2	99	93	64	7	
	3		7	35	89	

A, in the solid state; B, in saturated $CHCl_3$ solution; C, in diluted $CHCl_3$ solution.

Table 2. The Stability of Isolated **2**, **3**, **4** and **5** in the Solid State at Room Temperature (Percentage by HPLC)

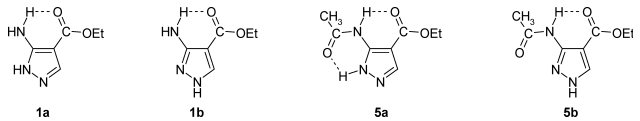
	Start	1 month	1 year
2	99	90	Absent
3	100	100	36
4	98	78[a)]	39
5	98	98	98

a) 3 months.

ring acetyl at peripheral nitrogen atom to the amino group, can be easily removed by methanolysis to give, respectively, the substrate **1** and the monoacetyled derivative **5** at the amino group, but the acetyl in compound **3** cannot be so easily removed. The stability of the isolated acetyl derivatives **2**, **3**, **4** and **5** in their solid states has also been investigated for a longer time period and was left standing (for up to one year) (Table 2). Compound **5** is the most stable, which does not change after a year. The least stable is compound **2**, which disappears completely after one year. Compounds **3** and **4** transform into compound **5** over some time period.

In order to determine the position of hydrogen at nitrogen atoms in compounds **1** and **5** in solution we performed NMR analysis and calculations. Compound **1** in the $CDCl_3$ and DMSO-d_6 solutions is a mixture of tautomers, according to NOESY, multinuclear HMBC and HSQC spectra and as well as calculations (Table 3). In addition, it was shown that **5** in DMSO-d_6 contains a mixture of tautomers which was corroborated by calculations (Table 3). As seen, the proton is mobile, and, in the solid phase, in compound **1**, it is at nitrogen atom, which is in a peripheral position to the amino

Table 3. Electronic Energies (E_{elec}), Scaled[a)] Zero Point Energies (ZPE's) and Relative Energies (ΔE) for the Studied Molecules Obtained by the B3LYP/6-31+G** Method



Compound	E_{elec} (a.u.)	ZPE (kcal/mol)	ΔE (kcal/mol)
1a	−509.4811123	80.69	0.49
1b	−509.4819211	80.71	0.00
1a in $CHCl_3$	−509.4984921	79.80	0.00
1b in $CHCl_3$	−509.4983103	79.92	0.23
1a in DMSO	−509.506205	79.75	0.00
1b in DMSO	−509.501966	79.73	0.52
5a	−662.1575483	104.22	0.00
5b	−662.1440119	103.92	8.19
5a in $CHCl_3$	−662.1691936	103.63	0.00
5b in $CHCl_3$	−662.1638087	103.38	3.12
5a in DMSO	−662.1741083	103.31	0.00
5b in DMSO	−662.1725007	103.07	0.77

a) Scaling factor 0.9804.[17)]

group (**1b**), and the proton in compound **5** is in position which is nearer to the amino group (**5a**). This behavior of **5** results from the internal hydrogen bond.

The compounds **1**, **2**, **3** and **5** were crystallized and X-ray structure analysis was performed to study their molecular structures.

Selected bond lengths are given in Table 4. The molecular structures of compounds **1**, **2**, **3** and **5** are presented in Fig. 4. As seen, in each compound there is the intramolecular N–H···O hydrogen bond between the exoamino group and the carbonyl of the ester. This hydrogen bond is the reason for the poor reactivity of the amino group, which reacts in the third sequence, after the ring nitrogen atoms, which react first.

Conclusion

Compound **1** has potential three centers for acetylation: the exocyclic amino group and two ring nitrogen atoms. The most easily acetylated is the ring nitrogen atom peripheral to the amino group. With 1—1.5 eq of Ac_2O at room temperature, regardless the polarity of solvent, the mixtures of **2** and **3** are formed in a ratio *ca.* 2 : 1. In DMF, in the presence of DMAP, the regioselectivity of acetylation, **2** to **3** amounts to 95 : 5, after 1 h. So, selective acetylation is possible. Compound **2** transfer the acetyl group from position *N*1 to *N*2, when it is heated. When one uses an large excess of Ac_2O, in

