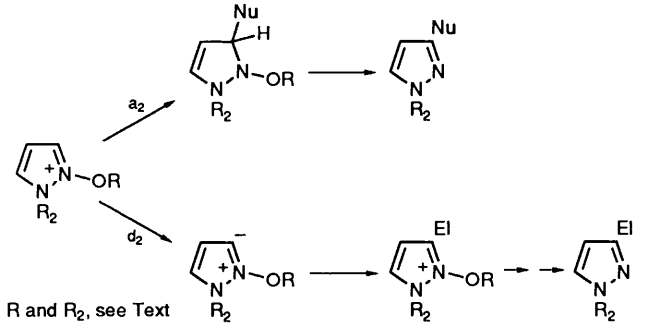
Activation of Exocyclic α-Positions of Azole *N*-Oxides by *O*-Silylation

Mikael Begtrup[*,a] **and Per Vedsø**[b]
[a] *Department of Organic Chemistry, Royal School of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen, Denmark*
[b] *Department of Organic Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark*

Exocyclic α-positions at immonium ring carbon atoms of pyrazole and 1,2,3-triazole 1-oxides are selectively attacked in a one-pot sequence comprising silylation with iodotrimethylsilane, deprotonation with 1,2,2,6,6-pentamethylpiperidine and allylic substitution of the trimethylsilyloxy group with the iodide ions liberated by the silylation. In this way 3- and 5-iodomethylpyrazoles as well as 4-iodomethyl-1,2,3-triazoles are obtained in good yields. These may be useful for the preparation of heteroarylmethyl derivatives since the iodine atom can be displaced by even weak nucleophiles such as acetate ions. The side chain iodination is complementary to *O*-alkylation of the *N*-oxides followed by nucleophilic attack which preferentially takes place at ring carbon atoms.

N-Oxidation † of azoles followed by *O*-alkylation or *O*-acylation activates their ring positions and exocyclic α-positions. The individual processes can be described in terms of the donor–acceptor concept using a numbered donor (d) and acceptor (a) notation.[1]

The ring position of the activated species are susceptible to nucleophilic attack followed by elimination of alcohol or carboxylic acid (path a_2, Scheme 1). Alternatively, the ring protons may be abstracted and the resulting anions allowed to react with electrophiles (path d_2). Thus, nucleophiles and electrophiles may be introduced into azole nuclei in a regioselective fashion.



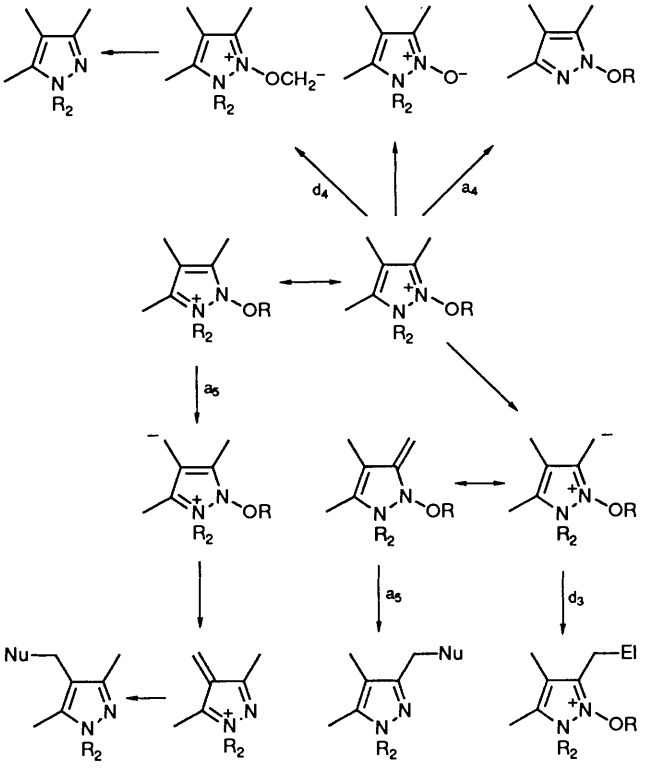
Scheme 1

Exocyclic α-protons may be abstracted and the generated anions allowed to react with electrophiles (path d_3, Scheme 2) or nucleophiles (path a_5). In a_5 type reactions the order of events is dependent on the position of the side chain. If situated at the immonium carbon atom (such as the 3- and 5-methyl groups in pyrazolium ions) deprotonation produces a neutral, *N*-OR substituted enamine fragment which may react with a nucleophile by 1,3 or 1,5-displacement of OR. If situated at an *N*-OR substituted enamine fragment (such as the 4-methyl groups in pyrazolium ions), deprotonation may lead to loss of $^-$OR producing an enammonium fragment which may be attacked by a nucleophile.

Other possible reactions of *N*-OR substituted azolium ions are *N*-dealkylation (path a_4), *O*-dealkylation, or deprotonation of the α-protons of *O*-alkyl groups with subsequent loss of a carbonyl compound (path d_4).

