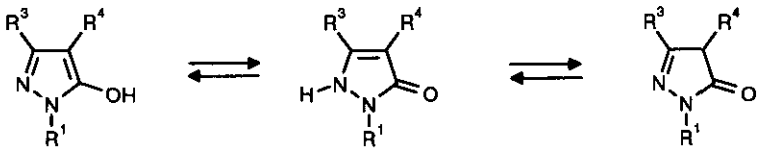
ALKYLATION OF PYRAZOLONES VIA THE MITSUNOBU REACTION[1,#]

Wolfgang Holzer,* Brigitte Plagens, and Karin Lorenz

Institute of Pharmaceutical Chemistry, University of Vienna,
Pharmaziezentrum, Althanstraße 14, A-1090 Vienna, Austria

Abstract - The reaction of 3-methyl-1-phenyl-2-pyrazolin-5-one and 4-acyl derivatives thereof (R^4 = COPh, 2-thienoyl, $COCH_2CH_2Ph$, COCH=CHPh) with various alcohols under 'Mitsunobu'-conditions was studied. In many cases selective *O*-alkylation could be achieved.

N-Substituted pyrazolones can exist in several tautomeric forms, i.e. the OH- (form A), the NH- (form B) and the CH-isomer (form C)[2] (Scheme 1). Appropriate substituents in 4-position of the pyrazole system (for instance COR, COOR) increase the number of possible tautomeric forms.[2]

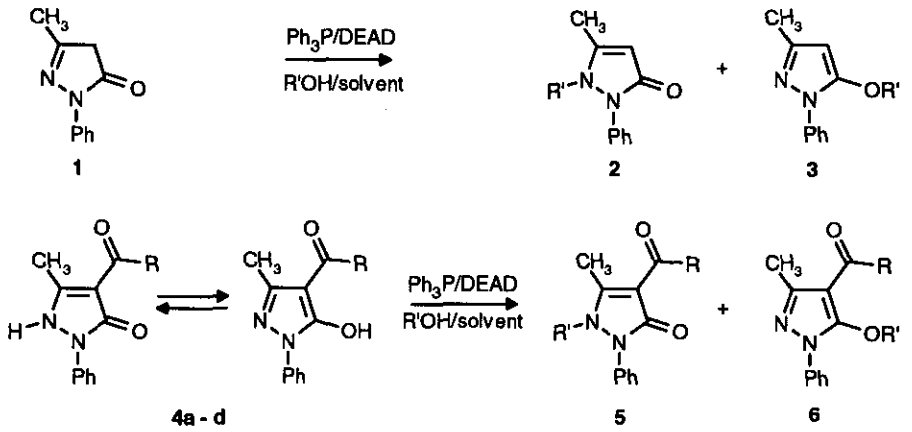


Scheme 1

The alkylation of such ambident compounds can lead to different alkylation products, the regioselectivity of the reaction strongly depending on the substrate, the alkylating agent and the reaction conditions.[3] Whereas the application of diazomethane frequently results in the predominant or exclusive formation of the corresponding *O*-methyl derivatives,[3] upon treatment of pyrazolones with 'conventional' alkylating agents such as dimethyl sulfate or alkyl halides often mixtures of *O*- and *N*-alkyl (and occasionally also *C*-alkyl) derivatives are obtained, with the *N*-substitution product being favoured in many reaction systems. As an example for the latter, the synthesis of the classical analgesic and antipyretic drug "Antipyrine" (**2**) *via* *N*-methylation of 3-methyl-1-phenyl-2-pyrazolin-5-one (**1**) with dimethyl sulfate (or methyl iodide) may serve.[3] An alternative approach to achieve alkylation of various classes of compounds under mild and neutral conditions is the Mitsunobu reaction,[4,5] which has proven to be a versatile and valuable synthetic tool. There are also a few examples where this type of reaction was used for alkylations of ambident nucleophiles.[5,6] As, to the best of our knowledge, the application of this method has not been systematically investigated in the pyrazolone case, we studied the reaction behaviour of 3-methyl-1-phenyl-

Dedicated to Prof. Herbert Oelschläger on the occasion of his 75th anniversary

2-pyrazolin-5-one (**1**) and some 4-acyl derivatives thereof (**4a** - **d**) under 'Mitsunobu' conditions (triphenylphosphine, diethyl azodicarboxylate = DEAD, alcohol R'OH, solvent) (Scheme 2).