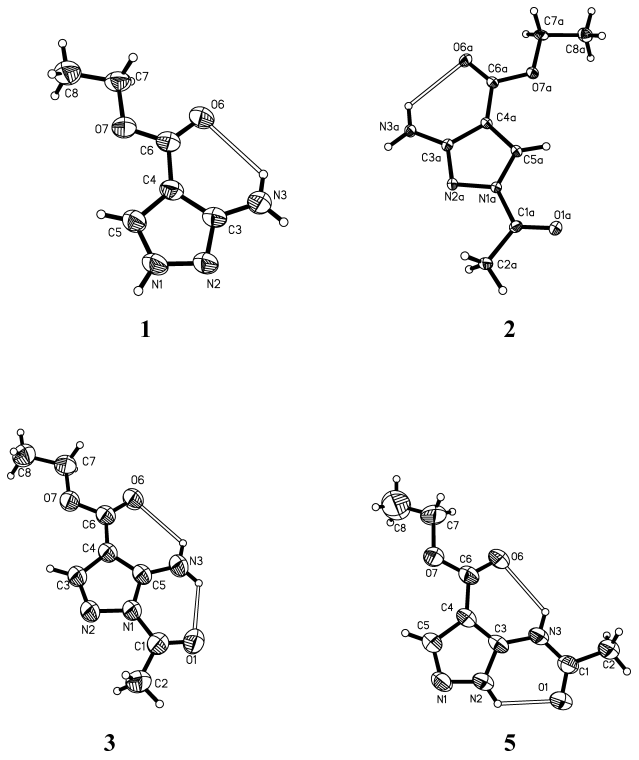


Fig. 4. Molecular Structure of **1**, **2**,[18] **3** and **5** Determined by the X-Ray Crystallography

Table 4. Selected Bond Lengths of **1**, **2**,[18] **3** and **5**

1		**2**		**3**		**5**	
N(1)–C(5)	1.324(2)	N(1)–C(5)	1.358	N(1)–C(5)	1.377(2)	N(2)–C(3)	1.348(3)
N(1)–N(2)	1.367(2)	N(1)–N(2)	1.392	N(1)–N(2)	1.395(2)	N(1)–N(2)	1.355(4)
N(2)–C(3)	1.333(3)	N(2)–C(3)	1.334	N(2)–C(3)	1.299(3)	N(1)–C(5)	1.316(4)
C(3)–C(4)	1.416(2)	C(3)–C(4)	1.442	C(3)–C(4)	1.408(2)	C(4)–C(5)	1.405(4)
C(4)–C(5)	1.387(2)	C(4)–C(5)	1.371	C(4)–C(5)	1.373(2)	C(3)–C(4)	1.377(4)
C(3)–N(3)	1.352(2)	C(3)–N(3)	1.350	—	—	—	—
N(1)–C(1)	—	N(1)–C(1)	1.406	N(1)–C(1)	1.397(3)	—	—
				C(5)–N(3)	1.338(2)	C(3)–N(3)	1.378(4)
N3⋯O6	2.959(2)	N3⋯O6	2.977—3.006	N3⋯O6	2.910(2)	N3⋯O6	2.961(4)
				N3⋯O1	2.740(2)	N2⋯O1	2.664(4)

