# Migration of an acyl group in the pyrazole system: synthesis of 1-acyl-3-hydroxy-1*H*-pyrazoles and related derivatives. A new preparation of *N*,*N*′-diacylhydrazines

**Vladimir Kepe, Franc Požgan, Amalija Golobič, Slovenko Polanc and Marijan Kočevar ***

*Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana, Slovenia*

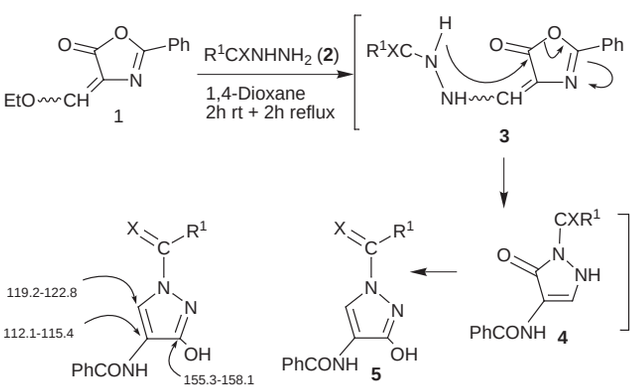
**A new general method for the synthesis of 1-acyl-3-hydroxy-1*H*-pyrazoles 5a–f and related derivatives 5g–i starting from 4-ethoxymethylene-2-phenyloxazol-5(4*H*)-one (1) and hydrazides, 4-phenylsemicarbazide, 4-phenylthiosemicarbazide and benzyl carbazate in boiling dioxane is described. The method includes a migration of an acyl or related unit. The X-ray study and NMR spectroscopic examination confirmed the structure of the products. A one-pot synthesis of *N*,*N*′-diacylhydrazines from hydrazides by the assistance of oxazolone 1 is also presented.**

Pyrazole derivatives are important as synthons and reagents in organic synthesis and have found applications as pharmaceuticals, agrochemicals, dyestuffs, *etc*.[1] Amongst them, 1-acyl-3-hydroxy-1*H*-pyrazoles and related compounds have not been thoroughly investigated, although several, mostly acetyl derivatives, have been prepared and studied.[2] Their potential as acetylating *N*-acyl agents has not been described, but it was found that the 3-acetoxy group of 3-acetoxy-1-acetyl-5-methylpyrazole has useful acetylating potential.[2b,d] The reaction of 3-substituted pyrazol-5(2*H*)-ones with isocyanates gave 5-hydroxy-1-carbamoyl derivatives, whereas the *O*-alkyl analogs afforded the corresponding 3-alkoxy-1-carbamoyl derivatives. For the explanation of this phenomenon an intramolecular hydrogen bond was postulated.[2g] Treatment of 3-amino-5-hydroxy-1*H*-pyrazole with aryl isocyanates resulted in the corresponding 5-amino-1-carbamoyl-3-hydroxypyrazole derivatives, which were further converted to their 3-amino-5-hydroxy isomers *via* the migration of substituted carbamoyl groups onto the nitrogen closer to the hydroxy group.[2h]

Here we present a simple and general synthesis of a series of 1-acyl-3-hydroxy-1*H*-pyrazoles and related compounds starting from the oxazolone derivative **1**[3] and hydrazides **2a**–**f**, semicarbazide **2g**, thiosemicarbazide **2h** or benzyl carbazate **2i** (Scheme 1). The method is based on the reactions of hydrazines with the oxazolone derivative **1** to give the hydrazinomethyleneoxazol-5(4*H*)-ones and hence the corresponding pyrazolone derivatives.[3,4] To our knowledge, hydrazides and related compounds have never been used in such a transformation. In the case of hydrazides we expected to obtain the corresponding 1-acyl-1*H*-pyrazol-5(2*H*)-ones **4**, since several stable compounds of this type are known.[5] To our surprise, upon stirring the reaction mixture of oxazolone derivative **1** and selected hydrazides **2** in dioxane for 2 h, followed by heating for 2 h, we isolated the rearranged 1-acyl-3-hydroxy-1*H*-pyrazoles **5** in high yield. In the case of compound **5a** the structure was confirmed by the X-ray structure analysis (Fig. 1). It has been shown that such compounds exist in the 3-OH-tautomeric form, thus supporting the previously described higher stability of this form of related 1-substituted derivatives in the crystal form and in aprotic solvents,[1b,c,2c] although in a recent NMR study three examples of 5-methyl-3-oxo-2,3-dihydropyrazole-1-carbothioic acid *S*-alkyl esters were described.[2i]

