Selective *N*-1 Alkylation of Unsymmetrically Substituted Pyrazoles

Nageshwar Malhotra, Birgitte Fält-Hansen and Jan Becher*

Department of Chemistry, Odense University, DK-5230,
Odense M, Denmark

Received March 5, 1991

A series of *C*-substituted pyrazoles have been *N*-alkylated. The alkylation occurs preferentially at the *N*-1 position when a *tert*-butyl group is present at the pyrazole C-3 position.

J. Heterocyclic Chem., **28**, 1837 (1991).

N-Alkylation of pyrazoles usually produces [1] a mixture of isomers even with a substituent at the C-3 position, thus *N*-alkylation is often nonspecific [2] and the only way to obtain regioselective *N*-1 alkylation is the use of controlled reaction conditions in combination with protecting groups [3]. Beck *et al.* [4] have recently reported regioselective alkylation of a pyrazole system using the sterically demanding isobutene.

In our synthetic strategy for the synthesis of macrocyclic systems based on pyrazoles as building blocks [5] we needed a specific alkylation procedure, as the possibility of variation of the reaction conditions with our substrates was limited due to the presence of reactive substituents in the 4- and 5-positions. Therefore we had to rely solely on steric constraints in order to obtain regiospecific *N*-alkylations.

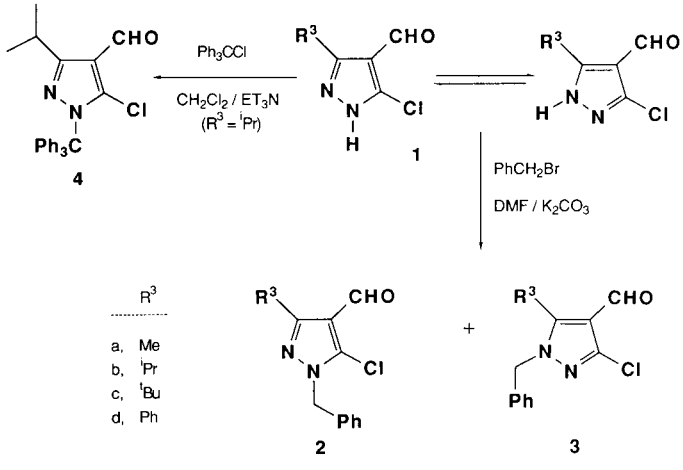
In this communication we report a study of the parameters which are required for such regioselective *N*-1 alkylation in 3-substituted-5-chloro-4-formyl- or 4-benzoylpyrazoles.

Based on steric arguments it was anticipated that alkylation at *N*-2 could be avoided *via* a bulky group at the 3-position in the pyrazole ring. Thus alkylation of the 5-chloro-4-formylpyrazoles **1a** and **1d** containing either a methyl or a phenyl group at C-3 using benzyl bromide in anhydrous DMF at reflux temperature with an equimolar amount of potassium carbonate produced the *N*-1 and *N*-2 benzylated isomers **2** and **3** in a 1:1 ratio as an inseparable mixture. On the other hand when the 3-isopropylpyrazole (**1b**) was alkylated under similar conditions the ratio of the *N*-1 and *N*-2 isomers was 60:40 (^{1}H nmr), however this mixture of isomers **2b** and **3b** also turned out to be difficult to separate *via* ptlc or using a Chromatotron^R.