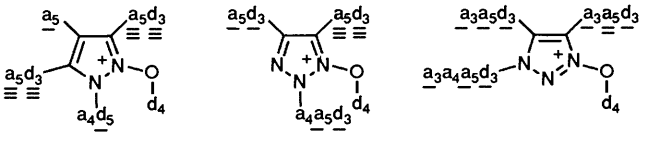
Apparently, only one a_5-type reaction has been reported.[2,3]

† The compounds studied have been named according to the IUPAC nomenclature. From this follows that numbering of ring positions starts at oxygen substituted nitrogen atoms.



Scheme 2

It accounted for 2 and 14% of the conversion when the 1-methoxy-5-methyl-2-phenyl-1,2,3-triazolium ion was treated with fluoride or methoxide ions. The main products were formed by attack at the ring position in an a_2-type reaction and by deprotonation of the methoxy group followed by deformylation in a d_4 type reaction. The reactivity and regioselectivity in a_5-type reactions has now been investigated more systematically in *N*-OR substituted pyrazolium and 1,2,3-triazolium ions. The predicted reactivity in these species is outlined in Scheme 3

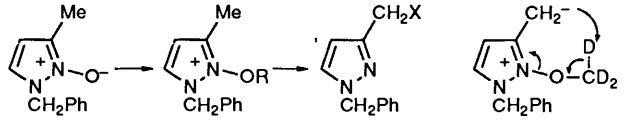


Scheme 3

where increasing reactivity is indicated with an increased number of bars according to the reasoning in ref. 1.

Results and Discussion

2-Substituted 1-methoxypyrazolium ions, such as **2a** were prepared in high yields by treatment of 2-substituted pyrazole 1-oxides* **1** with trimethyloxonium tetrafluoroborate. The 2-benzyl-1-methoxy-5-methylpyrazolium ion **2a** reacted with diisopropylethylamine in a d_4-type process with deprotonation followed by loss of formaldehyde to give 1-benzyl-3-methylpyrazole **3a**. Under similar conditions the 1-trideuteriomethoxy analogue **2b** produced the monodeuteriomethylpyrazole **3b**. This indicates that initial deprotonation takes place at the 5-methyl group and is followed by intramolecular proton transfer leading to the anion **4** which then eliminates formaldehyde. A similar mechanism through a six-membered cyclic transition state has been anticipated in the deprotonation–deformylation of 1-methoxypyridinium ions.[4,5]



1 **4**

R:
2a CH_3
b CD_3
c CPh_3
d $COCMe_3$
e $SiMe_3$

X:
3a H
b D
c $^+N(Et)(Pr^i)_2$, Y^-
d I
e OMe
f OCD_3
g OCOMe

Scheme 4

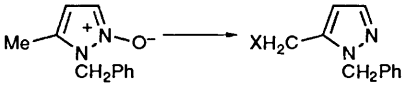
To avoid d_4-type reactions a series of activating *O*-substituents devoid of α-protons was considered. An *O*-*tert*-butyl group was not tried since 1-alkoxypyridinium ions possessing β-protons abstract these and eliminate pyridine *N*-oxide.[6] An *O*-triphenylmethyl group was abandoned since treatment of 2-benzyl-5-methylpyrazole 1-oxide **1** with triphenylmethyl tetrafluoroborate invariantly produced an equilibrium mixture of 2-benzyl-5-methyl-1-triphenylmethoxypyrazolium tetrafluoroborate **2c** and the two precursors. Attempts to introduce an *O*-4-nitrophenyl group by treatment of **1** with 4-nitrophenyldiazonium tetrafluoroborate[7] failed. *O*-Pivaloylation of **1** with pivaloyl chloride and silver triflate afforded **2d** in high yield but nucleophiles such as the thioacetate ion attacked this compound exclusively at the ring positions.

The trimethylsilyl group, however, proved to be suitable for selective activation of the exocyclic α-positions. While addition of chlorotrimethylsilane or 1-trimethylsilylimidazole to 2-benzyl-5-methylpyrazole 1-oxide **1** in chloroform caused no changes in the NMR spectra, the more powerful silylation agents[8] iodotrimethylsilane and trimethylsilyl triflate produced substantial changes in the ^1H and ^{13}C NMR chemical shifts and ^{13}C–H coupling constants of the pyrazole nucleus. The figures closely resembled those of the 2-benzyl-1-methoxy-5-methylpyrazolium ion **2a** indicating that 2-benzyl-5-methyl-1-trimethylsilyloxypyrazolium triflate **2e** is present in the solution. However, all attempts to isolate compound **2e** in the pure state failed.

The solution of 2-benzyl-5-methyl-1-trimethylsilyloxypyrazolium iodide **2e**, generated from 2-benzyl-5-methylpyrazole 1-oxide **1** and iodotrimethylsilane, was treated with a series of bases. Addition of diisopropylethylamine gave rise to a 3:2 mixture of the 3-iodomethylpyrazole **3d** and the diisopropyl(ethyl)(pyrazol-3-ylmethyl)ammonium iodide **3c**. Both compounds may be formed by an a_5-type reaction in which the 1-silyloxy compound **2e** is deprotonated at the 5-methyl group with formation of an *N*-silyloxyenamine fragment. Iodide ions liberated in the silylation step, or the amine, then displaces the silyloxy group by 1,3-substitution to give **3d** and **3c**, respectively. The expulsion of the silyloxy group may be catalysed by silylation of its oxygen atom.