Since the pyrazole derivatives with this substitution pattern have not been thoroughly investigated,[1,2,6] we performed a detailed NMR study including some two-dimensional experiments. Proton 5-H showed in DMSO-$d_6$ a strong singlet between 8.41 and 8.69 ppm for all compounds with the exception of compound **5h**, where it appeared at 8.95 ppm. The signals for the hydroxy groups appeared between 11.08 and 11.88 ppm. All $^{13}C$ signals of the pyrazole skeleton are also in narrow $\delta$ ranges as shown in Scheme 1. Some NMR signals of compound **5a** were also determined on the basis of HMBC and HMQC spectra. We believe that the data we obtained are consistent with the 3-hydroxy tautomeric form of compounds **5**. The proposed tautomeric form may also be supported by the fact that compound **5a** exhibits nearly the same IR spectroscopic characteristics in the carbonyl region as a KBr pellet and in DMSO solution.

Since the migration of the acyl group in our system is in contradiction with the previous observations in related systems[2d,g,h] and since we were not able to isolate the proposed intermediates **4**, we performed some additional experiments in




| 5 | $CXR^1$ | Yield (%)[a] | 5 | $CXR^1$ | Yield (%)[a] |
|---|---|---|---|---|---|
| **a** | COMe | 69 | **f** | $COCH_2NHCOPh$ | 87 |
| **b** | COPh | 86 | **g** | CONHPh | 82 |
| **c** | CO-Ph-*p*-$NO_2$ | 88 | **h** | CSNHPh | 74 |
| **d** | COTh | 79 | **i** | $CO_2CH_2Ph$ | 72 |
| **e** | COPy | 82 | | | |

[a]Isolated yields of TLC-pure compounds.

Th = 2-Thienyl; Py = 4-Pyridyl.

**Scheme 1**

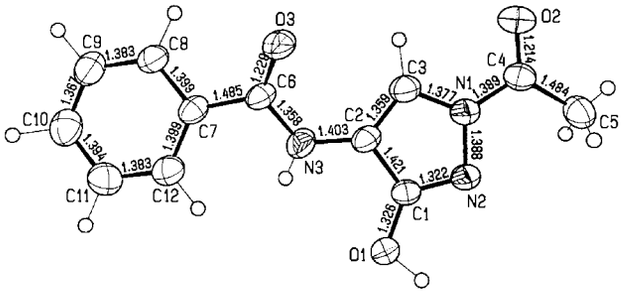
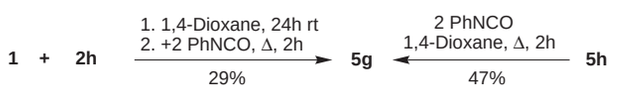
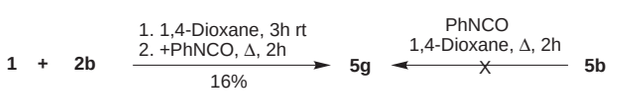



**Fig. 1** ORTEP view of compound **5a**: displacement ellipsoids are shown at 50% probability level. Bond distances are given in Å.

order to find evidence for the transformation of compounds **4** into **5**. For this reason, the reaction of the oxazolone derivative **1** with 4-phenylthiosemicarbazide (**2h**) was performed in the first step for 24 h at room temperature, thus forming the intermediate **3h**. In the second step 2 equivalents of phenyl isocyanate were added and upon heating in 1,4-dioxane for 2 h, the corresponding phenylcarbamoyl derivative **5g** was isolated as the main product in 29% yield (based on **1**), instead of the phenylthiocarbamoyl derivative **5h**. The same product was also obtained when the pyrazole derivative **5h** was refluxed in the presence of phenyl isocyanate. Since these experiments did not give any real evidence for the formation of derivative **4h**, the reaction of compound **1** with benzohydrazide (**2b**) was performed in the presence of phenyl isocyanate and the product **5g** was obtained in 16% yield (Scheme 2). An attempt to prepare compound **5g** from **5b** and phenyl isocyanate was not successful.




**Scheme 2**

The reaction between compounds **1** and **2b** in the presence of phenyl isocyanate, from which we isolated product **5g** (though in poor yield), could be evidence for the formation of the intermediate **4b** which was trapped by phenyl isocyanate. Of course, as shown in a separate experiment, product **5g** cannot be formed *via* compound **5b**.

We believe that the transformation of the intermediate **4** to **5** can be explained by the assistance of the nucleophilic oxygen of 1,4-dioxane, or eventually by the intermolecular migration of acyl groups between two molecules of the pyrazole derivative **4**. In the case of a carbamoyl or thiocarbamoyl group the appearance of an intermediary-formed phenyl isocyanate or phenyl isothiocyanate also cannot be excluded. The driving force for the migration might be higher thermodynamic stability of the products of type **5** in comparison with isomeric compounds **4**.

