Preparation of 1-Hydroxypyrazoles and 1-Hydroxy-1,2,3-triazoles by Dealkylation of Pyrazole and Triazole N-Oxides

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1-Hydroxypyrazoles were obtained from 2-benzylpyrazole 1-oxides by debenzylation with iodotrimethylsilane. 1-Hydroxy-1,2,3-triazoles were achieved from 2-benzyltriazole 1-oxides by debenzylation effected with conc. hydrobromic acid or from or 3-methoxybenzyltriazole 1-oxides by de-p-methoxybenzylolation accomplished by treatment with conc. sulfuric acid. 1-Methoxy-1,2,3-triazole was obtained by de-p-methoxybenzylolation of 1-methoxy-3-p-methoxybenzyl-1,2,3-triazolium tetrafluoroborate accomplished by treatment with conc. sulfuric acid. 1-Hydroxypyrazole was selectively N-benzylated in absence of base to give 2-benzylpyrazole 1-oxide which, upon selective substitution at the 3-position and subsequent debenzylation, produced 3-substituted 1-hydroxypyrazole.

1-Hydroxybenzotriazole (HOBt) is an important catalyst for acylations and phosphorylations.\(^1,2\) It is widely used in peptide \(^3-7\) and nucleotide synthesis.\(^8\) In peptide synthesis the requirements to the catalyst is maximum reactivity combined with minimum racemization during the coupling. Substituted 1-hydroxybenzotriazoles have been prepared in order to improve the catalytic properties.\(^9\) Since substituents only can be introduced in the benzene ring remote to the N-OH functionality only moderate changes in the catalytic properties are possible. A higher sensitivity to the nature of substitution is possible in the uncondensed parent, 1-hydroxy-1,2,3-triazole (7). An even broader range in properties can be envisaged if the nature of the heterocyclic ring also can be varied as demonstrated by comparison of the properties of 1-hydroxybenzotriazole and its 7-aza derivative.\(^9\)

Only a few uncondensed 1-hydroxy-1,2,3-triazoles have been reported. The 4,5-dicarboxylic acid derivative 7 (\(R^4=R^2=\text{COOH}\)) was prepared by oxidation of 1-hydroxybenzotriazole.\(^10\) 4-Methyl-5-carboxylic acid (7; \(R^1=\text{Me}, R^2=\text{COOH}\)), 4-methyl-5-benzoyl (7; \(R^1=\text{Me}, R^2=\text{COPh}\)) and 4-benzoyl-5-carboxylic acid (7; \(R^1=\text{COPh}, R^2=\text{COOH}\)) were obtained through reaction between diazoketone and hydroxylamine.\(^11\) The 5-tert-butylcarbonyl derivative 7; (\(R^3=\text{COBu}^1\)) was formed in a ring transformation of 4-amino-5-tert -butylisoxazole effected by diazotation.\(^12\) The parent 1-hydroxy-1,2,3-triazole 7 has been synthesized recently by direct oxidation of 1,2,3-triazole.\(^13\)

Some substituted 1-hydroxypyrazoles 3 have been obtained by nitrosation of \(\alpha,\beta\)-unsaturated oximes and subsequent cyclisation followed by partial reduction.\(^14-19\) The parent 1-hydroxypyrazole 3 has been prepared by direct oxidation of pyrazole with peroxyphthalic acid and base,\(^20\) with dibenzyl peroxide and base,\(^21,22\) or with 3-chloroperbenzoic acid.\(^13\) Alternatively, 1-hydroxypyrazole (3) was obtained by thermal degradation of substituted azoxyoxazacryliccylededecanones.\(^23\) Halogens can be introduced at the 4-position of 1-hydroxypyrazole (3) by standard substitution reactions.\(^18,24\) A wide variety of electrophiles can be introduced at the 5-position in the sequence O-benzylolation, deprotonation, reaction of the anion formed with an electrophile and debenzylation.\(^25\)

We now report effective and fairly general methods for the preparation of the parent 1-hydroxy-1,2,3-triazole 7 and 1-hydroxypyrazole 3, and derivatives by \(N\)-debenzylolation of the corresponding azole 1-oxides 1, 6 and 8.

Results and discussion

Preparation of azole 1-oxides. 2-Benzyl-1,2,3-triazole 1-oxides 6a are accessible through oxidative cyclization of \(\alpha\)-oximinobenzylhydrazones,\(^26\) while 2-benzylpyrazole 1-oxides 1 and 3-benzyltriazole 1-oxides 8a are prepared by oxidation of the corresponding 1-benzylpyrazoles or
1-benzyltriazoles. A variety of substituents can be introduced with high regioselectivity in the N-oxides by electrophilic or nucleophilic substitution reactions or by O-silylation followed by deprotonation and C-silylation. In this way a broad range of C-substituted pyrazole 1-oxides and 1,2,3-triazole 1-oxides become accessible.