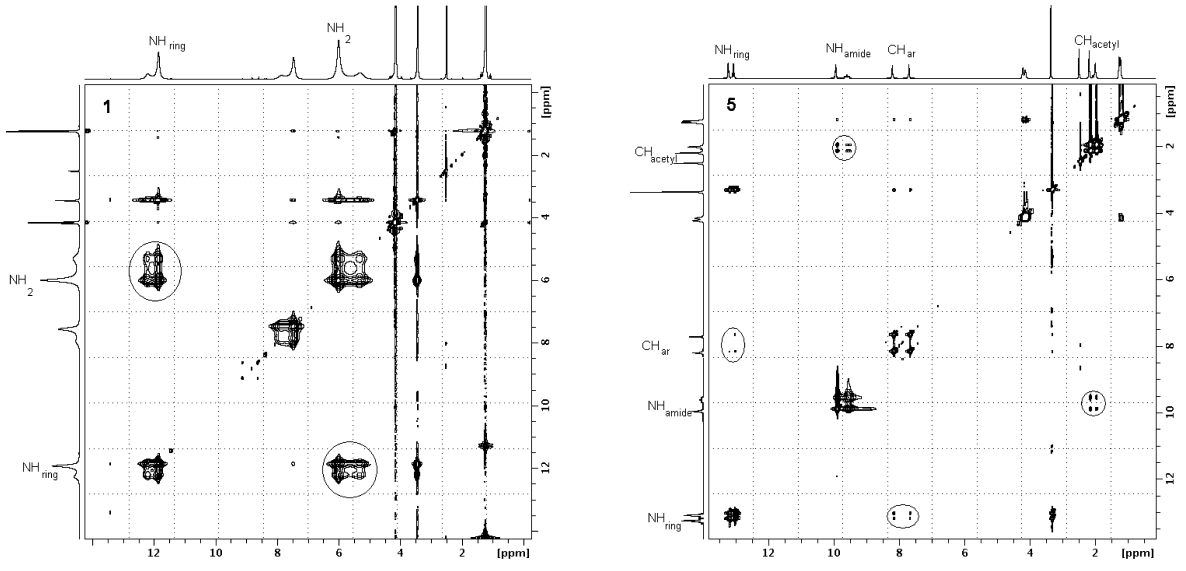


Fig. 5. NOESY of **1** and **5** in DMSO-d_6

room temperature, diacetylated compound **4** which has the additional acetyl at the amino group appears. Acting at **2** and **4** with methanol, one acetyl group from the ring nitrogen atom peripheral to the amino group is removed. Compounds **1** and **5** show prototropy. Compound **2** can be a good inert acylation agent.[19,20] This may have the significance for obtaining some anthelmintic agents[9] and hypoglycemic agents.[10]

Experimental

General Procedures The solvents from he reaction mixtures were removed *in vacuo* on a rotary evaporator at a bath temperature not exceeding 40 °C. TLC were performed on silica gel (DC Alufolien Kieselgel Merck #1.05553) in the solvent system: $CHCl_3$: methanol : acetic acid (45 : 4 : 1). Purities of compounds **1**—**6** were checked by HPLC by a Beckman "System Gold" with an Alltech Alltime C18 (RP 5 μm, 150×4.6 mm) column. The mobile phase was 0.1% TFA : acetonitrile (50 : 50) (unless given otherwise) at a 1 ml min^{-1} rate of flow. Detection was made at 210 nm. NMR spectra were measured on a 400 MHz Brucker spectrometer in the presence of tetramethylsilane. Resonances are based on HMBC and HSQC spectra. FT-IR spectra were recorded on a PU 9800 Philips Analytical spectrometer at 2 cm^{-1} resolution in KBr and CH_2Cl_2. GC-MS was performed with an HP 6890 gas chromatograph with a HP-5 column and a MS 5973 (EI) mass spectrometer as detector.

The calculations were carried out with the GAUSSIAN 03 package,[21] Geometry optimisation and vibrational analysis of the studied compounds were performed without constraint on the isolated molecules with the Becke3LYP density functional (DFT) hybrid method[22,23] in combination with the standard basis set 6-31+G. Zero-point energies (ZPEs) were calculated using analytical second derivatives and scaled down by factor 0.9804.[17] The polarizable continuum model (PCM), developed by Tomasi,[24] was applied to estimate the effect of solvation in DMSO on the energies of

the studied compounds. The structures in $CHCl_3$ and DMSO were fully optimized and the vibrational frequencies were calculated using the B3LYP/6-31+G** method. The Table 3 lists the electronic energies, zero-points energies and relative energies of the pyrazole derivative molecules **1** and **5** in the gas phase and in a $CHCl_3$ and DMSO solution.

Diffraction data for **1**, **3** and **5** were measured at 296 K on a KM4 diffractometer using graphite monochromated Cu$K\alpha$ radiation (λ=1.54178 Å) and a variable scan speed in the ω–2θ scan mode. The structures were solved by direct methods using the SHELXS-97[25] and refinement was performed by the full-matrix least-squares method on F^2 using the SHELXL-97[26] program. The non-hydrogen atoms were refined with anisotropic displacement parameters. H-atom positions were calculated from the geometry and were given isotropic factors of 1.2 U_{eq} of the bonded non-H-atoms.

Compound **1** crystallized as monoclinic in the space group $P2_1/n$, a=8.227(2) Å, b=8.283(1) Å, c=11.111(2) Å, β=96.83(3)°, V=752.0(2) Å^3, Z=4, d_{calc}=1.370 g cm^{-3}, F(000)=328, μ(Cu$K\alpha$)=0.890 mm^{-1}. In the θ range 6.45—74.99°, 1621 reflections were collected and 1542 unique reflections (R_{int}=0.023) were used in the refinement. For 102 parameters refined, the final discrepancy factors are $R1$=0.0326, $wR2$=0.0904 for 897 reflections with $I>2\sigma(I)$ and $R1$=0.0865, $wR2$=0.1071 for all data, S=1.040. Residual peaks on final difference map were −0.15 to 0.19 e Å^3 and extinction coefficient equals 0.010(1).