We also investigated the mobility of acyl groups by using the described compounds as an acylating system.[7] In a previous communication *N*-acyl pyrazoles were described as relatively inert acylating agents and that alcoholysis was dramatically accelerated under the influence of a strong acid or base.[8] Instead of starting from compounds **5** and appropriate nucleophiles, we carried out such acylation as a one-pot procedure in which intermediates have not been isolated. This was realized in the synthesis of previously known[9] symmetrically *N*,*N*′-disubstituted hydrazines **7a**–**j**. For this purpose, the oxazolone **1** and two equivalents of an appropriate derivative **6** were heated in dioxane for 0.5–2 h [reaction (1), Table 1].

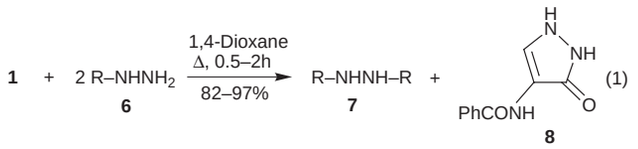



**Table 1** Synthesis of *N*,*N*′-diacylhydrazines **7a**–**j**

| Product **7** | R | Yield[a] (%) | Mp/°C | Lit. mp/°C |
|---|---|---|---|---|
| **7a** | PhCO | 97 | 242–243 | 237–238[9a] |
| **7b** | *p*-$NO_2$-PhCO | 91 | 301–303 | 297–298[9c] |
| **7c** | *o*-HO-PhCO | 86 | 315–317 | 315–316[9c] |
| **7d** | 2-ThienylCO | 89 | 274–277 | 276[9d] |
| **7e** | 3-PyridylCO | 84 | 230–232 | 227–228[9e] |
| **7f** | 4-PyridylCO | 91 | 258–260 | 254–255[9e] |
| **7g** | 2-PyrazinylCO | 90 | 218–220 | 223–225[9f] |
| **7h** | $PhCONHCH_2CO$ | 88 | 267–269 | 267–268[9g] |
| **7i** | PhNHCO | 94 | 255–257 | 250[9h] |
| **7j** | PhNHCS | 82 | 188–189 | 187[9i] |

[a] Isolated yields of TLC-pure compounds.

The separation of the products of type **7** from the pyrazolone by-product **8** was achieved from an alkaline aqueous solution of the crude material from which the products **7** separated, whereas pyrazolone derivative **8** was soluble under such conditions.

In conclusion, we have presented a very convenient synthesis of various 1-acyl-3-hydroxy-1*H*-pyrazoles and their structure determination as well as a method for the synthesis of various symmetrically *N*,*N*′-disubstituted hydrazines starting from easily available, chemically stable and cheap chemicals. The method also represents a possible route for the activation of hydrazides, which are known not to be useful donors of acyl units due to their high resonance stability.[10]

## Experimental

Melting points were determined on a Kofler micro hot stage and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded in DMSO-$d_6$ on a Bruker Avance DPX 300 spectrometer; $^1$H NMR spectra were recorded at 300.1 MHz (with TMS as an internal reference) and $^{13}$C NMR spectra at 75.4 MHz using solvent signal (39.5 ppm) as an internal reference. Coupling constants *J* are given in Hz. IR spectra of **5a** were taken on a Perkin-Elmer FTIR 1720 X spectrometer in a KBr pellet and in DMSO (99.5%, over molecular sieves, with less than 0.01% of water). Mass spectra were recorded on a VG-Analytical AutospecQ spectrometer. Elemental analyses (C, H, N) were performed on a Perkin-Elmer 2400 CHN analyzer. Thin-layer chromatography was carried out on Fluka silica gel TLC-cards. Merck silica gel 60 $PF_{254}$ containing gypsum was used to prepare chromatotron plates. 4-Ethoxymethylene-2-phenyloxazol-5(4*H*)-one (**1**),[3] pyrazine-2-carbohydrazide (**6g**)[11a] and 2-(benzoylamino)acetohydrazide (**6h**)[11b] were prepared as described in the literature. 1,4-Dioxane was purified as described previously.[12] All other compounds were used as received from commercial suppliers (Fluka, Aldrich).