Scheme 2

Several reactions of pyrazolones (**1**) and (**4**) in various solvents (THF, CH_2Cl_2, $CHCl_3$, CH_3CN, benzene) using methanol as the alkylating agent were performed. Additionally, some runs were carried out using other alcohols, such as benzyl alcohol, isopropanol and 2,3-epoxypropanol. Table 1 gives a survey about the results of our experiments. In many cases mixtures of *O*- and *N*-isomers were obtained with the *O*-alkyl product always being the main component. However, the application of THF or - particularly - benzene as the solvent frequently led to clean *O*-alkylation (for instance **4a** and methanol, isopropanol, benzyl alcohol, and 2,3-epoxypropanol, respectively). In contrast, in dichloromethane solutions no such a selectivity could be observed. Ratios **5** : **6** (**2** : **3**) were determined *via* ^{1}H-NMR analysis of the crude reaction mixtures, representative runs showing higher selectivities were worked up completely and the regioisomeric products (**5**) and (**6**) (**2** and **3**) were separated by medium pressure liquid chromatography.

In conclusion, the Mitsunobu reaction provides a mild (no strong bases required) and effective method for the alkylation of pyrazolones of type **1** and **4**, particularly in order to achieve access to *O*-alkyl derivatives being not (or not easily) amenable by the application of 'conventional' alkylating agents.[7]

EXPERIMENTAL

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. The IR spectra were obtained on a Perkin Elmer FTIR 1605 instrument. Mass spectra were recorded either on a Shimadzu QP1000 or on a Hewlett-Packard 5890/5970-MSD instrument (both EI, 70 eV). The NMR spectra were recorded from $CDCl_3$-solutions on a Varian UnityPlus spectrometer (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) at 28°C. The center of the solvent multiplet was used as an internal standard which

was related to TMS with δ 7.26 ppm (^{1}H) and δ 77.0 ppm (^{13}C). Medium pressure liquid chromatographic (MPLC) separations were performed on Lichroprep Si60 columns (size B, Merck®). Pyrazolones (**4a - d**) were prepared according to procedures given in the literature (**4b**,[8] **4c**,[9] **4d**[10]), compounds (**1**) and (**4a**) are commercially available.

Table 1. Yields and Product Distributions upon 'Mitsunobu'-Alkylation of Pyrazolones (**1**) and (**4a - d**)

pyrazolone	alcohol	solvent	**5** (**2**)[a]	**6** (**3**)[a]	**5** : **6** (**2** : **3**)[b]
1	MeOH	THF	14%[c]	53%[d]	1 : 3.5
1	MeOH	CH_2Cl_2	10%[c]	60%[d]	1 : 6.3
1	MeOH	benzene	0%	72%[d]	0 : 1
1	Me_2CHOH	THF	0%	45%	0 : 1
1	Me_2CHOH	benzene	0%	46%	0 : 1
4a	MeOH	THF	traces[e]	78%[e]	1 : 50
4a	MeOH	CH_2Cl_2	14%[e]	62%[e]	1 : 4.7
4a	MeOH	$CHCl_3$	8%[e]	64%[e]	1 : 7.4
4a	MeOH	MeCN	15%[e]	48%[e]	1 : 2.8
4a	MeOH	benzene	0%	93%[e]	0 : 1
4a	Me_2CHOH	THF	0%	55%	0 : 1
4a	Me_2CHOH	benzene	0%	61%	0 : 1
4a	$PhCH_2OH$	THF	0%	90%	0 : 1
4a	$PhCH_2OH$	CH_2Cl_2	8%[e]	62%[e]	1 : 7.1
4a	2,3-epoxypropanol	THF	0%	54%	0 : 1
4b	MeOH	THF	7%[e]	75%[e]	1 : 10.6
4b	MeOH	CH_2Cl_2	19%[e]	56%[e]	1 : 2.6
4b	MeOH	benzene	0%	50%[e]	0 : 1
4c	MeOH	THF	17%[e]	48%[e]	1 : 3.3
4c	MeOH	CH_2Cl_2	30%[e]	35%[e]	1 : 1.1
4c	MeOH	benzene	9%[e]	48%[e]	1 : 4.7
4d	MeOH	THF	11%[e]	62%[e]	1 : 5.7
4d	MeOH	CH_2Cl_2	25%[e]	50%[e]	1 : 1.7
4d	MeOH	benzene	5%[e]	54%[e]	1 : 9.4

[a]Yield of purified product after chromatographic separation. [b]Ratio determined by ^{1}H-NMR analysis of the crude reaction mixture. [c] ^{1}H-NMR in accordance to authentic material as well as to ref.[11] [d] ^{1}H-NMR in accordance to ref.[12] [e]Spectroscopic and analytical data of methylation products of pyrazolones (**4a - d**) are given in ref.[13] All novel compounds were characterized by NMR (^{1}H, ^{13}C), MS and IR spectra as well as by elemental analyses (see Experimental).