N-Debenzylation of these species to give the corresponding N-hydroxyazoles has been achieved by treatment with iodotrimethylsilane or hydrogen bromide.

In some cases the N-debenzylation was less satisfactory. Therefore, N-de-p-methoxybenzyl of the corresponding p-methoxybenzyl azole N-oxides was studied. The p-methoxybenzyl azole N-oxides 6b and 8b are prepared like the benzyl analogs. However, yields are sometimes lower.

N-Debenzylation with iodotrimethylsilane.

2-Benzylpyrazole 1-oxides. 2-Benzylpyrazole 1-oxides 1 were readily N-debenzylated by treatment with iodotrimethylsilane in the presence of catalytic amounts of a weak, hindered base, like 2,6-dimethylpyridine. The yields of the resulting 1-hydroxypyrazoles 3 were good to excellent. As shown previously, initial silylation of the N-oxide oxygen atom produces an N-silyloxy-N'-benzyl azolium ion 2. This is then debenzylated presumably by nucleophilic attack of the iodide ion liberated in the silylation step. Best yields are obtained if 2-3 equiv. of iodotrimethylsilane are used. The role of the 2,6-dimethylpyridine is not fully understood, but it is believed that it functions to maintain neutral conditions by neutralizing hydrogen iodide formed due to accidental presence of moisture.

The base used should not be too strong. When 2,6-dimethylpyridine (pKₐ = 5.77) was replaced with a stronger base like 1,2,2,6,6-pentamethyldiisopropylamine; (pKₐ = 11.25) the silylated 2-benzyl-5-methylpyrazole 1-oxide 2; R₂ = Me was deprotonated at the methyl group and the resulting N-silyloxyamine was attacked by the iodide ion at this position producing 1-benzyl-3-iodomethylpyrazole.

2- and 3-Benzyl-1,2,3-triazole 1-oxides. The iodotrimethylsilane mediated debenzylation of the 2-benzyltriazole 1-oxides 6a (R₄ = H and Me) to give the 1-hydroxytriazoles 7; R₄ = H and Me proceeded in modest yields. Thus 1-hydroxytriazoles 7 (R₄ = H and Me) were formed in 53 and 21% yield, respectively. In addition the iodonitrazoles 11 (R₄ = 1) or 11 (R₄ = Me, R₅ = 1) were formed together with the hydroxytriazoles 11 (R₄ = OH) or 11 (R₄ = Me, R₅ = OH). Most likely, the iodonitrazole 11 (R₄ = 1) and 11 (R₄ = Me, R₅ = 1) are formed from the intermediate 1-silyloxy-2-benzyltriazolium ion, which is attacked by the iodide ion at the immonium carbon atom whereupon hydroxymethyltrimethylsilane is eliminated with production of 11 (R₄ = 1) and 11 (R₄ = Me, R₅ = 1). The silyloxy group itself may serve as a nucleophile in a similar reaction producing 2-benzyl-4-silyloxytriazole (11; R₄ = OMe) and 2-benzyl-4-methyl-5-silyloxytriazole (11; R₄ = Me, R₅ = OMe), hydrolyzing to give 2-benzyl-4-hydroxytriazole and 2-benzyl-4-methyl-5-hydroxytriazole (11; R₄ = Me, R₅ = OH) during the work up.

Attempts to debenzylate 3-benzyltriazole 1-oxide 8a by treatment with iodotrimethylsilane and 2,6-dimethylpyridine gave complicated mixtures.

N-Debenzylation with hydrogen bromide.

2- and 3-Benzyl-1,2,3-triazole 1-oxides. Conc. hydrobromic acid proved to be superior to iodotrimethylsilane for the debenzylation of the 2-benzyltriazole 1-oxides 6a (R₄ = H or Me) to give the 1-hydroxytriazoles 7 (R₄ = H or Me) in excellent yields. This process is most likely initiated by protonation of the oxygen atom to give a 1-hydroxy-2-benzyltriazole ion which is then debenzylated by nucleophilic attack of the bromide ion.

In a similar fashion 2-benzyl-5-chloro-1,2,3-triazole 1-oxide (6a; R₂ = Cl), prepared by chlorination of
2-benzyl-1,2,3-triazole 1-oxide (6a; R<sup>5</sup> = H), was debenzylated to give 7 (R<sup>3</sup> = Cl) in high yields. Thus this method can be used for preparation of otherwise inaccessible 5-substituted 1-hydroxy-1,2,3-triazoles starting from 2-benzyl-1,2,3-triazole 1-oxide.