### General procedure for the preparation of *N*-(1-acetyl-3-hydroxy-1*H*-pyrazol-4-yl)benzamides 5a–i

A mixture of the oxazolone **1** (5 mmol) and a hydrazino derivative **2** (5 mmol) was stirred in dioxane (10 ml) at room temperature for 2 h followed by heating under reflux for 2 h. After the removal of the solvent under reduced pressure, dioxane (2.5 ml) and ethyl acetate (2.5 ml) were added. Upon cooling, the result-

ing solid was filtered off and washed with a small amount of dioxane. Yields are given in Scheme 1.

**Analytical and spectroscopic data of products 5a–i**

***N*-(1-Acetyl-3-hydroxy-1*H*-pyrazol-4-yl)benzamide 5a.** White solid, mp 219–222 °C, decomp. (dioxane); $\delta_H$ 2.49 (s, 3H, Me), 7.49–7.62 (m, 3H, Ph), 7.96 (m, 2H, Ph), 8.47 (s, 1H, 5-H), 10.05 (s, 1H, NH), 11.48 (br s, 1H, OH); $\delta_C$ 20.9 (*C*H$_3$), 114.1 (C-4), 119.2 (C-5), 127.8 (C-2′, C-6′), 128.4 (C-3′, C-5′), 131.9 (C-4′), 133.4 (C-1′), 156.8 (C-3), 165.1 (*C*ONH), 167.9 (*C*OMe); $\nu_{max}$/cm$^{-1}$ (KBr) 1718, 1661, 1635, 1601, 1571, 1513, 1484, 1394; (DMSO, 10% solution) 1711, 1663, 1620, 1602, 1565, 1529; *m*/*z* 245 (M$^+$, 18%), 105 (100) (Found: C, 58.8; H, 4.2; N, 17.2. Calc. for $C_{12}H_{11}N_3O_3$: C, 58.8; H, 4.5; N, 17.1%).

***N*-(1-Benzoyl-3-hydroxy-1*H*-pyrazol-4-yl)benzamide 5b.** White solid, mp 209–212 °C, decomp. (dioxane); $\delta_H$ 7.50–7.67 (m, 6H, two Ph), 7.97 (m, 4H, two Ph), 8.65 (s, 1H, 5-H), 10.15 (s, 1H, NH), 11.67 (br s, 1H, OH); $\delta_C$ 114.4, 120.9, 127.8, 128.0, 128.4, 130.3, 131.9, 132.06, 132.10, 133.3, 157.6, 164.9, 165.2; *m*/*z* 307 (M$^+$, 24%), 105 (100) (Found: C, 66.1; H, 4.1; N, 13.9. Calc. for $C_{17}H_{13}N_3O_3$: C, 66.4; H, 4.3; N, 13.7%).

***N*-[3-Hydroxy-1-(4-nitrobenzoyl)-1*H*-pyrazol-4-yl]benzamide 5c.** White solid, mp 294–296 °C, decomp. (dioxane); $\delta_H$ 7.51–7.64 (m, 3H, Ph), 7.98 (m, 2H, Ph), 8.16 (d, 2H, *J* 8.9, *p*-NO$_2$-Ph), 8.37 (d, 2H, *J* 8.9, *p*-NO$_2$-Ph), 8.67 (s, 1H, 5-H), 10.19 (s, 1H, NH), 11.85 (br s, 1H, OH); $\delta_C$ 115.2, 120.4, 123.0, 127.9, 128.4, 131.4, 132.0, 133.2, 138.2, 149.1, 158.0, 163.5, 165.3; *m*/*z* 352 (M$^+$, 22%), 105 (100) (Found: C, 57.8; H, 3.2; N, 16.05. Calc. for $C_{17}H_{12}N_4O_5$: C, 58.0; H, 3.4; N, 15.9%).

***N*-[3-Hydroxy-1-(2-thienylcarbonyl)-1*H*-pyrazol-4-yl]-benzamide 5d.** White solid, mp 235–238 °C, decomp. (dioxane); $\delta_H$ 7.30 (dd, 1H, $J_1$ 4.9, $J_2$ 4.0, 4′-H), 7.53–7.65 (m, 3H, Ph), 8.01 (m, 2H, Ph), 8.12 (dd, 1H, $J_1$ 4.9, $J_2$ 1.2, 5′-H), 8.35 (dd, 1H, $J_1$ 4.0, $J_2$ 1.2, 3′-H), 8.69 (s, 1H, 5-H), 10.17 (s, 1H, NH), 11.70 (br s, 1H, OH); $\delta_C$ 114.6, 120.4, 127.6, 127.8, 128.4, 132.0, 132.4, 133.3, 137.30, 137.33, 157.18, 157.24, 165.2; *m*/*z* 313 (M$^+$, 45%), 105 (100) (Found: C, 57.4; H, 3.7; N, 13.6. Calc. for $C_{15}H_{11}N_3O_3S$: C, 57.5; H, 3.5; N, 13.4%).

