Regioselective acylation of 1-hydroxypyrazoles *via* metalated intermediates

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A range of C-4 and C-5 acylated 1-benzyloxypyrazoles (**7a**–**e**) and (**4**) have been prepared *via* Pd(0) catalysed cross-coupling between acid chlorides and 1-benzyloxy-4-(tributylstannyl)pyrazole (**8**) or 1-benzyloxypyrazol-5-ylzinc chloride. 3-Acylated 2-(4-methoxybenzyl)-2*H*-pyrazole 1-oxides† (**15a**–**f**) were formed by reaction between the 3-magnesiated 2*H*-pyrazole 1-oxide (**14**) and acid chlorides. The benzyl group of **4** and **7a** and the 4-methoxybenzyl (PMB) group of **15a** were removed by treatment with conc. HCl or TFA in the presence of water, furnishing the corresponding C-acylated 1-hydroxypyrazoles.

Introduction

Heteroaromatic compounds are important building blocks in drug discovery. Therefore, the development of strategies for regioselective functionalisation of heterocyclic frameworks is of high interest to the pharmaceutical industry. Ring acylated pyrazoles have biological activities such as cytotoxic,[1] multi-drug resistance-modulating,[2] antiviral,[3] antiallergic,[4] anti-arthritic[5] and antibacterial activity.[6] In connection with a drug discovery program we became interested in the preparation of C-5 (**2a**), C-4 (**2b**) and C-3 (**2c**) acylated derivatives of 1-hydroxypyrazole (**1**) (Fig. 1) and, in particular, derivatives such

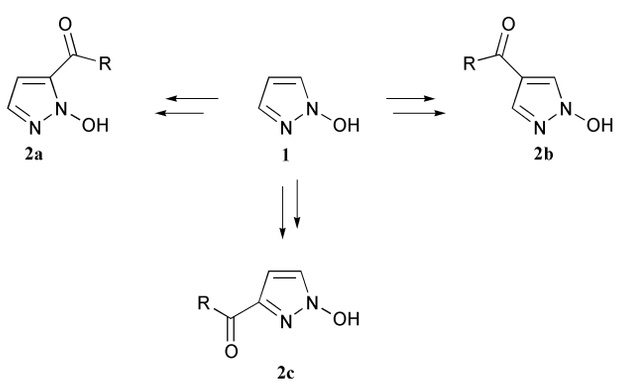


Fig. 1

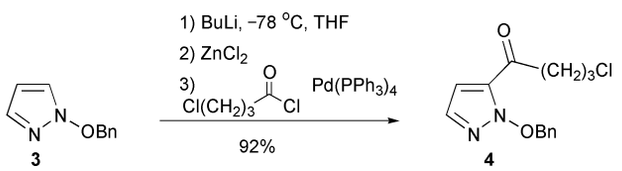
as **16**, **17** and **18** which could readily undergo further functionalisation. Lewis acid-promoted Friedel–Crafts type acylation occurs in the C-4 position of 1-substituted pyrazoles under relatively harsh conditions.[7] Only a few reports deal with the acylation of metalated pyrazole intermediates. Thus, 1,4-dilithiopyrazole has been acylated with aromatic and heteroaromatic alkyl carboxylates, while 1-substituted pyrazol-3-yl- and pyrazol-4-ylstannanes have been benzoylated under Pd(0) catalysis.[8] 1-Substituted pyrazoles acylated at C-5 have been prepared by C-5 lithiation followed by reaction with Weinreb amides,[9] or by transmetalation and Pd(0) catalysed cross-coupling with a series of acid chlorides.[10] Furthermore, Chatani *et al.*[11] have recently described the C-3 acylation of 1-methylpyrazole *via* ruthenium catalysed carbonylation effected by CO (3 atm), an olefin and 10 mol% $Ru_3(CO)_{12}$ in toluene at 160 °C.

In previous studies we reported protocols for selective monoarylation of **1**[12] in the C-3,[13] C-4[14] and C-5[10] positions using metalated intermediates. In this paper we report details for the preparation of C-3, C-4 and C-5 acylated 1-hydroxypyrazoles. The protocols for C-3 and C-4 acylation, which differ substantially from the protocols used for the corresponding arylation, provide convergent approaches for the regioselective preparation of C-acylated 1-hydroxypyrazoles.

Results and discussion

Preparation of 1-benzyloxy-5-(4-chlorobutyryl)pyrazole

The 5-acylated pyrazole **4** was synthesised in 92% yield according to our previously reported procedure for C-5 acylation[10] *via* *ortho*-lithiation of 1-benzyloxypyrazole,[15] transmetalation with $ZnCl_2$ followed by Pd(0) catalysed cross-coupling with 4-chlorobutyryl chloride in 92% yield (Scheme 1).