Attempts to debenzylate 3-benzyltriazole 1-oxide (8a) by treatment with conc. hydrobromic acid failed.

N-De-p-Methoxybenzyl-N-methoxybenzyl-N-methoxybenzyltriazole 1-oxide (6b) using conc. sulfuric acid.

2- and 3-p-Methoxybenzyl-1,2,3-triazole 1-oxides. 1-Hydroxy-1,2,3-triazole (7) can alternatively be prepared by de-p-methoxybenzylolation of 2-p-methoxybenzyl-

N-methoxy-3-p-methoxybenzyltriazolium tetrafluoroborate. 1-Methoxy-3-p-methoxybenzyltriazolium tetrafluoroborate (9b), obtained in almost quantitative yield by treatment of the corresponding p-methoxybenzyl-

N-oxide 8b with trimethylxonium tetrafluoroborate, could likewise be de-p-methoxybenzylated with conc. sulfuric acid to give 1-methoxy-1,2,3-triazole (10) in good yield.

Regioselective N-benzylation of 1-hydroxyprazole. 1-Hydroxyprazole (3) is regioselectively O-benzylated by benzyl bromide in the presence of N-ethylidisopropyl-

amine as a base to give 1-benzoxypyrazole (5). If the reaction is performed in the absence of base at 80 °C in chloroform, selective N-benzylation takes place with produ-

ction of 2-benzylprazole 1-oxide (1) in 82% yield. The reaction was monitored by NMR, showing the initial formation of 1-benzoxypyrazole (5) and 2-benzylprazole 1-oxide (1) which upon further heating were transformed to a 10:1 mixture of 2-benzylprazole 1-oxide (1) and unchanged 1-hydroxyprazole (3).

Most likely, both 1 and 5 are formed in a kinetically controlled process. The benzoxypyrazole (5) is then debenzylated by the hydrogen bromide formed by the alkylation to give the starting material 3, which subsequently is realkylated to 1 and 5. 2-Benzylprazole 1-oxide (1) does not undergo dealkylation under these conditions, and is therefore accumulated during extended reaction times. This sequence demonstrates that the hard proton can act as an efficient protection group for the hard oxygen in 1-hydroxyprazole (3).

The control of the regioselectivity of the benzylation of 1-hydroxyprazole (3) to give 1-benzoxypyrazole (5) or 2-benzylprazole 1-oxide (1) is most useful by the regioselective introduction of substituents in the 5- or the 3-position of 1-hydroxyprazoles. Thus, 5-substituted 1-hydroxyprazoles are obtained from 1-hydroxyprazole (3) by the sequence O-benzylation, selective abstraction of H-5, reaction of the anion formed with an electrophile and hydrogenolytic debenzylation. The otherwise inaccessible 3-substituted 1-hydroxyprazoles become available from 1-hydroxyprazole (3) by the sequence N-benzylation to give 2-benzylprazole 1-oxide (1), electrophilic substitution which takes place selectively at the 3-position of 1<sup>27</sup> completed by N-deborylation using iodotrimethylsilane and 2,6-dimethylpyridine as described above for the deborylation of 2-benzyl-3-chloropyrazole 1-oxide (1; R<sup>3</sup> = Cl) to give 1-hydroxy-3-chloropyrazole (3; R<sup>3</sup> = Cl).

Conclusion

1-Hydroxyprazoles 3 are best obtained by iodotrimethylsilane mediated deboronation of 2-benzylprazole 1-oxides 1, while 1-hydroxy-1,2,3-triazoles 7 usually are best obtained by deboronation of 2-benzyltriazole 1-oxides 6a with conc. hydrobromic acid or from 2- or 3-p-methoxybenzyltriazole 1-oxides by de-p-methoxybenzy-

lation accomplished by treatment with conc. sulfuric acid. De-p-methoxybenzylolation effected by conc. sulfuric acid can serve in the preparation of 1-methoxytriazoles as demonstrated by the conversion of 1-methoxy-3-p-

methoxybenzyltriazolium tetrafluoroborate (9b) to 1-methoxy-1,2,3-triazole (10).