***N*-[3-Hydroxy-1-(pyridin-4-ylcarbonyl)-1*H*-pyrazol-4-yl]-benzamide 5e.** Yellowish solid, 265–267 °C, decomp. (dioxane); $\delta_H$ 7.50–7.63 (m, 3H, Ph), 7.82 (d, 2H, *J* 5.9, Py), 7.98 (m, 2H, Ph), 8.65 (s, 1H, 5-H), 8.78 (deg d, 2H, Py), 10.19 (s, 1H, NH), 11.88 (br s, 1H, OH); $\delta_C$ 115.4, 120.2, 123.5, 127.9, 128.4, 132.0, 133.2, 139.8, 149.7, 158.1, 163.6, 165.3; *m*/*z* 308 (M$^+$, 34%), 105 (100) (Found: C, 62.0; H, 3.9; N, 18.1. Calc. for $C_{16}H_{12}N_4O_3$: C, 62.3; H, 3.9; N, 18.2%).

***N*-{3-Hydroxy-1-[2-(benzoylamino)acetyl]-1*H*-pyrazol-4-yl}-benzamide 5f.** White solid, mp 269–272 °C, decomp. (dioxane); $\delta_H$ 4.68 (d, 2H, *J* 5.7, NHC*H*$_2$), 7.48–7.62 (m, 6H, two Ph), 7.90–7.98 (m, 4H, two Ph), 8.48 (s, 1H, 5-H), 8.95 (t, 1H, *J* 5.7, N*H*CH$_2$), 10.11 (s, 1H, 4-NH), 11.72 (br s, 1H, OH); $\delta_C$ 41.3, 114.3, 119.5, 127.3, 127.8, 128.4 (two signals), 131.6, 131.9, 133.3, 133.7, 157.3, 165.2, 166.6, 166.8; *m*/*z* (FAB-MS) 365 (MH$^+$, 8%), 154 (100) (Found: C, 62.4; H, 4.3; N, 15.2. Calc. for $C_{19}H_{16}N_4O_4$: C, 62.6; H, 4.4; N, 15.4%).

***N*-[3-Hydroxy-1-(*N*-phenylcarbamoyl)-1*H*-pyrazol-4-yl]-benzamide 5g.** White solid, mp 230–233 °C, decomp. (dioxane); $\delta_H$ 7.12 (t, 1H, *J* 7.4, NH-*Ph*), 7.36 (deg dd, 2H, NH-*Ph*), 7.53–7.65 (m, 3H, COPh), 7.72 (d, 2H, *J* 7.8, NH-*Ph*), 7.98 (m, 2H, COPh), 8.48 (s, 1H, 5-H), 9.85 (s, 1H, NH), 10.09 (s, 1H, NH), 11.08 (br s, 1H, OH); $\delta_C$ 112.1, 120.4, 120.8, 123.8, 127.7, 128.5, 128.7, 132.0, 133.3, 137.7, 147.5, 155.3, 165.1; *m*/*z* (FAB-MS) 323 (MH$^+$, 20%), 154 (100) (Found: C, 63.05; H, 4.5; N, 17.2. Calc. for $C_{17}H_{14}N_4O_3$: C, 63.35; H, 4.4; N, 17.4%).

***N*-[3-Hydroxy-1-(*N*-phenylthiocarbamoyl)-1*H*-pyrazol-4-yl]-benzamide 5h.** White solid, mp 164–166 °C, decomp. (dioxane); $\delta_H$ 7.27 (t, 1H, *J* 7.4, NH-*Ph*), 7.42 (deg dd, 2H, NH-*Ph*), 7.52–7.66 (m, 5H, 3H of COPh and 2H of NH-*Ph*), 7.99 (m, 2H, COPh), 8.95 (s, 1H, 5-H), 10.14 (s, 1H, NH), 11.08 (s, 1H, NH), 11.48 (br s, 1H, OH); $\delta_C$ 113.7, 122.8, 125.3, 126.2, 127.7, 128.4, 128.5, 132.0, 133.2, 138.3, 156.4, 165.0, 173.4; *m*/*z* (FAB-MS) 339 (MH$^+$, 37%), 154 (100) (Found: C, 60.1; H, 4.4; N, 16.7. Calc. for $C_{17}H_{14}N_4O_2S$: C, 60.3; H, 4.2; N, 16.6%).