Scheme 1

Preparation of 4-acylated 1-benzyloxypyrazoles

In order to access 4-acylated 1-benzyloxypyrazoles we initially reacted the 4-magnesiated pyrazole **6a**, which is readily prepared from **1** as previously described,[14] with various acid chlorides. However, only benzoyl chloride produced the desired 4-benzoylated pyrazole **7b** in 68% yield,[14] whereas aliphatic acid

† According to IUPAC nomenclature the indicated hydrogen position takes numbering precedence, which means that position 1 should be that carrying the 4-methoxybenzyl group. In order not to change the numbering of the pyrazole ring positions in the pyrazole *N*-oxides we have numbered the position carrying the oxide as position 1.

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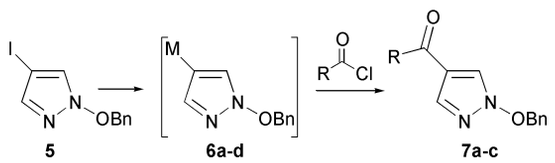
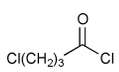
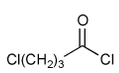
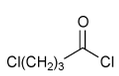
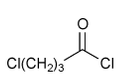
Table 1 Attempted preparation of 4-acylated 1-benzyloxypyrazoles



Entry	Metal halide (M)	Acyl chloride	Product	Yield(%)
1[a]	MgCl, **6a**		**7b**	68[b]
2[a]	MgCl, **6a**		**7c**	0[c]
3[a]	MgCl, **6a**		**7a**	0
4[d]	MnCl, **6b**		**7a**	0
5[e]	MnI, **6c**		**7a**	0
6[f]	ZnCl, **6d**		**7a**	43
7[f]	ZnCl, **6d**		**7b**	20
8[f]	ZnCl, **6d**		**7c**	31

[a] Pr^iMgCl was used for the I–Mg exchange. [b] See Ref. 14. [c] **3** was isolated as the only product. [d] **6b** was obtained *via* transmetalation of **6a** with $MnCl_2$·2LiCl. [e] **6c** was formed by direct oxidative addition of activated Mn* to **5**. [f] **6b** was generated *via* transmetalation of **6a** with $ZnCl_2$.

chlorides, such as acetyl chloride and 4-chlorobutyryl chloride possessing acidic α-protons, produced 1-benzyloxypyrazole **3** as the only product (Table 1, entries 1–3). Quenching with D_2O after the addition of the acid chloride furnished exclusively 1-benzyloxy[4-^{1}H]pyrazole (**3**) showing that **6a** most likely abstracts an α-proton from the acid chloride. Addition of catalytic or stoichiometric amounts of CuCN·2LiCl to **6a** did not change the outcome. Similarly, reaction of aliphatic nitriles with **6a** gave only **3**. Attempts to prepare ketone **7a** by reaction of pyrazol-4-ylmanganese halide **6b** or **6c** with an acid chloride also failed (Table 1, entries 4 and 5). Compounds **6b** and **6c** were generated, *via* transmetalation of **6a** with $MnCl_2$·2LiCl or by oxidative-addition of Rieke Manganese (Mn*)[16] to **5**.

In a recent review summarising the synthesis of ketones *via* reaction of acid chlorides with organometallic reagents, Dieter stated that "*Most useful synthetic methods generally utilize organocopper reagents and methods catalytic in palladium*".[17] We therefore investigated the use of Pd(0) catalysed cross-couplings for the preparation of **2b**.

Although 4-aryl, 5-aryl and 5-acyl substituted 1-benzyloxypyrazoles have been synthesised from the corresponding pyrazol-4-yl[14] (**6d**) and pyrazol-5-ylzinc halides,[10] reaction of **6d** with an acid halide in the presence of Pd(0) provided the 4-acylated 1-benzyloxypyrazoles (**7a**–**c**) in only low to moderate yields mainly due to zinc promoted ring opening of THF by the acid chloride (Table 1, entries 6–8).[18] Performing the reaction in Et_2O or in Et_2O–DMF to overcome the problem with ring opening of THF did not improve the outcome. Whereas the Stille type cross-coupling[19,20] between 1-benzyloxy-5-(tributylstannyl)pyrazole and acid chlorides failed,[10] the similar coupling using 1-benzyloxy-4-(tributylstannyl)pyrazole (**8**) and acid chlorides turned out to be the method of choice for preparation of 4-acylated 1-benzyloxypyrazoles (**7a**–**e**). Thus, treatment of *in situ* generated **8** with an acid chloride in the presence of 5 mol% $Pd(PPh_3)_4$, and catalytic amounts of CuI in THF at 50 °C furnished **7a**–**d** in 35–70% yield (Table 2, entries 1, 3–5). When the reaction between **8** and 4-chlorobutyryl chloride was performed at 50 °C in the absence of CuI, the yield of **7a** dropped from 70% to 38% (Table 2, entry 1), and when the reaction was performed at room temperature **7a** was isolated in 30% yield together with the destannylated product **3** (Table 2, entry 2).