The three new methods for N-dealkylation of prazole and triazole 1-oxides provides a route to otherwise inaccessible 1-hydroxyprazoles and -triazoles since deal-

kylation can be performed after regioselective introduc-

tion of substituents into the azole 1-oxides for which effective methods are available.<sup>27,35</sup>

Experimental

General. All reactions involving N-benzylation or N-

deboronation were performed using syringe techniques and screw cap sealed reaction vessels. By drying of solutions, magnesium sulfate was used unless otherwise stated. Solvents were removed in vacuo by rotary evaporation. Filtration through silica gel was performed using silica gel Merck 60 (70–230 mesh). Flash chromatography was performed as described in Ref. 37. All new compounds were colorless, unless otherwise stated. The purity of all compounds was confirmed using melting points, thin-layer chromatography and NMR spectra. When not otherwise stated, 1<sup>H</sup> and 13<sup>C</sup> NMR spectra were recorded at 200 and 50.32 MHz, respectively, on a Bruker AC-200 instrument.

Preparation of 1-hydroxyprazoles.

General procedure. 2-Benzylprazole 1-oxide (1) (160 mg), 2,6-dimethylpyridine (0.16 ml), chloroform (2.3 ml) and iodotrimethylsilane (0.50 ml) were heated to 70 °C for 14 h. Addition of conc. hydrochloric acid (1 ml), washing with diethyl ether (3 × 4 ml), extraction of the ether solution with conc. hydrochloric acid (0.5 ml), adjustment of the pH of the combined aqueous solutions with 33% NaOH to pH 13, washing with
dichloromethane (3 × 4 ml), addition of conc. hydrochloric acid to pH ca. 5, washing with diethyl ether, addition of 0.2 M phosphate buffer pH 5.0 (5 ml) and continuous extraction with dichloromethane–diethyl ether (1:2) for 2 h, and removal of the solvents gave 56 mg (73%) of 1-hydroxyprazol (3), m.p. 72 °C (ethyl acetate–hexane), identical with the material described previously.15

Similarly, 2-benzyl-5-methylpyrazole 1-oxide (1; R3 = Me) 34 (177 mg) after the acetylation, in this case to pH 4 with 1 M hydrochloric acid, followed by extraction with dichloromethane (10 × 4 ml), drying and removal of the dichloromethane gave 80 mg (87%) of 1-hydroxy-5-methylpyrazole (3; R3 = Me). Recrystallization (ethyl acetate–hexane) gave m.p. 107 °C. Found: C, 49.13; H, 6.18; N, 28.31. C18H17N3O2 requires C, 48.97; H, 6.16; N, 28.56%. 1H-NMR (CDCl3): δ 7.02 (1H, d, J = 2.49 Hz, H-3), 5.93 (1H, d, J = 2.49 Hz, H-4), 2.29 (3H, s, Me). 13C-NMR (CD2CN): 132.0 (s, C-5), 130.4 (d, C-3), 102.2 (d, C-4), 8.3 (q, Me).

2-Benzyl-3-chloropyrazole 1-oxide (1; R3 = Cl) 27 (150 mg) was treated according to the general procedure to give a reaction mixture which was stirred at 20 °C for 1 h with 1 M hydrochloric acid (2 ml). Extraction with dichloromethane–diethyl ether (1:1, 7 × 5 ml), removal of the solvents, addition of 1 M NaOH (2 ml), washing with dichloromethane–diethyl ether (1:1, 6 × 5 ml), addition of 4 M hydrochloric acid to ca. pH 0. Extraction with dichloromethane (6 × 5 ml), drying and removal of the dichloromethane gave 81 mg (96%) of 1-hydroxy-3-chloropyrazole (3; R3 = Cl). Recrystallization (chloroform) gave m.p. 108 °C. Found: C, 29.94; H, 2.59; N, 23.26. C23H17N3O2Cl requires C, 30.40; H, 2.55; N, 23.64%. 1H-NMR (CDCl3): δ 7.35 (1H, d, J = 2.42 Hz, H-5), 6.11 (1H, d, J = 2.42 Hz, H-4). 13C-NMR (CDCl3): δ 131.8 (s, C-3), 125.8 (d, C-5), 103.0 (d, C-4).

Preparation of 1,2,3-triazole N-oxides. p-Methoxybenzylazole, prepared as described in Ref. 38, was dissolved in dichloromethane (10 ml) and dried (magnesium sulfate). Removal of the dichloromethane at 20 °C gave the dry azide (5.14 g),* which was dissolved in acetone dried over 3 Å molecular sieves 39 (10.3 ml). Acetylenehexyloxycarbonyl amine (3.15 g) was added with stirring and cooling in a 20 °C bath. After stirring for 1 h the mixture was heated to reflux for 15 min. The solvent was removed and ethyl acetate (10 ml) was added. The mixture was heated to boiling, cooled to 20 °C, and filtered. The residue was washed with ethyl acetate (5 ml) and recrystallized from water (3.6 ml g⁻¹) to give 6.19 g (83%) of colorless 1-p-methoxybenzyl-1,2,3-triazole-4,5-dicarboxylic acid, m.p. 156–158 °C (decomp.). Washing with acetone gave m.p. 165 °C. Found C, 52.14; H, 4.07; N, 15.17. C12H11N3O2 requires C, 51.99; H, 4.00; N, 15.16.