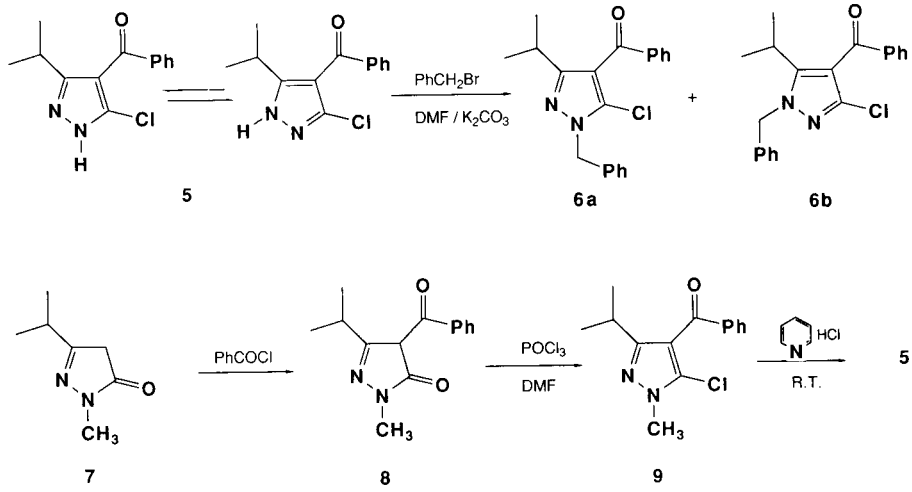
However when the 3-*tert*-butylpyrazole (**1c**) was alkylated using the same procedure the product-ratio of *N*-1 and *N*-2 isomers **2c** and **3c** was 80:20. An unexpected advantage in this case was the larger difference in the R_f values found for these isomers ($R_{f(2c)}$ = 0.65; $R_{f(3c)}$ = 0.55) which in fact was large enough to allow an effective chromatographic separation and hence a correct assignment of structure. Thus in the ^{1}H nmr spectrum of the 2-benzyl isomer **3c** a 0.33 ppm downfield shift of the CH_2-signal was accompanied by a splitting of the phenyl group signal when compared to the 1-benzyl isomer **2c**. These differences are obviously due to hindered rotation of the *N*-2 benzyl group in the isomer **3c**.

The presence of a more bulky group at C-4 instead of a formyl group at this position might augment the steric hindrance through a gear effect [6]. The required 4-benzoyl-5-chloro-3-isopropylpyrazole (**5**) was prepared by demethylation using Butler and DeWald's method [7] (Scheme 2). However it was found that benzylation of pyrazole derivative **5** gave the *N*-1 and *N*-2 benzylated products **6a** and **6b**, in almost the same ratio (60:40) as found previously for the 4-formylpyrazole **1b**, and this result therefore demonstrates that a benzoyl group at the C-4 position in this type of pyrazole has no effect on the regioselectivity in the least with an isopropyl group at the C-3 position. It is solely the presence of a bulky group at C-3 which will preferentially direct the benzylation at the *N*-1 position. However alkylation of 3-isopropylpyrazole **1b** using the sterically demanding triphenylmethyl chloride as alkylation agent results in isolation of the *N*-1 alkylated pyrazole **4** as the sole reaction product. We have previously shown [8] that 1-substituted-5-chloro-4-formylpyrazoles yields the 5-*S*-*tert*-butylpyrazoles in high yields upon reaction with sodium *tert*-butylthiolate, however as expected this efficient reaction completely failed using pyrazole **4** as substrate thus confirming the structure assigned to **4**.

Scheme 1



Scheme 2



EXPERIMENTAL

Mass spectra were recorded on a Varian MAT 311A; infrared spectra on a Perkin Elmer 1750 in potassium bromide discs; and ^{1}H nmr on a Brüker AC 250FT, δ in ppm from TMS. Melting points (uncorrected) were obtained on a Büchi melting point apparatus. The tlc and ptlc plates made from Merck silica gel and chloroform was used as the eluent. The starting pyrazolones **1** were prepared according to Veibel *et al.* [9] and the 4-benzoylpyrazole according to Jensen [10]. The chloroformylation was carried out as previously described [8].

3-Alkyl-5-chloro-4-formyl-1*H*-pyrazoles. General Method [8].

Phosphorus oxychloride (22.5 ml, 0.245 mole) was dropped into ice cold DMF (8 ml, 0.1 mole) with stirring. After one hour the required 3-alkyl-5-pyrazolone [9] (0.035 mole) was added in one portion and the resulting mixture refluxed for one hour. The reaction mixture was then cooled and added to water (300 ml, 0°), the *p*H was adjusted to 7.5 (4*M* sodium hydroxide) whereupon a saturated sodium chloride solution (100 ml) was added. The precipitated product was isolated, washed with water and recrystallized from ethanol/water.

5-Chloro-4-formyl-3-isopropylpyrazole (**1b**).

The general method gave compound **1b**, 2.9 g (48%), mp 146-147°; ir: 1650 cm^{-1}; ^{1}H nmr (dimethyl sulphoxide-d_6): δ 9.81 (s, 1H, CHO), 3.55 (q, 1H, CH, J = 7 Hz), 1.28 (d, 6H, CH_3, J = 7 Hz); ms: (m/z) (relative intensity) 172 (M^+, 68), 157 (100), 144 (16).