To further optimise the Stille cross-coupling we compared the reaction between **8** and 4-chlorobutyryl chloride using $Pd_2(dba)_3$ in the presence of phosphine ligands such as **9** and **10** which have been effective in Stille type couplings.[21] In addition electron rich ligands 2-(dicyclohexylphosphino)biphenyl (**11**) and 2-(di-*tert*-butylphosphino)biphenyl (**12**), which have been used successfully in carbon–carbon[22] and carbon–heteroatom[23,24] bond forming procedures, were investigated (Fig. 2). The comparison revealed that the yield of **7a** increased

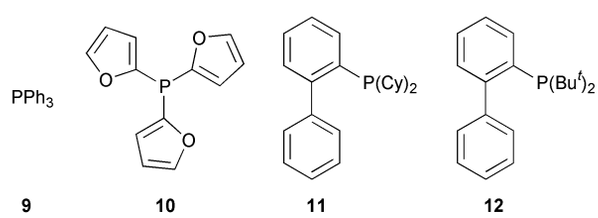


Fig. 2 Ligands used for the Stille cross-coupling.

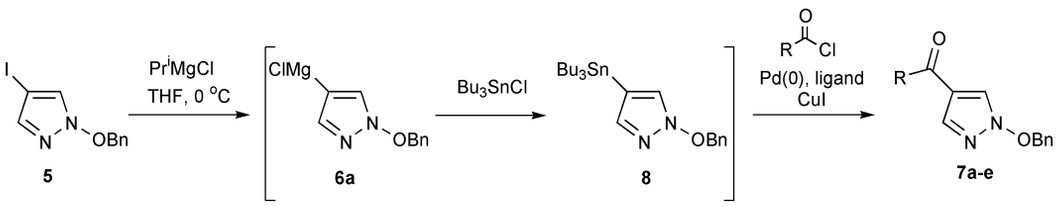
from 22% to 83% when PPh_3 was replaced with the more bulky electron rich ligand **12** (Table 2, entries 6 and 9). Complete conversion of **8** took place at room temperature, but significant destannylation to **3** was observed as a side reaction. Destannylation was minimised by performing the reaction at 50 °C. This gave a maximum yield (91%, Table 2, entry 10) of **7a**. Using these optimised conditions a range of 4-acylated 1-benzyloxypyrazoles **7a**–**e** were prepared in 57–93% yield (Table 2, entries 10–14).

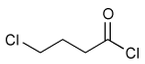
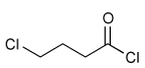
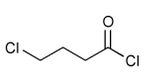
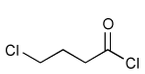
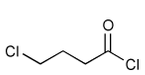
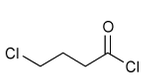
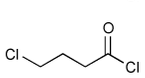
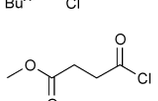
In contrast to the synthesis of 5-acylated 1-benzyloxypyrazoles which were successfully made under Negishi type conditions, but failed when the Stille coupling was employed, the corresponding 4-acylated derivatives are preferably formed using Stille type conditions.

Preparation of 3-acylated 2-(4-methoxybenzyl)-2*H*-pyrazole 1-oxides

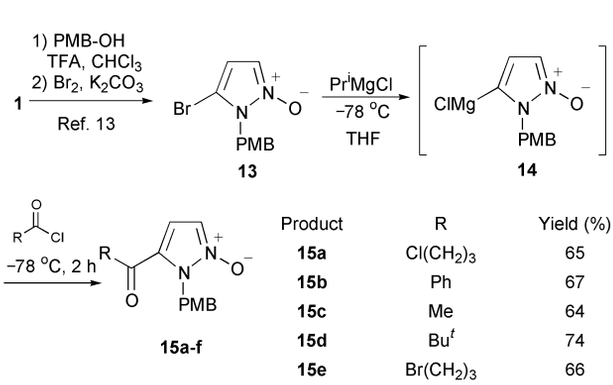
Access to 3-acylated 1-hydroxypyrazoles was achieved using our recently reported protocol for C-3 functionalisation[13] of **1**. This method is based on *N*-*p*-methoxybenzylation of **1** providing the corresponding 2-(4-methoxybenzyl)-2*H*-pyrazole 1-oxide which undergoes regioselective bromination at the C-3 position. Subsequent bromine–magnesium exchange with Pr^iMgCl at −78 °C afforded the corresponding 3-magnesiated pyrazole (**14**) (Scheme 2).[13] Surprisingly, transmetalation of **14** with either $ZnCl_2$ or Bu_3SnCl followed by Pd(0) catalysed acylation failed to give 3-acylated pyrazoles. Instead direct addition to **14** of various acid chlorides at −78 °C produced a series of 3-acylated 2-PMB-2*H*-pyrazole 1-oxides (**15a**–**f**) in 64–74% yield. Even acid chlorides possessing ester (**15f**) or alkyl bromide (**15e**) functionalities were tolerated under these low temperature conditions. The crude products were devoid of 2-(4-methoxybenzyl)-2*H*-pyrazole 1-oxide showing that no abstraction of α-protons from the acid chlorides or the formed pyrazolyl ketones **15a**, **15c**, **15e** and **15f** occurred. Furthermore no double addition forming tertiary alcohols were observed.