1-p-Methoxybenzyl-1,2,3-triazole-4,5-dicarboxylic acid (5.0 g) and diethylene glycol (20 ml) were heated with stirring in a 230–240 °C bath. When no more carbon dioxide was evolved (after ca. 20 min), the mixture was cooled to 20 °C. 1 M aqueous sodium hydroxide (20 ml) was added, and the mixture heated to reflux for 1 h. Dilution with water (80 ml), extraction with dichloromethane (3 × 15 ml), reduction of the volume to 20 ml, washing with water (2 × 10 ml), drying (magnesium sulfate), and removal of the dichloromethane gave a residue which was carefully triturated with diethyl ether (5 × 3 ml). The residue consisted of 2.01 g (63%) of colourless 1-p-methoxybenzyl-1,2,3-triazole, m.p. 91–92 °C. Recrystallization (ethanol–hexane) gave m.p. 93–95 °C. Found C, 63.56; H, 5.95; N, 22.11. C13H13N3O2 requires C, 63.48; H, 5.86; N, 22.21%. 1H-NMR (CDCl3): δ 7.64 (1H, d, J = 0.9 Hz, H-4), 7.42 (1H, d, J = 0.9 Hz, H-5), 7.18 and 6.83 (4H, AA′BB′, p-C6H4), 5.45 (2H, s, CH2), 3.86 (3H, s, Me).

1-p-Methoxybenzyl-1,2,3-triazole (1 g) was dissolved with heating in ethyl acetate (1 ml). After cooling to 20 °C m-chloroperbenzoic acid (1.2 mol equiv.) was added. After stirring for 15 h the mixture was diluted with dichloromethane (10 ml), and washed with 1 M sodium hydroxide (8 ml). The aqueous solution was extracted with dichloromethane (2 × 8 ml). The combined organic solutions were dried, the dichloromethane was removed, diethyl ether (10 ml) was added, and the suspension was filtered through silica gel (Merck 60, 2 g). Extraction with further 20 ml of diethyl ether and removal of the diethyl ether gave 20% of unchanged starting material. Subsequent extraction with ethyl acetate–methanol (1:1) (50 ml) and removal of the solvents produced 45% of 3-p-methoxybenzyl-1,2,3-triazole 1-oxide (8b), m.p. 113–115 °C. Recrystallization (ethyl acetate) gave m.p. 118–120 °C. Found: C, 54.24; H, 5.31; N 20.36. C13H13N3O2 requires C, 58.53; H, 5.40; N, 20.48%. 1H-NMR (CDCl3): δ 7.27 (1H, d, J = 0.6 Hz, H-4), 7.25 (1H, d, J = 0.6 Hz, H-5), 7.27 and 6.89 (4H, AA′BB′, p-C6H4), 5.18 (2H, s, CH2), 3.80 (3H, s, Me).

Hydroxyamine hydrochloride (6.95 g) and sodium carbonate (11.1 g), thoroughly mixed, were added with stirring as fast as possible to an 40% aqueous solution of glyoxal (11.4 ml) and water (46 ml). Immediately after all material had dissolved, p-methoxybenzylhydrazine* (13.8 g) dissolved in methanol (40 ml) was added. After being stirred for 0.5 h the suspension was added during 10 min to a refluxing mixture of copper(II) sulfate (100 g), pyridine (100 ml), and water (400 ml). After heating to reflux for 0.5 h and cooling to 20 °C 2 M sulfuric acid was added to ca. pH 3. After filtration the residue and the filtrate were successively extracted with ethyl acetate (3 × 100 ml). Drying of the extract, reduction of its volume to ca. 50 ml, filtration through silica gel (12 g), heating to reflux for 15 min with activated carbon (8 g), filtration, and removal of the ethyl acetate gave an oil which was extracted with chloroform (2 × 8 ml). The chloroform was removed, diethyl ether (20 ml) was added and the mixture was kept at −25 °C.