General Procedure for the 'Mitsunobu'-Alkylation of Pyrazolones (**4**)

To a solution of the pyrazolone (1 mmol), Ph_3P (393 mg, 1.5 mmol) and the alcohol (1.25 mmol) in 20 mL of the indicated solvent were added slowly 261 mg (1.5 mmol) of diethyl azodicarboxylate and the mixture was stirred for 20 h at room temperature. Then 1 mL of methanol was added, the mixture was poured onto

water (20 mL) and exhaustively extracted with dichloromethane. The combined CH_2Cl_2-phases were succesively washed with 2N NaOH, water (several times) and brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was subjected to medium pressure liquid chromatography (silica gel, eluent: dichloromethane - ethyl acetate) to afford pure *N*- and *O*-alkyl products (**5**) and (**6**) (**2** and **3**), respectively. For yields and product distributions see Table 1.

5-Isopropoxy-3-methyl-1-phenyl-1*H*-pyrazole (Reaction of **1** and Isopropanol)
Colorless oil; ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.71 (m, 2H, NPh H-2,6), 7.39 (m, 2H, NPh H-3,5), 7.21 (m, 1H, NPh H-4), 5.46 (s, 1H, pyrazole H-4), 4.43 (m, J = 6.1 Hz, 1H, OCH), 2.27 (s, 3H, 3-Me), 1.38 (d, J = 6.1 Hz, 6H, Me of isopropyl); ^{13}C-NMR ($CDCl_3$): δ (ppm) 153.9 (pyrazole C-5, ^2J(C5,H4) = 6.0 Hz, ^3J(C5,OCH) = 2.8 Hz), 148.7 (pyrazole C-3, ^2J(C3,3-Me) = 6.6 Hz, ^2J(C3,H4) = 3.6 Hz), 139.0 (NPh C-1), 128.6 (NPh C-3,5), 125.6 (NPh C-4), 121.8 (NPh C-2,6), 86.9 (pyrazole C-4, ^1J = 175.3 Hz, ^2J(C4, 3-Me) = 3.4 Hz), 75.5 (OCH, ^1J = 145.1 Hz, ^2J(O<u>C</u>H,C<u>H</u>$_3$) = 4.2 Hz), 21.9 (Me of isopropyl, ^1J = 126.7 Hz, ^2J(<u>C</u>H$_3$,OC<u>H</u>) = 1.2 Hz, ^3J(<u>C</u>H$_3$,C<u>H</u>$_3$) = 4.7 Hz), 14.5 (3-Me, ^1J = 127.2 Hz); MS (*m/z*, %): 216 (M^+, 29), 175 (17), 174 (100), 173 (24), 145 (14), 130 (11), 129 (31), 117 (11), 105 (15), 104 (12), 78 (16), 77 (61), 68 (16), 51 (36), 43 (39), 42 (13), 41 (32). *Anal.* Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.36; H, 7.69; N, 12.88.

(5-Isopropoxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)phenylmethanone (Reaction of **4a** and Isopropanol)
Yellowish oil; ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.85 (m, 2H, CPh H-2,6), 7.71 (m, 2H, NPh H-2,6), 7.56 (m, 1H, CPh H-4), 7.47 (m, 2H, CPh H-3,5), 7.43 (m, 2H, NPh H-3,5), 7.31 (m, 1H, NPh H-4), 3.95 (m, 1H, OCH), 2.40 (s, 3H, 3-Me), 0.80 (d, J = 6.2 Hz, 6H, Me of isopropyl); ^{13}C-NMR ($CDCl_3$): δ (ppm) 190.3 (C=O), 153.1 (pyrazole C-5), 151.0 (pyrazole C-3, ^2J(C3,3-Me) = 6.9 Hz), 138.9 (CPh C-1), 138.0 (NPh C-1), 132.3 (CPh C-4), 129.3 (CPh C-2,6), 128.8 (NPh C-3,5), 128.2 (CPh C-3,5), 127.2 (NPh C-4), 123.3 (NPh C-2,6), 107.8 (pyrazole C-4, ^3J(C4,3-Me) = 2.5 Hz), 81.0 (OCH, ^1J = 147.8 Hz), 21.6 (Me of isopropyl, ^1J = 126.8 Hz), 14.7 (3-Me, ^1J = 128.7 Hz); MS (*m/z*, %): 320 (M^+, 7), 279 (19), 278 (100), 277 (86), 201 (17), 200 (47), 105 (55), 91 (13), 77 (53), 67 (12), 51 (12), 43 (28); IR (KBr): 1639 cm^{-1} (C=O). *Anal.* Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.73; H, 6.27; N, 8.60.