***N*-[3-Hydroxy-1-(benzyloxycarbonyl)-1*H*-pyrazol-4-yl]benzamide 5i.** White solid; mp 208–210 °C, decomp. (dioxane); $\delta_H$ 5.38 (s, 2H, CH$_2$), 7.40–7.59 (m, 8H, Ph and 3H of COPh), 7.95 (m, 2H, COPh), 8.41 (s, 1H, 5-H), 10.05 (s, 1H, NH), 11.53 (br s, 1H, OH); $\delta_C$ 68.6, 112.8, 122.1, 127.8, 128.3, 128.4, 128.51, 128.54, 131.8, 133.3, 135.2, 148.8, 157.3, 165.0; *m*/*z* (FAB-MS) 338 (MH$^+$, 65%), 91 (100) (Found: C, 63.9; H, 4.3; N, 12.5. Calc. for $C_{18}H_{15}N_3O_4$: C, 64.1; H, 4.5; N, 12.5%).

**Reaction of oxazolone 1 with 4-phenylthiosemicarbazide (2h) in the presence of phenyl isocyanate**

A mixture of oxazolone **1** (434 mg, 2 mmol) and **2h** (99%, 338 mg, 2 mmol) was stirred in dioxane (4 ml) at room temperature for 24 h. After evaporation under reduced pressure, EtOAc (1.5 ml) was added to the residue and, upon cooling, 374 mg (55%) of crude **3h** was obtained. The mixture of crude **3h** in 1,4-dioxane (3 ml) and phenyl isocyanate (98%, 255 mg, 2.01 mmol) was heated under reflux for 2 h. After separation as described in the general procedure, *N*-phenylcarbamoyl derivative **5g** (188 mg, 29% based on oxazolone **1**) was obtained.

**Reaction of *N*-[3-hydroxy-1-(*N*-phenylthiocarbamoyl)-1*H*-pyrazol-4-yl]benzamide (5h) with phenyl isocyanate**

A mixture of **5h** (200 mg, 0.591 mmol) and phenyl isocyanate (144 mg, 1.185 mmol) in 1,4-dioxane (2 ml) was heated under reflux for 2 h. After separation as described in the general procedure, *N*-phenylcarbamoyl derivative **5g** (89 mg, 47%) was obtained.

**Reaction of oxazolone 1 with benzohydrazide (2b) in the presence of phenyl isocyanate**

A mixture of oxazolone **1** (326 mg, 1.50 mmol) and **2b** (98%, 205 mg, 1.51 mmol) in dioxane (3 ml) was stirred at room temperature for 3 h. Upon cooling and filtering off, 382 mg (83%) of crude **3b** was obtained. To the boiling mixture of crude **3b** in 1,4-dioxane (4 ml), phenyl isocyanate (170 mg, 1.40 mmol) was added and heated under reflux for 2 h. After separation following the general procedure, a crude mixture of products in which approximately 61 mg (based on $^1$H NMR analysis, 16% based on **1**) of compound **5g** was obtained. The pure **5g** can be obtained by purification on a chromatotron by using first a mixture CHCl$_3$–EtOAc (10 : 1), then CHCl$_3$–EtOAc (1 : 1), and finally EtOAc as eluents.

**Reaction of *N*-[1-benzoyl-3-hydroxy-1*H*-pyrazol-4-yl]benzamide (5b) with phenyl isocyanate**

A mixture of **5b** (100 mg, 0.325 mmol) and phenyl isocyanate (43 mg, 0.354 mmol) in 1,4-dioxane (2 ml) was heated under reflux for 2 h. After separation following the general procedure, the starting material **5b** (70 mg, 70%) was recovered and no formation of **5g** was confirmed by TLC.

**General procedure for the preparation of symmetrically disubstituted *N*,*N*′-diacylhydrazines (7)**

A mixture of a hydrazine derivative **6** (10 mmol) and oxazolone **1** (5 mmol) in 1,4-dioxane (10 ml) was heated under reflux for 0.5 h (compounds **7b**, **7i** and **7j**) or for 2 h (all other compounds). Water (5 ml) was added to the cooled mixture and the pH value was adjusted to 10 with 1 M NaOH in order to dissolve pyrazolone **8**. The product was filtered off and thoroughly washed with dioxane. Yields of products **7** are given in Table 1.

***N*-(2,3-Dihydro-3-oxo-1*H*-pyrazol-4-yl)benzamide 8.** This compound can be isolated from the water layer by acidification to pH 5 with acetic acid and filtration of the resulting solid, mp 205–206 °C (lit.,[3] 204–205 °C).