Anal. Calcd. for $C_7H_9N_2ClO$: C, 48.71; H, 5.26; N, 16.23. Found: C, 48.95; H, 5.42; N, 16.67.

5-Chloro-4-formyl-3-*tert*-butylpyrazole (**1c**).

The general method gave compound **1c**, 1.97 g (30%), sublimes at 220°; ir: 1650 cm^{-1}; ^{1}H nmr (dimethyl sulphoxide-d_6): δ 10.00 (s, 1H, CHO), 1.40 (s, 9H, CH_3); ms: (m/z) (relative intensity) 186 (M^+, 51), 171 (100), 153 (12), 144 (32), 143 (21).

Anal. Calcd. for $C_8H_{11}N_2ClO$: C, 51.48; H, 5.94; N, 15.01. Found: C, 51.34; H, 6.04; N, 15.35.

Alkylation, General Procedure.

To a solution of the appropriate 3-substituted-4-formyl or 4-benzoyl-5-chloropyrazoles (0.25 mole) in anhydrous DMF (50 ml) containing anhydrous potassium carbonate (0.26 mole) was added benzyl bromide (0.26 mole) whereupon the reaction mixture was refluxed for 4-5 hours. Progress of the reaction was monitored by tlc and after completion the DMF was removed *in vacuo*. Water was added and the product extracted with ethyl acetate. Drying (sodium sulfate), filtration and concentration *in vacuo* followed by preparative layer chromatography (ptlc) yielded the pure products. The compounds prepared *via* this method are listed below.

Mixture of 1- and 2-Benzyl-5-chloro-4-formyl-3-methylpyrazoles **2a** and **3a**.

This mixture of isomers was obtained in 78% yield (ratio **2a:3a** = 50:50), mp 60-72°; ir: 1673 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 9.86 (s, 1H, CHO), 9.85 (s, 1H, CHO), 7.14-7.34 (m, 10H, H arom), 5.29 (s, 2H, CH_2), 5.23 (s, 2H, CH_2), 2.49 (s, 3H, CH_3), 2.46 (s, 3H, CH_3); ms: (m/z) (relative intensity) 234 (M^+, 34), 199 (10), 91 (100).

Anal. Calcd. for $C_{12}H_{11}N_2ClO$: C, 61.42; H, 4.72; N, 11.96. Found: C, 61.25; H, 4.78; N, 11.60.

Mixture of 1- and 2-Benzyl-5-chloro-4-formyl-3-isopropylpyrazoles **2b** and **3b**.

This mixture of isomers was obtained in 80% yield (ratio **2b:3b** = 60:40), as a viscous oil; ir (film): 1683 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 9.89 (s, 1H, CHO), 9.85 (s, 1H, CHO), 7.12-7.36 (m, 10H, H arom), 5.33 (s, 2H, CH_2), 5.31 (s, 2H, CH_2), 3.37-3.48 (m, 1H, CH), 3.19-3.33 (m, 1H, CH), 1.21-1.31 (2d, 12H, CH_3); ms: (m/z) (relative intensity) 262 (M^+, 30), 247 (6), 227 (18), 171 (12), 91 (100).

Anal. Calcd. for $C_{14}H_{15}N_2ClO$: C, 64.00; H, 5.75; N, 10.66. Found: C, 63.82; H, 5.75; N, 10.59.

1-Benzyl-3-*tert*-butyl-5-chloro-4-formylpyrazole (**2c**).

This compound was obtained in 80% yield as a viscous oil after separation using ptlc; ir (film): 1685 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 9.90 (s, 1H, CHO), 7.22-7.36 (m, 5H, H arom), 5.29

(s, 2H, CH_2), 1.38 (s, 9H, CH_3); ms: (m/z) (relative intensity) 276 (M^+, 19), 261 (7), 185 (16), 91 (100).

Anal. Calcd. for $C_{15}H_{17}N_2ClO$: C, 65.10; H, 6.19; N, 10.12. Found: C, 64.86; H, 6.18; N, 10.09.

2-Benzyl-3-*tert*-butyl-5-chloro-4-formylpyrazole (**3c**).