Table 2 Stille cross-coupling reactions for the preparation of 4-acylated 1-benzyloxypyrazoles



Entry	Pd(0)/ligand	Acyl chloride	Product	Reaction conditions	Isolated yield
1	$Pd(PPh_3)_4$ [a]		**7a**	50 °C, 1 h	70 (38) [b]
2	$Pd(PPh_3)_4$ [a]		**7a**	rt, *ca.* 5 h	30
3	$Pd(PPh_3)_4$ [a]		**7b**	50 °C, 1 h	68
4	$Pd(PPh_3)_4$ [a]		**7c**	50 °C, *ca.* 20 h	70
5	$Pd(PPh_3)_4$ [a]		**7d**	50 °C, *ca.* 20 h	35
6	$Pd_2(dba_3)$, **9** [c]		**7a**	rt, 7 h	22
7	$Pd_2(dba_3)$, **10** [c]		**7a**	rt, 5 h	45
8	$Pd_2(dba_3)$, **11** [c]		**7a**	rt, 4 h	53
9	$Pd_2(dba_3)$, **12** [c]		**7a**	rt, 2 h	83
10	$Pd_2(dba_3)$, **12** [c]		**7a**	50 °C, 45 min	91
11	$Pd_2(dba_3)$, **12** [c]		**7b**	50 °C, 30 min	93
12	$Pd_2(dba_3)$, **12** [c]		**7c**	50 °C, 30 min	78
13	$Pd_2(dba_3)$, **12** [c]		**7d**	50 °C, *ca.* 20 h	57
14	$Pd_2(dba_3)$, **12** [c]		**7e**	50 °C, 1 h	72

[a] Using 5 mol% Pd $(PPh_3)_4$. [b] Without addition of CuI. [c] Using 3 mol% Pd_2dba_3 and 6 mol% ligand.



Product	R	Yield (%)
15a	$Cl(CH_2)_3$	65
15b	Ph	67
15c	Me	64
15d	Bu^t	74
15e	$Br(CH_2)_3$	66
15f	$MeOOC(CH_2)_2$	72

Scheme 2 Preparation of 3-acylated 2-PMB-2*H*-pyrazole 1-oxides.

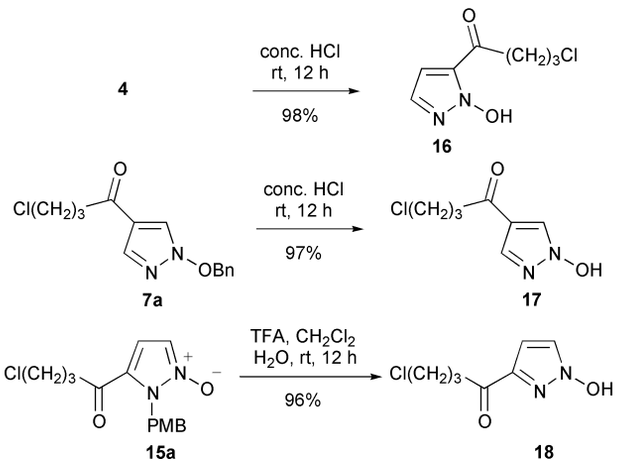
Deprotection. Preparation of 2a–c

By way of example, the benzyl group of **4** and **7a** was removed by treatment with conc. HCl at room temperature providing the acylated 1-hydroxypyrazoles **16** and **17** as analytically pure material in 97% and 98% yield, respectively (Scheme 3).

The PMB-group of **15a** was readily removed by treatment with TFA in CH_2Cl_2 at room temperature in the presence of water as a cation scavenger, producing analytically pure **18** in 96% yield.

Conclusions

The procedures described herein represent convergent approaches for conversion of 1-hydroxypyrazole (**1**) to the



Scheme 3 Preparation of *C*-acylated 1-hydroxypyrazoles

corresponding C-3, C-4 and C-5 acylated derivatives using selectively metalated 1-benzyloxypyrazoles or pyrazole 1-oxides. The nature of the metal used in the different ring positions is crucial. Thus, 5-acylated 1-benzyloxypyrazoles are best prepared from pyrazol-5-ylzinc chloride while 4-acylated 1-benzyloxypyrazoles are prepared from pyrazol-4-ylstannane. Finally 3-acylated derivatives are accessed *via* acylation of 3-magnesiated 2*H*-pyrazole 1-oxide.

Experimental

General

All reactions involving air-sensitive reagents were performed under N_2 or argon using syringe–septum cap techniques. All glassware was flame-dried prior to use. Flash column chromatography (FC) was performed using silica gel (Merck, 40–64 mesh). TLC was performed using Merck silica gel 60 F254 aluminium sheets. The sheets were visualised under UV-light (254 nm) or by spraying with ammonium cerium molybdate. Melting points are uncorrected. All new compounds were colourless, unless otherwise stated. Infra-red spectra were obtained on Perkin-Elmer Spectrum One FT-IR spectrometer. NMR spectra were recorded on a 300 MHz or a 400 MHz Varian spectrometer. Elemental analyses were performed by the Microanalytical Laboratory, Department of Physical Chemistry, University of Vienna, Austria.