**X-Ray crystallography**

**Crystal data.** $C_{12}H_{11}N_3O_3$, $M = 245.2$, monoclinic, $a =$

11.443(1), $b = 5.035(1)$, $c = 19.676(2)$ Å, $\beta = 99.39(1)°$, $V = 1118.5(3)$ Å$^3$ (by least-squares refinement on diffractometer angles for 50 automatically centred reflections with $8.20° \leqslant \theta \leqslant 13.38°$), $T = 293$ K, $\lambda = 0.71069$ Å, space group $P2_1/c$ (No. 14), $Z = 4$, $D_x = 1.456$ g cm$^{-3}$, colorless plate: 0.65 × 0.16 × 0.05 mm, $\mu$(Mo-K$\alpha$) = 0.101 mm$^{-1}$.

**Data collection and processing.** Enraf–Nonius CAD4 diffractometer, graphite-monochromated Mo-K$\alpha$ radiation, $\omega$–2$\theta$ scans with $\omega$ scan width $(0.85 + 0.30 \tan \theta)°$; 10822 reflections measured ($\theta_{max} = 28°$, $-15 < h < 15$, $-6 < k < 6$, $-25 < l < 25$), 2694 unique (merging $R = 0.0315$), giving 1247 with $I > 2.5\sigma(I)$. No corrections for absorption were required. Intensity decay = 0.22% (correction was applied).†

**Structure solution and refinement.** The structure was solved (all non-H atoms) by direct methods (SIR92).[13] Full-matrix least-squares refinement on $F$ with all non-H atoms anisotropic; hydrogen atoms were located from a $\Delta F$ synthesis and were not refined. The weighting scheme $w = 6.0 \times W_f \times W_s$ where $W_f(|F_o| < 6.75) = (|F_o|/6.75)^{1.2}$, $W_f(|F_o| > 24.0) = (24.0/|F_o|)$, $W_f(6.75 \leqslant |F_o| \leqslant 24.0) = 1.0$ and $W_s(\sin\theta < 0.37) = (\sin\theta/0.37)$ and $W_s(0.37 \leqslant \sin\theta) = 1.0$. The correction for the secondary extinction[14] was applied with $g = 0.19(6) \times 10^4$. In the final least-square cycle there were 2087 contributing reflections (included were those unobserved reflections for which $F_c$ was greater than $F_o$) and 164 parameters. The final $R$ and $R_w$ values were 0.052 and 0.055, respectively. The final maximum shift/esd was 0.0001. The maximal residual density in the final difference map was 0.439 e Å$^{-3}$ and the minimal was −0.389 e Å$^{-3}$. The XTAL3.4[15] system of crystallographic programs was used for the correlation and reduction of data, structure refinement and interpretation. ORTEPII[16] was used to produce molecular graphics.

## Acknowledgements

We thank the Ministry of Science and Technology for financial support. Dr B. Kralj and Dr D. Žigon (Center for Mass Spectroscopy, "Jožef Stefan" Institute, Ljubljana, Slovenia) are gratefully acknowledged for mass measurements.

† Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/243.

## References

1 (*a*) R. Fusco, in *The Chemistry of Heterocyclic Compounds: Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings*, ed. R. H. Wiley, Interscience, New York, 1967, p. 3; (*b*) J. Elguero, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, vol. 5, p. 167; (*c*) J. Elguero, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. C. Scriven, Pergamon Press, Oxford, 1996, vol. 3, p. 1.

2 (*a*) A. Weissberger and H. D. Porter, *J. Am. Chem. Soc.*, 1943, **65**, 1495; (*b*) M. Irie, T. Miyasaka and K. Arakawa, *J. Biochem.* (*Tokyo*), 1972, **72**, 65; (*c*) K. Arakawa, T. Miyasaka and H. Ochi, *Chem. Pharm. Bull.*, 1974, **22**, 207; (*d*) K. Arakawa, T. Miyasaka and H. Ochi, *Chem. Pharm. Bull.*, 1974, **22**, 214; (*e*) H. Ochi, T. Miyasaka and K. Arakawa, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 2991; (*f*) A. Hadi, N. Martin, C. Seoane and J. L. Soto, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1045; (*g*) K. Mitsuhashi, H. Takayanagi, S. Matsuno and K. Tanaka, *J. Heterocycl. Chem.*, 1982, **19**, 1389; (*h*) J. T. Drummond and G. Johnson, *J. Heterocycl. Chem.*, 1988, **25**, 1123; (*i*) Ú. Í. Jónsson, H. Kristinsson, H. Nussbaumer, V. Skúlason and T. Winkler, *Synthesis*, 1995, 805.