This compound was obtained in 28% yield as a viscous oil after separation using ptlc; ir (film): 1686 cm^{-1}; ^1H nmr (deuteriochloroform): δ 10.04 (s, 1H, CHO), 7.26-7.36 (m, 3H, H arom), 6.90-7.01 (m, 2H, H arom), 5.62 (s, 2H, CH_2), 1.44 (s, 9H, CH_3); ms: (m/z) (relative intensity) 276 (M^+, 8), 241 (33), 91 (100).

Anal. see above.

Mixture of 1- and 2-Benzyl-5-chloro-4-formyl-3-phenylpyrazoles **2d** and **3d**.

This mixture of isomers was obtained in 82% yield (ratio **2d:3d** = 50:50), mp 95-110°; ir: 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.88 (s, 1H, CHO), 9.63 (s, 1H, CHO), 7.00-7.77 (m, 20H, H arom), 5.34 (s, 2H, CH_2), 5.12 (s, 2H, CH_2); ms: (m/z) (relative intensity) 296 (M^+, 28), 261 (19), 205 (2), 91 (100).

Anal. Calcd. for $C_{17}H_{13}N_2ClO \cdot 0.25H_2O$: C, 67.78; H, 4.52; N, 9.30. Found: C, 67.75; H, 4.51; N, 9.19.

5-Chloro-4-formyl-3-isopropyl-1-triphenylmethylpyrazole (**4**).

A mixture of 5-chloro-4-formyl-3-isopropylpyrazole (**1b**) (5.85 g, 0.034 mole), triphenylmethyl chloride (9.7 g, 0.035 mole), triethylamine (3.54 g, 0.035 mole) and methylene chloride (200 ml) was refluxed for 2 hours. After cooling the reaction mixture was washed with water, dried (sodium sulfate) and concentrated *in vacuo*. Trituration of the resulting oil with ethanol gave compound **4**, 5.5 g (39%), mp 156-158°; ir: 1682 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.93 (s, 1H, CH), 7.30 (m, 15H, H arom), 3.45 (q, 1H, J = 7 Hz, CH), 1.20 (d, 6H, J = 7 Hz, CH_3); ms: (m/z) (relative intensity) 414 (10), 243 (100), 165 (40).

Anal. Calcd. for $C_{26}H_{23}N_2ClO$: C, 75.26; H, 5.59; N, 6.75. Found: C, 75.60; H, 5.61; N, 6.77.

4-Benzoyl-5-chloro-3-isopropylpyrazole (**5**).

Pyridinium hydrochloride (5.0 g, 0.045 mole) and 4-benzoyl-5-chloro-3-isopropyl-1-methylpyrazole (**9**) (1.0 g, 0.0038 mole) were mixed at 160°, whereupon the melt was heated at 220° for 10 hours. The cooled dark reaction product was added to water (200 ml, 0°), extraction with ether, washing of the organic phase with water followed by aqueous sodium hydrogencarbonate and drying (sodium sulfate), filtration and concentration *in vacuo* yielded compound **5** as tan crystals 0.55 g (61%), mp 106-108°; ir: 1626 cm^{-1}; ^1H nmr (deuteriochloroform): δ 10.50 (s, 1H, deuterium oxide exchangeable), 7.30-8.20 (m, 5H, H arom), 3.40 (h, 1H, J = 7 Hz, CH), 1.38 (d, 6H, J = 7 Hz, CH_3); ms: (m/z) (relative intensity) 248 (M^+, 100), 233 (50), 105 (55), 77 (83).

Anal. Calcd. for $C_{13}H_{13}N_2ClO$: C, 62.78; H, 5.27; N, 11.26. Found: C, 62.91; H, 5.36; N, 11.00.

Mixture of 1- and 2-Benzyl-4-benzoyl-5-chloro-3-isopropylpyrazoles **6a** and **6b**.

This mixture of isomers was obtained in 73% yield (ratio **6a:6b** = 60:40), mp 55-70°; ir: 1646 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.16-7.83 (m, 20H, H arom), 5.35 (s, 2H, CH_2), 5.32 (s, 2H, CH_2), 3.09-3.29 (m, 2H, CH), 1.16-1.27 (2d, 12H, CH_3); ms: (m/z) (relative intensity) 338 (M^+, 36), 323 (11), 303 (7), 105 (18), 91 (100).