The molecular structure of compound **2** was presented in a separate publication[18] due to its specific association.

Compound **3** crystallized in the orthorhombic, space group *Pnam*, a=11.456(2) Å, b=12.632(3) Å, c=6.549(1) Å, V=947.7(3) Å^3, Z=4, d_{calc}=1.382 g cm^{-3}, F(000)=416, μ(Cu$K\alpha$)=0.991 mm^{-1}. In the θ range 5.21—80.77°, 2202 reflections were collected and 1135 unique reflections (R_{int}=0.056) were used in calculations. For 86 parameters refined, the final discrepancy factors are $R1$=0.0425, $wR2$=0.1238 for 970 reflections with $I>2\sigma(I)$, and $R1$=0.0494, $wR2$=0.1310 for all data, S=1.067. Residual peaks on the final difference map were −0.15 to 0.25 e Å^3 and the extinction coefficient equals 0.005(1).

Compound **5** is monoclinic, in the space group $P2_1/c$, a=4.9000(1) Å, b=23.147(5) Å, c=8.391(2) Å, β=93.97(3), V=949.4(4) Å^3, Z=4, d_{calc}=1.380 g cm^{-3}, F(000)=416, μ(Cu$K\alpha$)=0.909 mm^{-1}. Of 1980 reflections collected in the θ range 3.82—72.13°, 1858 were unique (R_{int}=0.0517) and used in the refinement. For 130 parameters refined, the final discrepancy factors are $R1$=0.0539, $wR2$=0.1319 for 780 reflections with $I>2\sigma(I)$, and $R1$=0.1743, $wR2$=0.1737 for all data, S=1.015. Residual peaks on the final difference map were −0.32 to 0.37 e Å^3 and the extinction coefficient equals 0.010(2).

Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre as CCDC 631805 for compound **1**, CCDC 631806 for compound **3** and CCDC 631807 for compound **5**. Copies of the data can be obtained on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ U.K. (Fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

Ethyl 3-Amino-1*H*-pyrazole-4-carboxylate (1a+1b) Ethyl 3-amino-1*H*-pyrazole-4-carboxylate was obtained according to refs. 27—29; mp 101—104 °C, lit.[29] mp 100—101 °C; TLC: *Rf* 0.61; HPLC: t_R 2.30 min. 100% purity; ^{1}H-NMR (DMSO-d_6) δ (ppm): (a mixture of tautomers): 1.049—1.245 (m, 3H, CH_3), 4.121—4.174 (q, 2H, CH_2), 5.307 and 6.004 (d, 2H, NH_2), 7.460—9.121 (m, 1H, CH_{ar}), 11.416—12.204 (d, 1H, NH); ($CDCl_3$) δ (ppm): 1.2287—1.323 (t, 3H, $CH_{3\ ester}$), 4.214—4.268 (q, 2H, $CH_{2\ ester}$), 7.185 (s, 2H, NH_2), 7.684 (s, 1H, CH_{ar}). ^{13}C-NMR (DMSO-d_6) δ (ppm): 163.88 (C=O), 151.39 (C^3), 139.58 (C^4), 93.52 (C^5_{ar}), 58.72 (CH_2), 14.53 (CH_3); FT-IR (cm^{-1}) (KBr): 3481 (NH_{ring}), 3402, 3302, 3238 ($NH_{2\ bonded}$) 2982, 2906 (CH_2CH_3), 1671 ($C=O_{ester\ bonded}$), 1621 ($\delta NH_{2\ bonded}$); (CH_2Cl_2): 3454 3383 (NH_2), 1695 ($C=O_{ester\ bonded}$), 1624 ($\delta NH_{2\ bonded}$).