(5-Benzyloxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)phenylmethanone (Reaction of **4a** and Benzyl Alcohol)
Colorless oil which solidified on standing to give crystals of mp 72 °C; ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.84 (m, 2H, COPh H-2,6), 7.62 (m, 2H, NPh H-2,6), 7.59 (m, 1H, COPh H-4), 7.48 (m, 2H, COPh H-3,5), 7.42 (m, 2H, NPh H-3,5), 7.36 (m, 1H, NPh H-4), 7.22 (m, 1H, CH_2<u>Ph</u> H-4), 7.14 (m, 2H, CH_2<u>Ph</u> H-3,5), 6.80 (m, 2H, CH_2<u>Ph</u> H-2,6), 4.72 (s, 2H, OCH_2), 2.32 (s, 3H, 3-Me); ^{13}C-NMR ($CDCl_3$): δ (ppm) 190.4 (C=O), 153.4 (pyrazole C-5), 150.6 (pyrazole C-3), 139.2 (COPh C-1), 137.7 (NPh C-1), 134.3 (CH_2<u>Ph</u> C-1), 132.5 (COPh C-4), 129.3 (COPh C-2,6), 128.9 (COPh C-3,5), 128.7 (CH_2<u>Ph</u> C-4), 128.6 (CH_2<u>Ph</u> C-2,6), 128.4 (NPh C-3,5), 128.3 (CH_2<u>Ph</u> C-3,5), 127.4 (NPh C-4), 123.3 (NPh C-2,6), 107.7 (pyrazole C-4), 77.6 (OCH_2), 14.9 (3-Me); MS (*m/z*, %): 368 (M^+, 17), 105 (100), 91 (9), 77 (34); IR

(KBr): 1642 cm^{-1} (C=O). *Anal.* Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 78.15; H, 5.71; N, 7.64.

(5-(2,3-Epoxypropoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)phenylmethanone (Reaction of **4a** with 2,3-Epoxypropanol)

Yellowish oil; ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.84 (m, 2H, COPh H-2,6), 7.71 (m, 2H, NPh H-2,6), 7.58 (m, 1H, COPh H-4), 7.48 (m, 2H, COPh H-3,5), 7.47 (m, 2H, NPh H-3,5), 7.34 (m, 1H, NPh H-4), 4.02 (dd, J = 11.2 Hz and 3.2 Hz, 1H, C5-OCH_2), 3.71 (dd, J = 11.2 Hz and 6.2 Hz, 1H, C5-OCH_2), 2.84 (m, 1H, epoxide CH), 2.59 (m, 1H, epoxide CH_2), 2.29 (m, 1H, epoxide CH_2), 2.27 (3-Me); ^{13}C-NMR ($CDCl_3$): δ (ppm) 190.4 (C=O), 153.7 (pyrazole C-5, ^3J(C5,OCH_2) = 2.7 Hz), 150.3 (pyrazole C-3, ^2J(C3,3-Me) = 6.9 Hz), 139.2 (COPh C-1), 137.5 (NPh C-1), 132.5 (COPh C-4), 129.1 (COPh C-2,6), 129.0 (COPh C-3,5), 128.4 (NPh C-3,5), 127.5 (NPh C-4), 123.1 (NPh C-2,6), 107.1 (pyrazole C-4, ^3J(C4,3-Me) = 2.6 Hz), 76.4 (C5-O$\underline{C}H_2$), 49.1 (epoxide CH), 44.1 (epoxide CH_2), 14.9 (3-Me, ^1J = 128.7 Hz); MS (*m/z*, %): 334 (M^+, 21), 279 (11), 278 (45), 277 (34), 261 (12), 200 (18), 181 (11), 149 (25), 147 (14), 119 (14), 111 (14), 105 (100), 104 (13), 97 (19), 95 (17), 91 (57), 85 (15), 83 (23), 81 (43), 79 (11), 78 (19), 77 (76), 75 (11), 73 (14), 71 (34), 70 (13), 69 (31), 67 (20), 59 (17), 57 (66), 56 (12), 55 (39), 51 (25); IR (KBr): 1639 cm^{-1} (C=O). *Anal.* Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.67; H, 5.57; N, 8.36.

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7. Thus, for instance, reaction of **4a** with excessive epichlorohydrin under basic conditions selectively affords the corresponding *N*-alkyl compound, whereas application of 2,3-epoxypropanol under 'Mitsunobu' conditions leads to the *O*-alkyl isomer as the sole product.
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