* Azides are potentially explosive.
PREPARATION OF N-HYDROXYAZOLES

for 1 d. Filtration gave 5.75 g (28%) of 2-p-methoxybenzyl-1,2,3-triazole-1-oxide (6b), m.p. 99–100 °C. Recrystallization (ethyl acetate–hexane) did not change the m.p. Found: C, 58.47; H, 5.40; N, 20.50. C_{10}H_{13}NO_2 requires C, 58.53; H, 5.40; N, 20.48%. 1H-NMR (CDCl₃): δ 7.47 (1H, d, J = 5.0 Hz, H-4), 7.28 (1H, d, J = 5.0 Hz, H-5), 7.33 and 6.83 (4H, AA'BB', p-C₆H₄), 5.45 (2H, s, CH₂), 3.76 (3H, s, Me).

Preparation of 1-hydroxy-1,2,3-triazoles.

**Debenzylation with iodosotrimethylsilane.**

2-Benzyltriazole 1-oxide 6a 26 (162 mg), chloroform (1.5 ml), 2,6-dimethylpyridine (0.081 ml) and iodosotrimethylsilane (0.50 ml) were heated to 50°C for 1.5 h. Addition of conc. hydrochloric acid (1.0 ml) and toluene (3 ml), stirring at 20°C for 10 min, isolation of the organic solution, extraction of the aqueous solution with toluene (5 × 4 ml), extraction of the combined organic solutions with conc. hydrochloric acid (0.5 ml) and adjustment of the pH of the combined aqueous solutions to 12 by means of 33% aqueous NaOH gave a solution which was extracted with toluene (5 × 4 ml), acidified to pH 4 with conc. hydrochloric acid and extracted with toluene (5 × 4 ml). A 0.2 M phosphate buffer pH 4.0 (5 ml) and sodium chloride (5 g) were added and the mixture was extracted continuously with dichloromethane–diethyl ether (1:1) for 20 h. Removal of the solvents and washing with dichloromethane–diethyl ether (1:1) (2 × 2 ml) gave 42 mg (53%) of 1-hydroxy-1,2,3-triazole (7), m.p. 89–91 °C. The compound was identical with the material described below.

The byproducts were isolated by preparative TLC (dichloromethane–diethyl ether–hexane [1:1:8]) of the content of the combined toluene solutions. This gave 10 mg (4%) of 2-benzyl-4-iodo-1,2,3-triazole (11; R = Ph) (R = 0.55), m.p. 75 °C (hexane), m/z 285 (M⁺, 23%), 158 ([M-1]⁺, 4), 130 (7), 103 (8), 92 (9), 91 (100), 65 (13). 1H-NMR (CDCl₃): δ 7.47 (1H, s, H-5), 7.34 (5H, br s, Ph), 5.59 (2H, s, CH₂), 1.37 (s, CH₃). The next fraction contained 31 mg (21%) of 2-benzyl-1,2,3-triazole (11) (R = 0.30), identical with an authentic sample. 13C-NMR (CDCl₃): δ 135.1 (s, C-1’), 134.3 (d, C-4 and C-5), 128.6 (d, C-2’ or C-3’), 128.1 (d, C-4’), 128.1 (d, C-2’ or C-3’), 89.3 (s, C-4), 59.1 (t, CH₂). The next fraction contained 18 mg (11%) of 2-benzyl-4-hydroxy-1,2,3-triazole (11; R = OH) (R = 0.06), identical with the material described previously. 13C-NMR (CDCl₃): δ 159.3 (s, C-4), 134.5 (s, C-1’), 128.7 (d, C-2’ or C-3’), 128.4 (d, C-4’), 127.9 (d, C-2’ or C-3’), 58.4 (t, CH₂).