Materials. All solvents and reagents were obtained from Fluka, Sigma-Aldrich or Strem chemicals and used without further purification, except THF which was distilled from Na–benzophenone under N_2. Compound **3**,[15] **5**,[14] **13**[13] and $Pd(PPh_3)_4$[25] were prepared as previously described. Pr^iMgCl[26] and *n*-BuLi[27] were titrated prior to use.

1-Benzyloxy-5-(4-chlorobutyryl)pyrazole 4

To a stirred solution **3** (174 mg, 1 mmol) in THF (8 mL) was added dropwise 1.6 M *n*-BuLi in hexane (0.75 mL, 1.2 mmol) at −78 °C over 2 min. Stirring was continued for 5 min, whereupon 1 M $ZnCl_2$ in diethyl ether (3 mL, 3 mmol) was added. The solution was allowed to warm to rt, and 4-chlorobutyryl chloride (169 mg, 1.2 mmol) and $Pd(PPh_3)_4$ (2 mol%) were added. Stirring was continued at rt for 2 h before quenching with sat. NH_4Cl (10 mL). Water (5 mL) was added to dissolve the formed precipitate and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. FC provided 258 mg (92%) of **4** as an oil, which upon standing slowly crystallised: mp 41–42 °C. R_f (EtOAc–heptane 3 : 7) 0.26. ν_{max} (solid)/cm^{-1}: 2950, 1687 (C=O), 1509, 1306, 1215. δ_H ($CDCl_3$): 7.50–7.34 (m, 5H), 7.30 (d, 1H, *J* 2.4), 6.70 (d, 1H, *J* 2.4), 5.39 (s, 2H), 3.60 (t, 2H *J* 6.8), 2.92 (t, 2H, *J* 6.8), 2.15–2.08 (m, 2H); δ_C ($CDCl_3$): 188.1, 133.3, 133.0, 132.4, 130.2, 129.5, 128.7, 108.4, 81.2, 44.2, 37.5, 26.1 (Found: C, 60.32; H, 5.29; N, 10.05. Calcd. for $C_{14}H_{15}ClN_2O_2$: C, 60.33; H, 5.42; N, 10.05%).

General procedure for preparation of 4-acyl substituted 1-benzyloxypyrazoles 7a–e

To a stirred solution of **5** (150 mg, 0.5 mmol) in THF (3 mL) at 0 °C was added 2.2 M Pr^iMgCl (0.27 mL, 0.6 mmol) in THF over a period of 2 min. Stirring was continued for 1 h at 0 °C before Bu_3SnCl (220 mg, 0.75 mmol) was added. After 1 h at rt the reaction mixture was heated to 50 °C and the acid chloride (1.0 mmol), CuI (1–2 mg) and a premixed solution of **12** (5 mg, 0.015 mmol) and $Pd_2(dba)_3$ (7 mg, 0.0075 mmol) in THF (1 mL) was added. The premixed catalyst solution was stirred in another flask for approx. 30 min at rt prior to use. The reaction mixture was stirred at 50 °C until TLC showed full conversion of the *in situ* generated **8**. The reaction mixture was quenched with sat. NH_4Cl (3 mL) and then water (3 mL) added to dissolve the formed precipitate. Extraction with CH_2Cl_2 (3 × 10 mL) and concentration of the combined organic phases gave the crude product, which was redissolved in diethyl ether (10 mL). The ether solution was vigorously stirred for 1 h at rt with a 10% aqueous solution of KF (5 mL). The white solid was filtrated off and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The crude products were purified by flash chromatography using EtOAc–heptane as eluent.

1-Benzyloxy-4-(4-chlorobutyryl)pyrazole 7a. Acid chloride: 4-chlorobutyryl chloride. FC gave 127 mg (91%) of **7a**: mp 64–65 °C (heptane). R_f (EtOAc–heptane 3 : 7) 0.25. ν_{max} (solid)/cm^{-1}: 3124, 2965, 1668 (C=O), 1535, 1397, 1255. δ_H ($CDCl_3$): 7.75 (d, 1H, *J* 0.8), 7.44 (d, 1H, *J* 0.8), 7.40–7.32 (m, 3H), 7.32–7.28 (m, 2H), 5.32 (s, 2H), 3.59 (t, 2H, *J* 6.7), 2.83 (t, 2H, *J* 7.0), 2.18–2.08 (m, 2H); δ_C ($CDCl_3$): 192.8, 135.0, 133.2, 129.9, 129.9, 129.1, 125.1, 120.7, 80.92, 44.7, 36.8, 26.8 (Found: C, 60.50; H, 5.42; N, 9.96. Calcd. for $C_{14}H_{15}ClN_2O_2$: C, 60.33; H, 5.42; N, 10.05%).

