A Comparative Study on the Synthesis of Pyrazolo[4,3-*c*]quinoline Oxides by Reductive Cyclisations

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Alternate routes for the reductive cyclisation of 4-acetyl-3-methyl-5-(2-nitrophenyl)-1-phenylpyrazole under different conditions are described. Whereas 3,4-dimethyl-1-phenylpyrazolo[4,3-*c*]quinoline 5-oxide is formed by mild noncatalytic reductions, catalytic and transfer hydrogenation processes cause the diastereoselective formation of *cis*-4,11-dihydro-3,5-dimethyl-1-phenylpyrazolo[4,3-*c*]quinoline 6-oxide.

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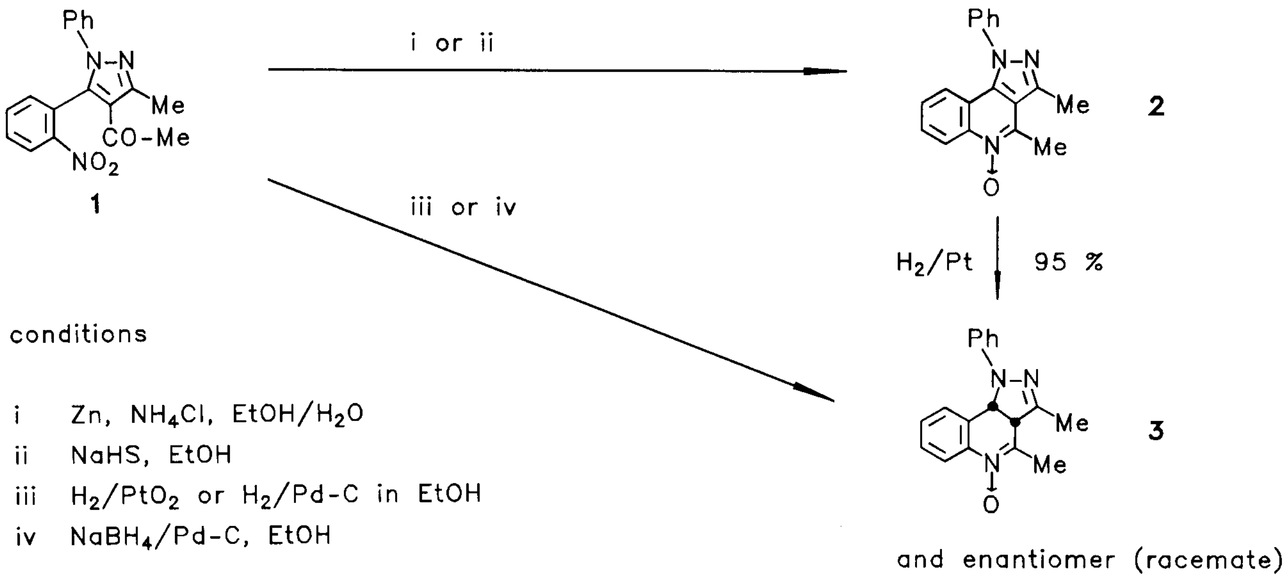
Aromatic nitro compounds with reactive *ortho* side chains are valuable educts for various *N*-heterocycles, which are either available by several syntheses involving neighboring group interactions [1-4] or by reductive cyclisations [5-8], characterized by reduction of the nitro group prior to interaction with the side chain. We found the latter especially to be of interest for the synthesis of partially oxidized heterocycles like DIBOA [9], an allelochemical from *Gramineae* species, heterocyclic hydroxamic acids and cyclic *N*-oxides [10-12], respectively. It is a typical feature, that normally two products can be derived from one *ortho*-nitro compound by the suitable choice of the conditions for the reductive cyclisation, due to the fact, that both an intermediate NHOH- or NH_2-group can undergo an intramolecular cyclisation. However, such reactions are usually not accompanied by stereoselectivity.