Similarly, 2-benzyl-4-methyltriazole 1-oxide (6a; R = Me) 26 (83 mg) gave 9 mg (21%) of 1-hydroxy-4-methyl-1,2,3-triazole (7; R = Me). The compound was identical with the material described below. The byproducts were isolated by preparative TLC (dichloromethane–diethyl ether–hexane [1:1:3]) of the content of the combined toluene solutions which gave 27 mg (20%) of 2-benzyl-4-methyl-5-iodo-1,2,3-triazole (11; R = Me) (R = 0.85) as an oil (m/z 299 (M⁺, 24%), 180 (9), 92 (8), 91 (100), 65 (13)). 1H-NMR (CDCl₃): δ 7.34 (5H, s, Ph), 5.52 (2H, s, CH₂), 2.26 (3H, s, Me). 13C-NMR (CDCl₃): δ 148.8 (s, C-4), 134.5 (s, C-1’), 128.7 (d, C-2’ or C-3’), 128.3 (d, C-4’), 128.0 (d, C-2’ or C-3’), 92.2 (s, C-5), 58.5 (t, CH₂), 11.1 (q, Me). The next fraction contained 16 mg (21%) of 2-benzyl-4-methyl-1,2,3-triazole (11; R = Me) (R = 0.52). 1H-NMR (CDCl₃): δ 7.38 (1H, s, H-5), 7.38–7.25 (5H, m, Ph), 5.53 (2H, s, CH₂), 2.31 (3H, s, Me). 13C-NMR (CDCl₃): δ 144.1 (s, C-4), 135.4 (s, C-1’), 133.6 (d, C-5), 128.6 (d, C-2’ or C-3’), 128.1 (d, C-4’), 128.7 (d, C-2’ or C-3’), 58.2 (t, CH₂), 10.5 (q, Me). The third fraction contained 22 mg (27%) of 2-benzyl-4-methyl-5-hydroxy-1,2,3-triazole (11; R = Me) (R = 0.18), m.p. 107–110 °C. 1H-NMR (CDCl₃): δ 7.36–7.25 (5H, m, Ph), 5.29 (2H, s, CH₂), 2.21 (3H, s, Me). 13C-NMR (CDCl₃): δ 156.9 (s, C-5), 135.0 (s, C-1’), 129.0 (s, C-5), 128.6 (d, C-2’ or C-3’), 128.2 (d, C-4’), 127.9 (d, C-2’ or C-3’), 58.0 (t, CH₂), 8.5 (q, Me).

**Debenzylation with HBr.** 2-Benzyltriazole 1-oxide 6a (162 mg) and conc. hydrobromic acid (1.0 ml) were heated to 80 °C for 3 h. Washing with dichloromethane (4 × 4 ml), addition of 33% aqueous NaOH to ca. pH 4, washing with toluene (4 × 4 ml), addition of 0.2 M phosphate buffer pH 4.0 (5 ml), saturation with sodium chloride, continuous extraction as described above by the dealkylation of 6a with iodosotrimethylsilane followed by removal of the solvents and extraction with boiling acetone (4 × 4 ml) gave 76 mg (97%) of 1-hydroxytriazole (7), m.p. 88–90 °C. Recrystallization (acetone) gave m.p. 93 °C. (Reported 13 m.p. 92–93 °C.)

Similarly, 2-benzyl-4-methyltriazole 1-oxide (6a; R = Me) (71 mg) gave 37 mg (99%) of 1-hydroxy-4-methyl-1,2,3-triazole (7; R = Me), m.p. 105–107 °C. Recrystallization (THF) gave m.p. 108 °C. Found C, 36.29; H, 5.17; N, 42.54. C₇H₉N₂O requires C, 36.36; H, 5.09; N, 42.41%. 1H-NMR (CDCl₃): δ 7.59 (1H, q, J = 0.8 Hz, H-5), 2.27 (3H, d, J = 0.8 Hz, Me). 13C-NMR (acetone-d₆): δ 138.9 (s, C-4), 116.0 (d, C-5), 8.8 (q, Me).

Similarly, 2-benzyl-5-chlorotriazole 1-oxide (6a; R = Cl) 26 (193 mg) in 4 h, omitting saturation with sodium chloride during work up and using dichloromethane for the continuous extraction, gave a dichloromethane solution which was discarded and an aqueous solution which was then saturated with sodium chloride and extracted continuously for 30 h with dichloromethane–diethyl ether to give 86 mg (78%) of 1-hydroxy-5-chloro-1,2,3-triazole (7; R = Cl). Recrystallisation (chlorform–acetone) gave m.p. 128 °C (decomp.). Found: C, 19.76; H, 1.70; N, 33.54. C₇H₉N₂ClO requires C, 20.10; H, 1.69; N, 35.16%. 1H-NMR (CDCl₃): δ 10.75 (1H, br s, OH), 7.84 (1H, s, H-4). 13C-NMR (Acetone-d₆): δ 128.0 (d, C-4), 119.3 (s, C-5).

553
De-p-methoxybenzyla
tion with H₂SO₄. 2-p-
Methoxybenzyltriazole 1-oxide 6b (1.07 g) and conc. sul-
furic acid (0.8 ml) were heated with efficient stirring to
120 °C for 1 h. After cooling to 20 °C the mixture was
triturated with dry diethyl ether (20 ml). The residue
was triturated further with dry diethyl ether (10 ml) and
a 15% solution of ammonia in dry methanol (10 ml).
After filtration and extraction with 2-propanol
(3 x 10 ml) the combined filtrates were evaporated to
dryness to give a residue which was dissolved in water
(5 ml). Washing with dichloromethane (3 x 10 ml), fil-
tration through activated carbon, removal of the water,
and drying at 0.1 mmHg over phosphorus pentoxide
produced 0.35 g (96%) of 1-hydroxy-1,2,3-triazole (7),
mp. 90–92 °C, identical with the material above.