4-Benzoyl-1-benzyloxypyrazole 7b. Acid chloride: benzoyl chloride. FC gave 129 mg (93%) of **7b**: mp 79–80 °C (heptane) (lit.[14] mp 77–79 °C). R_f (EtOAc–heptane 3 : 7) 0.38. δ_H ($CDCl_3$): 7.80 (d, 1H, *J* 0.8), 7.70–7.65 (m, 2H), 7.56 (tt, 1H, *J* 7.0, 1.5), 7.40–7.30 (m, 8H), 5.36 (s, 2H); δ_C ($CDCl_3$): 188.4, 138.8, 136.5, 133.4, 132.5, 130.0, 129.4, 129.1, 129.0, 129.0, 127.0, 119.3, 81.0 (Found: C, 73.08; H, 5.17; N, 9.94. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07%).

4-Acetyl-1-benzyloxypyrazole 7c. Acid chloride: acetyl chloride. FC gave 84 mg (78%) of **7c**: mp 81–82 °C (heptane). R_f (EtOAc–heptane 3 : 7) 0.25. ν_{max} (solid)/cm^{-1}: 3123, 3105, 1661 (C=O), 1541, 1405, 1267. δ_H ($CDCl_3$): 7.72 (d, 1H, *J* 0.8), 7.42 (d, 1H, *J* 0.8), 7.40–7.34 (m, 3H), 7.32–7.28 (m, 2H), 5.32 (s, 2H), 2.33 (s, 3H); δ_C ($CDCl_3$): 191.6, 135.2, 133.2, 129.9, 129.9, 129.1, 125.1, 121.3, 80.9, 27.7 (Found: C, 66.89; H, 5.81; N, 12.69. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96%.)

1-Benzyloxy-4-pivaloylpyrazole 7d. Acid chloride: pivaloyl chloride. FC gave 74 mg (57%) of **7d**: mp 58–59 °C (heptane). R_f (EtOAc–heptane 3 : 7) 0.46. δ_H ($CDCl_3$): 7.78 (d, 1H, *J* 0.8), 7.40–7.34 (m, 3H), 7.32–7.28 (m, 3H), 5.31 (s, 2H), 1.20 (s, 9H); δ_C ($CDCl_3$): 199.9, 135.9, 133.2, 129.9, 129.7, 128.9, 125.8, 117.7, 80.7, 43.6, 27.3 (Found: C, 69.73; H, 6.88; N, 10.74. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84%).

1-Benzyloxy-4-(3-methoxycarbonyl)propionylpyrazole 7e. Acid chloride: 3-(methoxycarbonyl)propionyl chloride. FC gave 104 mg (74%) of **7e**: mp 90–91 °C (heptane–EtOAc).

R_f (EtOAc–heptane 3 : 7) 0.15. ν_{max} (solid)/cm^{-1}: 3109, 1726 (C=O), 1661 (C=O), 1540, 1353, 1306. δ_H ($CDCl_3$): 7.76 (d, 1H, *J* 0.8), 7.48 (d, 1H, *J* 0.8), 7.40–7.34 (m, 3H), 7.33–7.28 (m, 2H), 5.31 (s, 2H), 3.68 (s, 3H), 2.99 (t, 2H, *J* 6.8), 2.68 (t, 2H, *J* 6.8); δ_C ($CDCl_3$): 191.6, 173.2, 134.7, 133.1, 129.7, 129.7, 129.0, 128.9, 120.3, 80.7, 51.8, 34.5, 27.6 (Found: C, 62.48; H, 5.60; N, 9.66. Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72%).

General procedure for preparation of 3-acyl substituted 2-(4-methoxybenzyl)-2*H*-pyrazole 1-oxides 15a–f

To a stirred solution of **13** (1 mmol) in THF (10 mL) at −78 °C was added 2.2 M Pr^{i}MgCl (0.50 mL, 1.1 mmol) over a period of 2 min. Stirring was continued for 15 min at −78 °C before the acid chloride (1.5 mmol) was added. After 2 h at −78 °C the mixture was quenched with sat. NH_4Cl (5 mL). Water (5 mL) was added to dissolve the formed precipitate and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The crude products were purified by flash chromatography using EtOAc–heptane as eluent.

3-(4-Chlorobutyryl)-2-(4-methoxybenzyl)-2*H*-pyrazole 1-oxide 15a. Acid chloride: 4-chlorobutyryl chloride. FC (EtOAc–heptane 1 : 1 ⟶ 3 : 1) gave 158 mg (64%) of **15a** as an oil. R_f (EtOAc) 0.46. ν_{max} (film)/cm^{-1}: 3144, 2959, 1671 (C=O), 1512, 1465, 1444, 1375, 1245, 1176, 1030. δ_H ($CDCl_3$): 7.39 (dt, 2H, *J* 8.8, 2.0), 7.21 (d, 1H, *J* 2.8), 6.89 (d, 1H, *J* 2.8), 6.81 (dt, 2H, *J* 8.8, 2.0), 5.76 (s, 2H), 3.76 (s, 3H), 3.60 (t, 2H, *J* 6.8), 2.95 (t, 2H, *J* 6.5), 2.19–2.16 (m, 2H); δ_C ($CDCl_3$): 186.6, 159.7, 130.3, 127.8, 126.4, 119.4, 114.1, 109.6, 55.4, 47.4, 44.4, 35.7, 27.0 (Found: C, 58.07; H, 5.34; N, 8.78. Calcd. for $C_{15}H_{17}ClN_2O_3$: C, 58.35; H, 5.55; N, 9.07%).