Ethyl 1-Acetyl-3-amino-1*H*-pyrazole-4-carboxylate (2) To a suspension of **1** (775 mg, 5 mmol) and DMAP (121 mg, 1 mol) in DMF (0.5 ml) was added Ac_2O (0.71 ml, 7.5 mmol), after 1 h at room temperature a white precipitate was filtered off and washed with DMF (1 ml) to furnish **2** (550 mg, 56% isolated yield), mp 110 °C; TLC: *Rf* 0.86; HPLC: t_R 3.0 min, 99% purity; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.246—1.282 (t, 3H, $CH_{3\ ester}$), 2.501 (s, 3H, $CH_{3\ acetyl}$), 4.200—4.253 (q, 2H, CH_2), 5.924 (s, 2H, NH_2), 8.448 (s, 1H, CH_{ar}); ^{13}C-NMR (DMSO-d_6) δ (ppm): 168.46 ($C=O_{acetyl}$), 163.05 ($C=O_{ester}$), 156.85 (C^3), 131.92 (C^4), 105.13 (C^5_{ar}), 60.26 (CH_2), 21.61 ($CH_{3\ acetyl}$), 14.21 ($CH_{3\ ester}$); FT-IR (cm^{-1}) (KBr): 3480, 3360 ($NH_{2\ bonded}$), 2980 (CH_2CH_3), 1713 ($C=O_{acetyl\ bonded}$), 1700 ($C=O_{ester\ bonded}$), 1629 ($\delta NH_{2\ bonded}$); (CH_2Cl_2): 3498, 3393 ($NH_{2\ bonded}$), 1735 ($C=O_{acetyl\ free}$), 1707 ($C=O_{ester\ bonded}$), 1611 ($\delta NH_{2\ bonded}$). Analysis for $C_8H_{11}N_3O_3$ Calcd C 48.73%, H 5.62%, N 21.31, Found C 48.74%, H 5.36%, N 21.19%.

Ethyl 1-Acetyl-5-amino-1*H*-pyrazole-4carboxylate (3) A solution of **2** (200 mg, 1.01 mmol) in $CHCl_3$ (1 ml) was refluxed for 2 h. The solvent was evaporated to dryness, giving a white precipitate. This was applied on a column and eluted with CH_2Cl_2. White powder. 88.9 mg (45%), mp 71—73 °C; TLC: *Rf* 0.89; HPLC: t_R 4.0 min; 100% purity; ^{1}H-NMR δ (DMSO-d_6) (ppm): 1.237—1.272 (t, 3H, $CH_{3\ ester}$), 2.503 (d, 3H, $CH_{3\ acetyl}$), 4.175—4.228 (q, 2H, $CH_{2\ ester}$); 7.346 (s, 2H, NH_2), 7.752 (s, 1H, CH_{ar}); ^{13}C-NMR δ (DMSO-d_6) (ppm): 173.62 ($C=O_{acetyl}$), 162.94 ($C=O_{ester}$), 152.62 (C^5), 142.75 (C^4), 93.50 (C^3_{ar}), 59.32 (CH_2), 23.24 ($CH_{3\ acetyl}$), 14.7643 ($CH_{3\ ester}$); FT-IR (cm^{-1}) (KBr): 3385, 3363 ($NH_{2\ bonded}$), 3114, 3085 (CH_{ar}), 2989, 2980, 2919 (CH_2CH_3), 1726 ($C=O_{acetyl\ bonded}$), 1678 ($C=O_{ester\ bonded}$), 1615 ($\delta NH_{2\ bonded}$). Analysis for $C_8H_{11}N_3O_3$ Calcd C 48.73%, H 5.62%, N 21.31, Found C 48.63%, H 5.69%, N 21.25%.

Ethyl 1-Acetyl-3-(acetylamino)-1*H*-pyrazole-4-carboxylate (4) (A) To **5** (117 mg, 0.59 mmol) was added Ac_2O (1 ml, 10.5 mmol)), the solution left standing 24 h at room temperature and the anhydride removed to furnish **4** (128 mg, 90%, mp 97—98 °C; TLC: *Rf* 0.83; HPLC: t_R 2.53 min, 98% purity; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.329—1.365 (t, 3H, $CH_{3\ ester}$), 2.312 (s, 3H, $CH_{3\ acetyl}$), 4.295—4.349 (q, 2H, $CH_{2\ ester}$), 8.554 (s, 1H, CH_{ar}), 9.149 (s, 1H, NH); ^{13}C-NMR, (DMSO-d_6) δ (ppm): 169.42 ($2C=O_{acetyl}$), 161.49 ($C=O_{ester}$), 148.09 (C^3), 131.91 (C^4), 111.75 (C^3_{ar}), 22.86 ($CH_{3\ acetyl}$), 21.32 ($CH_{3\ ester}$); FT-IR (cm^{-1}) (KBr): 3344 (NH), 3090 (CH_{ar}), 1753 ($C=O_{acetyl\ free}$), 1703 ($C=O_{acetyl\ bonded}$), 1681 ($C=O_{ester\ bonded}$); (CH_2Cl_2): 3359 (NH_{bonded}), 1747 ($C=O_{acetyl\ free}$), 1714 ($C=O_{acetyl\ free}$), 1699 ($C=O_{ester\ bonded}$). Analysis for $C_{10}H_{13}N_3O_4$ Calcd C 50.21%, H 5.48%, N 17.57, Found C 50.19%, H 5.23%, N 17.63%.