We wish to report here the behaviour of 4-acetyl-3-methyl-5-(2-nitrophenyl)-1-phenylpyrazole **1** under several cyclisation conditions. Nitro precursor **1** is easily accessible by cyclocondensation of 3-(2-nitrobenzoyl)pentan-2,4-dione [12] with phenylhydrazine. Reduction of **1** with zinc dust in an aqueous-ethanolic solution of ammonium chloride or with an ethanolic solution of sodium hydrogensulphide resulted in the formation of 3,4-dimethyl-1-phenylpyrazolo[4,3-*c*]quinoline 5-oxide **2**.

However, the product of a catalytic hydrogenation of compound **1** over platinum dioxide or palladium/charcoal was not the corresponding quinoline but a dihydro compound **3**, unexpectedly. It was also obtained from **1** by transfer hydrogenation with sodium borohydride over palladium/charcoal. Furthermore, compound **3** could be synthesized in excellent yield through catalytic hydrogenation of the *N*-oxide **2**.

Some further attempts to prepare the corresponding quinoline by stronger reducing agents, *e.g.* tin(II) chloride or zinc in acetic acid, were unsuccessful. Thus, some conclusions on the pathway of reaction can be drawn. Obviously, the intermediate hydroxylamine derived from **1**, which is formed in all kinds of reduction, has such a high tendency for intramolecular cyclisation to form the *N*-

Scheme



oxide **2**, that this reaction is favoured in general in comparison with the further reduction to the intermediate amine. We assume that the formation of the dihydropyrazole system (iii and iv) takes place after cyclisation to the quinoline ring and not at the arylhydroxylamine stage.

The *N*-oxide **2** is by means of catalytically activated hydrogen regioselectively reduced at the C = C-bond of the pyrazole. Thus, theoretically four stereoisomers have to be expected. However, the nature of the *cis*-hydrogenation at the surface of the catalyst effects diastereoselectivity and hence only one pair of enantiomers is to be observed. The ^{1}H-nmr spectrum shows two sharp singlets for the methyl groups and an AB-spectrum of the protons in 4,11-position with J_{AB} 8.1 Hz indicating a gauche-conformation of the protons according to an a/e-configuration. Thus, compound **3** has to be regarded as the racemate of (4-*S*,11-*R*)- and (4-*R*,11-*S*)-dihydro-3,5-dimethyl-1-phenylpyrazolo[4,3-*c*]quinoline 6-oxide.

EXPERIMENTAL

Melting points were determined on a Boetius micro hot stage apparatus and are corrected. The ^{1}H nmr spectra were recorded on a 80 MHz Tesla BS 587A spectrometer with hexamethyldisiloxane as the internal standard. The ir spectra were obtained on Carl Zeiss Jena Specord M 80 spectrometer in potassium bromide. Mass spectra were recorded on a Varian MAT CH6 mass spectrometer (70 eV EI ionisation, source temperature 200°). All elemental analyses were performed on a Hereaus CHN-O-Rapid analyzer.

4-Acetyl-3-methyl-5-(2-nitrophenyl)-1-phenylpyrazole (**1**).

3-(2-Nitrobenzoyl)pentane-2,4-dione (4.98 g, 20 mmoles) [12] and phenylhydrazine (2.16 g, 20 mmoles) are refluxed in ethanol (50 ml) with 96% sulphuric acid (0.1 g) for 3 hours. Pyrazole **1** separates in yellow crystals (5.32 g, 83%), mp 174-176° (ethanol); ^{1}H-nmr (DMSO-d$_6$): δ = 2.22 (s, 3H, methyl), 2.44 (s, 3H, methyl), 7.62-8.54 (m, 9H, aromatics); ir: 1640 cm^{-1}, ν C = O; ms: 321 (M$^+$, 2).

Anal. Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.70, N, 13.08. Found: C, 67.27; H, 4.71; N, 12.91.

3,4-Dimethyl-1-phenylpyrazolo[4,3-*c*]quinoline 5-Oxide (**2**).

Method i.

A solution of compound **1** (3.21 g, 10 mmoles) in ethanol (80 ml) is combined with a solution of ammonium chloride (2.1 g, 40 mmoles) in water (20 ml) and zinc dust (2.3 g, 35 mmoles) is added in portions within 2 minutes with stirring. The filtrate obtained after 30 minutes is evaporated to dryness, extracted with 1 *N* sodium hydroxide (2 x 40 ml) and acidified to yield *N*-oxide **2** (1.77 g, 61%), mp 72-73° (methanol).