3-Benzoyl-2-(4-methoxybenzyl)-2*H*-pyrazole 1-oxide 15b. Acid chloride: benzoyl chloride. FC (EtOAc–heptane 1 : 1 ⟶ 3 : 1) gave 209 mg (67%) of **15b** as an oil, which upon standing slowly crystallised: mp 86–87 °C (heptane–EtOAc). R_f (EtOAc) 0.55. ν_{max} (solid)/cm^{-1}: 3150, 2959, 1636 (C=O), 1513, 1465, 1444, 1370, 1246, 1177, 1032. δ_H ($CDCl_3$): 7.75 (dt, 2H, *J* 8.8, 2.0), 7.59 (tt, 1H, *J* 7.6, 1.2), 7.50–7.40 (m, 4H), 7.23 (d, 1H, *J* 2.4), 6.81 (dt, 2H, *J* 8.8, 2.0), 6.63 (d, 1H, *J* 2.4), 5.84 (s, 2H), 3.74 (s, 3H); δ_C ($CDCl_3$): 182.9, 159.7, 137.8, 133.0, 130.4, 129.3, 128.8, 128.0, 126.3, 119.3, 114.2, 112.7, 55.4, 47.3 (Found: C, 70.03; H, 5.19; N, 8.99. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09%).

3-Acetyl-2-(4-methoxybenzyl)-2*H*-pyrazole 1-oxide 15c. Acid chloride: acetyl chloride. FC (EtOAc–heptane 1 : 1 ⟶ 3 : 1) gave 158 mg (64%) **15c**: mp 92–94 °C (heptane–EtOAc). R_f (EtOAc) 0.32. ν_{max} (solid)/cm^{-1}: 3143, 2955, 1661 (C=O), 1512, 1464, 1444, 1371, 1243, 1176, 1029. δ_H ($CDCl_3$): 7.40 (dt, 2H, *J* 8.8, 2.0), 7.18 (d, 1H, *J* 2.8), 6.81–6.75 (m, 3H), 5.75 (s, 2H), 3.74 (s, 3H), 2.43 (s, 3H); δ_C ($CDCl_3$): 185.3, 159.6, 130.4, 127.9, 126.7, 119.3, 114.1, 110.0, 55.4, 47.3, 26.9 (Found: C, 63.19; H, 5.61; N, 11.24. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38%).

3-Pivaloyl-2-(4-methoxybenzyl)-2*H*-pyrazole 1-oxide 15d. Acid chloride: pivaloyl chloride. FC (EtOAc–heptane 1 : 1 ⟶ 3 : 1) gave 213 mg (74%) of **15d** as a light yellow oil. R_f (EtOAc) 0.48. ν_{max} (film)/cm^{-1}: 3147, 2969, 1652 (C=O), 1513, 1458, 1445, 1366, 1245, 1176, 1031. δ_H ($CDCl_3$): 7.27 (dt, 2H, *J* 8.8, 2.0), 7.18 (d, 1H, *J* 2.8), 6.81 (d, 1H, *J* 2.8), 6.77 (dt, 2H, *J* 8.8, 2.0), 5.72 (s, 2H), 3.73 (s, 3H), 1.25 (s, 9H); δ_C ($CDCl_3$): 195.0, 159.5, 130.0, 128.3, 118.5, 114.0, 109.0, 55.4, 47.3, 44.5, 28.3, one carbon signal overlapped (Found: C, 66.42; H, 6.78; N, 9.47. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72%).

3-(4-Bromobutyryl)-2-(4-methoxybenzyl)-2*H*-pyrazole 1-oxide 15e. Acid chloride: 4-bromobutyryl chloride. FC (EtOAc–heptane 1 : 1 ⟶ 3 : 1) gave 233 mg (66%) of **15e** as an oil. R_f (EtOAc) 0.47. δ_H ($CDCl_3$): 7.38 (dt, 2H, *J* 8.8, 2.0), 7.25 (d, 1H, *J* 2.8), 6.91 (d, 1H, *J* 2.8 Hz), 6.81 (dt, 2H, *J* 8.8, 2.0), 5.76 (s, 2H), 3.76 (s, 3H), 3.47 (t, 2H, *J* 6.8), 2.96 (t, 2H, *J* 6.8 Hz), 2.27–2.24 (m, 2H); δ_C ($CDCl_3$): 186.6, 159.4, 130.1, 127.6, 126.3, 119.4, 113.9, 109.6, 55.1, 47.1, 36.6, 33.0, 26.7 (Found: C, 50.79; H, 4.68; N, 7.89. Calcd. for $C_{15}H_{17}BrN_2O_3$: C, 51.01; H, 4.85; N, 7.93%).