(B) To **1** (1.55 g, 10 mmol) was added Ac_2O (12 ml, 133 mmol), the solution left standing 24 h at room temperature and the anhydride removed. To the residue was added diethyl ether and the precipitate was filtered off to give **4** as a white powder (1.396 g, 58%), mp 97—98 °C. The remaining characteristics are as above.

Ethyl 5-(Acetylamino)-1*H*-pyrazole-4-carboxylate (5a+5b) Compound **4** (400 mg, 1.67 mmol) was dissolved in methanol (6 ml), left standing 24 h at room temperature and filtered off to furnish **5** (209 mg, 64%), mp 201—202 °C; TLC: *Rf* 0.74; HPLC: t_R 1.99 min, 98% purity; ^{1}H-NMR (DMSO-d_6) δ (ppm) (a mixture of tautomers): 1.180—1.224, (q, 3H, $CH_{3\ ester}$), 1.939—2.125 (q, 3H, $CH_{3\ acetyl}$), 4.071—4.187 (m, 2H, CH_2), 7.649 and 8.155 (2s, 1H, CH_{ar}), 9.550 and 9.888 (2s, 2H, NH_{amide}), 13.023 and 13.183 (2s, 1H, NH_{ring}); ^{13}C-NMR (DMSO-d_6): 169.09 ($C=O_{acetyl}$), 162.95 ($C=O_{ester}$), 138.90 (C_5), 133.10 (C_4), 98.96 (C_{ar}), 59.45 ($CH_{2\ ester}$), 22.95 ($CH_{3\ acetyl}$), 14.27 ($CH_{3\ ester}$). Ethyl 3-(acetylamino)-1*H*-pyrazole-4-carboxylate: ^{1}H-NMR (CD_2Cl_2) in 230 K, δ (ppm): 1.286—1.324 (t, 3H, $CH_{3\ ester}$), 2.239 (s, $3H_{acetyl}$), 4.211—4.264 (q, 2H, $CH_{2\ ester}$), 7.708 (s, 1H, CH_{ar}), 9.544 (s, 1H, NH_{amide}), 11.856 (s, 1H, NH_{ring}); FT-IR (cm^{-1}): (KBr): 3342 ($NH_{ring\ bonded}$) 3250 ($NH_{acetyl\ bonded}$), 2979, 2934 (CH_3CH_2), 1696 ($C=O_{acetyl\ bonded}$), 1681 ($C=O_{ester\ bonded}$); (CH_2Cl_2): 3416 ($NH_{ring\ bonded}$), 3356 ($NH_{amide\ bonded}$), 1694 ($C=O_{acetyl\ bonded}$), 1683 ($C=O_{ester\ bonded}$). Analysis for $C_8H_{11}N_3O_3$ Calcd C 48.73%, H 5.62%, N 21.31, Found C 48.64%, H 5.55%, N 21.13%.

Ethyl 1-Acetyl-3-(bisacetyl)amino-1*H*-pyrazole-4-carboxylate (6) To **5** (316 mg, 1.60 mmol), Ac_2O (2 ml, 21 mmol) was added and the solution was heated at oil bath temperature 100—120°C for 8 h. The solvent was removed and the residue was again dissolved in Ac_2O (2 ml, 21 mmol) and heated as above. The solvent was removed to give **6** (580 mg), t_R 12.63 min, 83% purity, contaminated with **4**, t_R 4.67 min (0.1% TFA : acetonitrile= 70 : 30); EI-MS *m/z* 281, ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.268—308 (t, 3H, $CH_{3\ ester}$), 2.239 (s, 6H, $2\times CH_{3\ acetyl}$), 2.666 (s, 3H, $CH_{3\ acetyl}$), 4.258 (q, 2H, $CH_{2\ ester}$), 8.718 (s, 1H, CH_{ar}); ^{13}C-NMR ($CDCl_3$) δ (ppm): 172.04 and 168.63 ($2\times C=O_{acetyl}$), 160.74 ($C=O_{ester}$), 150.09 (C^4), 133.32 (C^5), 114.37 (C^4), 61.57 ($CH_{2\ ester}$), 26.17 ($2\times CH_{3\ acetyl}$), 24.73 ($CH_{3\ acetyl}$), 14.26 ($CH_{3\ ester}$).

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