3 J. W. Cornforth, *The Chemistry of Penicillin*, ed. H. T. Clarke, J. R. Johnson and R. Robinson, Princeton University Press, Princeton, 1949, p. 730.

4 (*a*) Y. S. Rao and R. Filler, in *The Chemistry of Heterocyclic Compounds: Oxazoles*, ed. A. Weissberger and E. C. Taylor, Interscience, New York, 1986, p. 361; (*b*) F. W. Hartner, Jr., in ref. 1*c*, vol. 3, p. 261; (*c*) S.-S. Homami and A. K. Mukerjee, *Indian J. Chem., Sect. B*, 1992, **31**, 411.

5 O. A. Attanasi, L. De Crescentini, P. Filippone, E. Foresti, R. Galeazzi, I. Ghiviriga and A. R. Katritzky, *Tetrahedron*, 1997, **53**, 5617, and references cited therein.

6 M. Begtrup, G. Boyer, P. Cabildo, C. Cativiela, R. M. Claramunt, J. Elguero, J. I. García, C. Toiron and P. Vedso, *Magn. Reson. Chem.*, 1993, **31**, 107.

7 (*a*) T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley, New York, 1991; (*b*) P. J. Kocieñski, *Protecting Groups*, Georg Thieme Verlag, Stuttgart, 1994.

8 C. Kashima, H. Harada, I. Kita, I. Fukuchi and A. Hosomo, *Synthesis*, 1994, 61.

9 (*a*) C. M. Anderson and E. C. Gilbert, *J. Am. Chem. Soc.*, 1942, **64**, 2369; (*b*) H. Zhao, N. Neamati, S. Sunder, H. Hong, S. Wang, G. W. A. Milne, Y. Pommier and T. R. Burke, Jr., *J. Med. Chem.*, 1997, **40**, 937; (*c*) H. Zhao and T. R. Burke, Jr., *Tetrahedron*, 1997, **53**, 4219; (*d*) G. Kossmehl and G. Manecke, *Makromol. Chem.*, 1969, **123**, 233 (*Chem. Abstr.*, 1969, **71**, 3748b); (*e*) R. Graf, *J. Prakt. Chem.*, 1933, **138**, 289 (*Chem. Abstr.,* 1934, **28**, 769[7]); (*f*) O. Dalmer, C. Diehl and E. Walter, **USP 2 176 063**, 1940 (*Chem. Abstr.*, 1940, **34**, 1820[2]); (*g*) S. Grudziński, *Roczniki Chem.*, 1959, **33**, 655 (*Chem. Abstr.*, 1960, **54**, 2184c); (*h*) R. E. Rosenkranz, K. Allner, R. Good, W. v. Philipsborn and C. H. Eugster, *Helv. Chim. Acta*, 1963, **46**, 1259; (*i*) M. Freund and S. Wischewiansky, *Chem. Ber.*, 1893, **26**, 2877; (*j*) O. Prakash, V. Sharma and A. Sadana, *Synth. Commun.*, 1997, **27**, 3371.

10 H. Paulsen and D. Stoye, *The Chemistry of Amides*, Interscience, London, 1970, p. 515; (*b*) P. D. Bailey, I. D. Collier and K. H. Morgan, in *Comprehensive Organic Functional Group Transformations*, ed. A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Pergamon Press, Oxford, 1995, vol. 5, p. 257; (*c*) R. D. Connell, in ref. 10*b*, p. 309.

11 (*a*) G. Carrara, F. M. Chiancone, V. D'Amato, E. Ginoulhiac, C. Martinuzzi, U. M. Teotino and N. Visconti, *Gazz. Chim. Ital.*, 1952, **82**, 652 (*Chem. Abstr.*, 1954, **48**, 6423d); (*b*) Th. Curtius, *Chem. Ber.*, 1890, **23**, 3023.

12 B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, Longman (co-published with Wiley), New York, 1989, 5th edn., p. 407.

13 A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi and G. Polidori, *J. Appl. Crystallogr.*, 1994, **27**, 435.

14 A. C. Larson, *Crystallographic Computing*, ed. F. R. Ahmed, S. R. Hall and C. P. Huber, Munksgaard, Copenhagen, 1970, p. 291.

15 S. R. Hall, G. S. D. King and J. M. Stewart, *The Xtal3.4 User's Manual*, University of Western Australia, Lamb, Perth, 1995.

16 C. K. Johnson, *ORTEPII*, Report ORNL-5138, Oak Ridge National Laboratory, Tennessee, USA, 1976.

*Paper* 8/03973I
*Received* 27*th May* 1998
*Accepted* 8*th July* 1998