3-(3-(Methoxycarbonyl)propionyl)-2-(4-methoxybenzyl)-2*H*-pyrazole 1-oxide 15f. Acid chloride: 3-methoxycarbonylpropionyl chloride. FC (EtOAc–heptane 1 : 1 ⟶ 3 : 1) gave 229 mg (72%) of **15f**: mp 68–70 °C (heptane–EtOAc). R_f (EtOAc) 0.30. ν_{max} (solid)/cm^{-1}: 3142, 2955, 1734 (C=O), 1667 (C=O), 1513, 1470, 1445, 1378, 1246, 1176, 1030. δ_H ($CDCl_3$): 7.36 (dt, 2H, *J* 8.8, 2.0), 7.18 (d, 1H, *J* 2.8), 6.88 (d, 1H, *J* 2.8), 6.78 (dt, 2H, *J* 8.8, 2.0), 5.73 (s, 2H), 3.73 (s, 3H), 3.67 (s, 3H), 3.07 (t, 2H, *J* 6.8), 2.70 (t, 2H, *J* 6.8); δ_C ($CDCl_3$): 185.9, 173.0, 159.6, 130.4, 127.8, 126.2, 119.4, 114.1, 109.6, 55.4, 52.1, 47.4, 33.6, 27.9 (Found: C, 60.09; H, 5.64; N, 8.60. Calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80%).

5-(4-Chlorobutyryl)-1-hydroxypyrazole 16

A mixture of **4** (140 mg, 0.5 mmol) and conc. HCl (3 mL) was stirred at rt for 16 h. The mixture was evaporated to dryness. The crystals were added to water (5 mL) and CH_2Cl_2 (5 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* producing 93 mg (98%) of analytically pure **16**: mp 104–105 °C (EtOAc–heptane). ν_{max} (solid)/cm^{-1}: 3100–2200 (br OH), 1694 (C=O), 1404, 1323, 1202, 966. δ_H ($CDCl_3$): 7.21 (d, 1H, *J* 2.7), 6.78 (d, 1H, *J* 2.7), 3.66 (t, 2H, *J* 6.2), 3.09 (t, 2H, *J* 7.0), 2.26–2.23 (m, 2H); δ_C ($CDCl_3$): 194.2, 130.4, 126.1, 107.1, 43.7, 35.7, 26.1 (Found: C, 44.72, H, 4.66, N, 14.63. Calcd. for $C_7H_9ClN_2O_2$: C, 44.58; H, 4.81; N, 14.85%).

4-(Chlorobutyryl)-1-hydroxypyrazole 17

Compound **17** was prepared from **7a** (140 mg, 0.5 mmol) by the method described for compound **16**. This provided 92 mg (97%) of analytically pure **17**: mp 80–81 °C (EtOAc–heptane). ν_{max} (solid)/cm^{-1}: 3300–2200 (br OH), 1672 (C=O), 1531, 1278, 1008. δ_H ($CDCl_3$): 7.88 (d, 1H, *J* 0.8), 6.69 (d, 1H, *J* 0.8), 3.63 (t, 2H, *J* 6.2), 2.91 (t, 2H, *J* 7.0), 2.19–2.16 (m, 2H); δ_C ($CDCl_3$): 192.8, 133.8, 123.9, 121.1, 44.2, 36.2, 26.0 (Found: C, 44.66, H, 4.66, N, 14.63. Calcd. for $C_7H_9ClN_2O_2$: C, 44.58; H, 4.81; N, 14.85%).

3-(Chlorobutyryl)-1-hydroxypyrazole 18

To a solution of **15a** (154 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) was added TFA (2 mL) and a few drops of water. Stirring was continued for 12 h at rt. The reaction mixture was evaporated to dryness and the resulting yellow oil was partitioned between 2 M NaOH (5 mL) and diethyl ether (5 mL). The aqueous phase was isolated and the organic phase was extracted with 2 M NaOH (4 × 10 mL). The combined aqueous phases were acidified by 4 M HCl to pH 1 and the aqueous phases was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* providing 90 mg (96%) of analytically pure **18**: mp 73–75 °C. ν_{max} (solid)/cm^{-1}: 3300–2300 (br OH), 1678 (C=O), 1489, 1349, 1056. δ_H ($CDCl_3$): 7.40 (d, 1H, *J* 2.4), 6.74 (d, 1H, *J* 2.4), 3.63 (t, 2H, *J* 6.2), 3.03 (t, 2H, *J* 7.0), 2.20–2.17 (m, 2H); δ_C ($CDCl_3$): 193.1, 142.4, 124.0, 106.1, 44.4, 35.3, 26.3 (Found: C, 44.60, H, 5.01, N, 14.60. Calcd. for $C_7H_9ClN_2O_2$: C, 44.58; H, 4.81; N, 14.85%).

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