Method ii.

Through a solution of pyrazole **1** (3.21 g, 10 mmoles) in boiling ethanol (250 ml) and 2 *N* sodium hydroxide (25 ml) is passed hydrogen sulfide for 30 minutes. After cooling, acidification, filtration, evaporation of the solvent and crystallization of the residue from methanol **2** is obtained in pale yellow needles (1.83 g, 57%), mp 72-73°; ^{1}H-nmr (DMSO-d$_6$): δ = 2.36 (s, 3H, methyl), 2.41 (s, 3H, methyl), 6.99-7.78 (m, 9H, aromatics); ir: 1630 cm^{-1}, ν C = C; ms: 289 (M$^+$, 28), 273 (3), 260 (10), 77 (100).

Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.72. Found: C, 74.64; H, 4.86; N, 14.22.

cis-4,11-Dihydro-3,5-dimethyl-1-phenylpyrazolo[4,3-*c*]quinoline 6-Oxide (**3**), Racemate.

Method iii.

Compound **1** (3.21 g, 10 mmoles) in ethanol (150 ml) is hydrogenated under normal conditions over platinum dioxide or 10% Pd/C (100 mg) until no more hydrogen is consumed (*ca.* 680 ml). After separation from the catalyst **3** is obtained in pale yellow crystals (2.39 g, 82%), mp 135-136° (methanol).

Method iv.

To a solution of pyrazole **1** (3.21 g, 10 mmoles) in boiling ethanol (250 ml) is added 10% Pd/C (200 mg) and (in portions) sodium borohydride (1.6 g, 40 mmoles). After stirring for 2 hours without external heating the solution is filtered, reduced to 10% of the starting volume *in vacuo*, poured into water (100 ml) and adjusted to *p*H 6, which causes separation of crude **3** as a pasty mass. Crystallization from methanol yields pure **3** as pale yellow crystals (1.81 g, 62%), mp 135-136°; ^{1}H nmr (DMSO-d$_6$): δ = 2.14 (s, 3H, methyl), 2.16 (s, 3H, methyl), 6.60 and 6.80 (AB-signal; 4,11-H, J_{AB} 8.1 Hz), 6.90-7.59 (m, 9H, aromatics); ir: 1620 cm^{-1}, ν C = C; ms: 291 (M$^+$, 77), 276 (26), 274 (29), 120 (100).

Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.39; H, 5.95; N, 14.33.

REFERENCES AND NOTES

[1] P. N. Preston and G. Tennant, *Chem. Rev.*, **72**, 627 (1972).

[2] S. Hauptmann, G. Blattmann and W. Schindler, *J. Prakt. Chem.*, **318**, 835 (1976).

[3] M. D. McFarlane, D. J. Moody and D. M. Smith, *J. Chem. Soc., Perkin Trans. 1*, 691 (1988).

[4] I. W. Harvey, M. D. McFarlane, D. J. Moody and D. M. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1939 (1988).

[5] R. T. Coutts, H. W. Peel and E. M. Smith, *Can. J. Chem.*, **43**, 3221 (1965).

[6] H. Wilde, S. Hauptmann, G. Ostermann and G. Mann, *J. Prakt. Chem.*, **326**, 829 (1984).

[7] T. J. McCord, R. M. Warner, P. L. Shafer, R. M. D. Disher and A. L. Davis, *J. Heterocyclic Chem.*, **22**, 141 (1985).

[8] H. Wilde, S. Hauptmann, A. Kanitz, M. Franzheld and G. Mann, *J. Prakt. Chem.*, **327**, 297 (1985).

[9] D. Sicker, B. Prätorius, G. Mann and L. Meyer, *Synthesis*, 211 (1989).

[10] D. Sicker, D. Reifegerste, S. Hauptmann, H. Wilde and G. Mann, *Synthesis*, 331 (1985).

[11] D. Heilmann and D. Sicker, *J. Prakt. Chem.*, **332**, 265 (1990).

[12] D. Sicker, A. Rabe, A. Zakrzewski and G. Mann, *J. Prakt. Chem.*, **329**, 1063 (1987).