Similarly, 3-p-methoxybenzyltriazole 1-oxide (8b) pro-
duced 96% of 1-hydroxy-1,2,3-triazole (7).

Preparation of 1-methoxy-1,2,3-triazole. 3-p-
Methoxybenzyl-1,2,3-triazole 1-oxide 8b (1.75 g) and tri-
methylloxonium tetrafluoroborate 43 (1.36 g) were dis-
solved in sulfur dioxide (ca. 10 ml). After reflux
under nitrogen with a dry ice and drying tube (with calcium
sulfate) for 1 h the sulfur dioxide was allowed to
vaporize. Recrystallization (dry methanol–dry diethyl
ereth) gave 2.53 g (97%) of 1-methoxy-3-p-
methoxybenzyl-1,2,3-triazolium tetrafluoroborate (9b),
mp. 58–61 °C. Found: C, 43.35; H, 4.35. Calc. for
C₁₅H₂₃N₂O₂BF₄: C, 43.05; H, 4.6. ¹H-NMR (CDCl₃): δ 8.47
(1H, d, J = 1.4 Hz, H-4), 8.42 (1H, d, J = 1.4 Hz,
H-5), 7.44 and 6.91 (4H, AA'BB'-pattern, p-C₆H₄), 5.65
(2H, s, CH₂), 4.48 (3H, s, NOMe), 3.80 (3H, s, COMe).

1-Methoxy-3-p-methoxybenzyltriazolium tetrafluoro-
borate 9b (1.39 g) and conc. sulfuric acid (0.6 ml) were
heated with efficient stirring to 120 °C for 1 h. After
cooling to 10 °C the mixture was triturated with dry
diethyl ether (20 ml). The residue was triturated with
dry diethyl ether (10 ml) and a 15% solution of ammonia
in dry methanol (10 ml). After filtration and extraction
with dichloromethane (3 x 10 ml) the combined filtrates
were washed with water (2 x 10 ml). The aqueous
solution was extracted with dichloromethane (2 x 10 ml).
The extract was combined with the filtrates, dried and
evaporated to dryness. The residue was dissolved in
diethyl ether (5 ml). Filtration through activated carbon
and removal of the ether gave 0.33 g (73%) of colorless
1-methoxy-1,2,3-triazole 10, m.p. ca. 10 °C, which was
reprecipitated from diethyl ether–hexane. An analytic
sample of 10 was obtained by ball tube distillation at
0.1 mmHg (oven temperature 50 °C). Found: C, 36.65;
H, 5.27; N, 42.39. C₁₁H₁₅N₂O requires C, 36.36; H, 5.09;
N 42.40. ¹H NMR (CDCl₃): δ 7.63 (1H, d, J = 1.2 Hz,
H-4 or H-5), 7.58 (1H, d, J = 1.2 Hz, H-5 or H-4), 4.25
(3H, s, Me). ¹³C NMR (CDCl₃): δ 130.4 (d, C-4), 116.0
(d, C-5), 65.9 (q, Me).

Selective N-benzylation of 1-hydroxypyrazole.
1-Hydroxypyrazole 3 (516 mg), benzyl bromide
(0.81 ml) and chloroform (6 ml) were heated to 80 °C
for 19 h.* Conc. hydrochloric acid (7 ml) was then
added. The organic layer was separated, the mixture was
washed with dichloromethane (3 x 10 ml), the volume of
the washings was reduced to ca. 5 ml and back-extracted
with conc. HCl (2 x 1 ml). To the combined HCl phases
was added 33% aqueous NaOH to pH 13. Extraction
with dichloromethane (5 x 10 ml), drying and removal
of solvents gave 873 mg (82%) 2-benzylpyrazole 1-oxide
(1), m.p. 68 °C (reported 27 m.p. 68–69 °C). To the aque-
ous solution was added 4 N HCl to ca. pH 3. Extraction
with diethyl ether (10 x 10 ml), drying and removal of
solvents gave 36 mg (7%) unchanged starting material 3.

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* When the reaction was monitored by ¹H-NMR a 71:25:4
mixture of the starting material (3), 2-benzylpyrazole-1-oxide
(1) and 1-benzylxopyrazole (5) was present after 1 h at 80 °C
(proved by adding the pure substances to the mixture). After
19 h at 80 °C ¹H-NMR showed only starting material (3) and
2-benzylpyrazole-1-oxide (1) in the ratio 9:1. Further heat-
ing at 80 °C did not result in further conversion of starting
material 3; instead minor impurities arose.

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