Anal. Calcd. for $C_{20}H_{19}N_2ClO$: C, 70.90; H, 5.65; N, 8.27. Found: C, 70.52; H, 5.55; N, 8.28.

4-Benzoyl-3-isopropyl-1-methyl-5-pyrazolone (**8**).

A mixture of 3-isopropyl-1-methyl-5-pyrazolone (**7**) [9] (4.02 g, 0.029 mole) and calcium hydroxide (3.78 g, 0.05 mole) in dioxane (35 ml, 70°) was stirred while benzoyl chloride (3.32 ml, 0.029 mole) was slowly added, after addition the mixture was kept at 70° for 30 minutes followed by reflux for 4 hours. The resulting red reaction mixture was added to hydrochloric acid (2*M*, 25 ml, 0°) and the white crystals which precipitated after one hour were isolated, 4.41 g (63%), mp 158-159° (ligroin, bp 80-100°); ir : 1607 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.75 (s, 1H, deuterium oxide exchangeable), 7.40-6.60 (m, 5H, H arom), 3.60 (s, 3H, CH_3), 2.90 (h, 1H, J = 7 Hz, CH), 1.00 (d, 6H, J = 7 Hz, CH_3); ms: (m/z) (relative intensity) 244 (M^+, 100), 215 (38), 105 (56), 77 (61).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.65; H, 6.68; N, 11.36.

4-Benzoyl-5-chloro-3-isopropyl-1-methylpyrazole (**9**).

4-Benzoyl-5-hydroxy-3-isopropyl-1-methylpyrazole (**8**) and phosphorus oxychloride (1 ml, 0.011 mole) were heated (110°) in a closed reaction flask [11] for 10 hours. After cooling the dark reaction product was mixed with methylene chloride (5 ml) and a little activated carbon. Reflux followed by filtration and concentration *in vacuo* yielded 0.5 g (93%) of tan crystals, mp 89-90° (ligroin, bp 80-100°); ir: 1642 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.30-8.00 (m, 5H, H arom), 3.82 (s, 3H, CH_3), 3.25 (h, 1H, J = 7 Hz, CH), 1.25 (d, 6H, J = 7 Hz, CH_3); ms: (m/z) (relative intensity) 262 (M^+, 100), 105 (51), 77 (89).

Anal. Calcd. for $C_{14}H_{15}N_2ClO$: C, 64.00; H, 5.75; N, 10.66. Found: C, 64.35; H, 5.85; N, 10.65.

Acknowledgement.

A Danish Science Research Council post-doctoral grant to Dr. N. Malhotra is gratefully acknowledged.

REFERENCES AND NOTES

[1a] R. Fusco, Pyrazoles, in The Chemistry of Heterocyclic Compounds, A. Weissberger, ed, Vol **22**, Interscience, New York, 1967, Chapter 4, p 71; [b] J. Elguero, Pyrazoles and their Benzo Derivatives, in Comprehensive Heterocyclic Chemistry, Vol **5**, A. R. Katritzky and C. W. Rees, eds, K. T. Potts ed, Pergamon Press, Oxford, 1984, p 222.

[2] M. R. Grimmett, K. H. R. Lim and R. T. Weavers, *Aust. J. Chem.*, **32**, 2203 (1979).

[3] M. Begtrup, *Bull. Soc. Chim. Belg.*, **97**, 573 (1988).

[4] J. R. Beck, J. Aikins, M. P. Lynch, J. R. Rizzo and E. V. P. Tao, *J. Heterocyclic Chem.*, **26**, 3 (1989).

[5] N. Malhotra, H. Toftlund, G. Bojesen and J. Becher, *J. Chem. Soc. Chem. Commun.*, 1349 (1989).

[6] L. Hennig, D. Bendler, R. Haessner and G. Mann, *Z. Chem.*, **28**, 27 (1988).

[7] D. E. Butler and H. A. DeWald, *J. Org. Chem.*, **40**, 1353 (1975).

[8] J. Becher, P. H. Olesen, N. A. Knudsen and H. Toftlund, *Sulfur Letters*, **4**, 175 (1986).

[9] S. Veibel, K. Eggersen and S. C. Linholt, *Acta Chem. Scand.*, **8**, 768 (1954).

[10] B. Skytte Jensen, *Acta Chem. Scand.*, **13**, 1668 (1959).

[11] M. Begtrup, *J. Chem. Educ.*, 974 (1987).