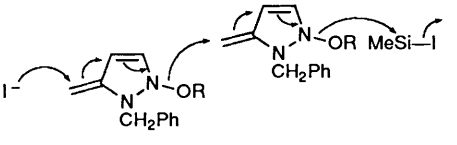
To avoid formation of **3c**, which is unsuitable for further transformations since the ammonium group is not readily displaced with other nucleophiles, more sterically hindered and non-nucleophilic bases were employed. The sterically hindered bases 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 2,6-di-*tert*-butyl-4-methylpyridine, dicyclohexylmethylamine, 2,2,6,6-tetramethylpiperidine, 1-benzyl-2,2,6,6-tetramethylpiperidine (BTMP) and 1,2,2,6,6-pentamethylpiperidine (PMP) were tried. However, only PMP proved successful. According to molecular modelling and their resistance towards alkylation by trimethyloxonium tetrafluoroborate, BTMP, PMP and 2,6-di-*tert*-butyl-4-methylpyridine are the most sterically hindered in the above-mentioned series. Of these, PMP is the strongest base† explaining its superiority. Thus, 2-benzyl-5-methylpyrazole 1-oxide **1** reacted with iodotrimethylsilane in the presence of PMP to give 1-benzyl-3-iodomethylpyrazole **3d** as the sole product in 75% yield.

Although only 2 equiv. of iodotrimethylsilane should be necessary, 3–4 equiv. were required for complete conversion of the starting material **3d**. Also the base had to be added in excess.



5

X:
6a H
b I
c $OSiMe_3$
d OH



Scheme 5

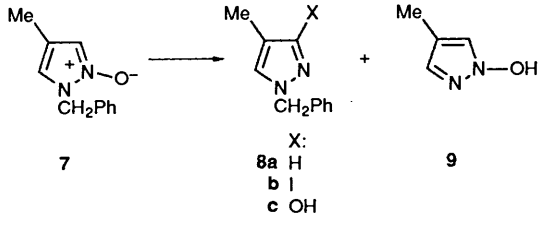
2-Benzyl-3-methylpyrazole 1-oxide **5** reacts similarly by 1,5-displacement to give 1-benzyl-5-iodomethylpyrazole **6b**. In this case, 1-benzyl-5-trimethylsilyloxymethylpyrazole **6c** was formed as a by-product. The trimethylsilyloxy compound **6c** could not be converted into the iodomethyl compound **6b** by treatment with hydrogen iodide or iodotrimethylsilane. The formation of compound **6c** indicates that a trimethylsilyloxy group from a second molecule of *N*-silyloxyenamine acts as the nucleophile. This implies that electrophilic catalysis is transmitted through two molecules of *N*-silyloxyenamine (see Scheme 5). This hypothesis was supported by the following observations: (i) The product distribution was unaffected by addition of an excess of iodide ions (as tetrabutylammonium iodide), (ii) the use of increasing amounts of iodotrimethylsilane caused increasing

* Throughout the manuscript the term pyrazole 1-oxide is used to refer to the pyrazolium-1-olate structure.

† pK_a of PMP is 11.25[9] while pK_a of 2,6-di-*tert*-butylpyridine is 3.58.[10] The pK_a of BTMP is not known but it may be too hindered to be able to abstract a proton from the silyloxypyrazole **2e**.

ratios between the iodomethyl compound **6b** and the trimethylsilyloxy compound **6c**, and (iii) this ratio decreased when the reaction mixture was diluted.

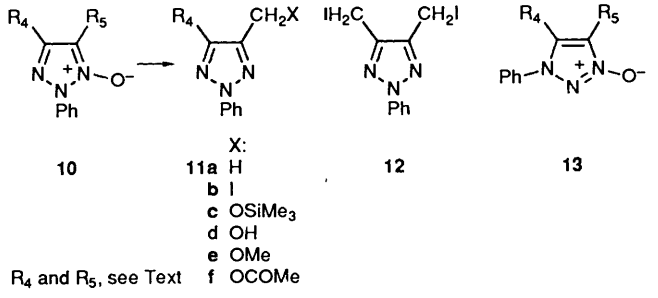
The relative reactivity of the exocyclic α-positions at C-3 and C-5, which can not be predicted by the donor–acceptor analysis,[1] was determined in a competition experiment in which a 1:1 mixture of the 3-methyl- **5** and the 5-methyl-pyrazole 1-oxide **1** was treated with iodotrimethylsilane and PMP demonstrating that the 3-methyl group reacts five times faster than does the 5-methyl group. As anticipated from the donor–acceptor analysis,[1] 2-benzyl-4-methylpyrazole 1-oxide **7** did not react at the methyl group but at the more reactive ring position to give 1-benzyl-3-iodo-4-methylpyrazole **8b** and 1-benzyl-3-hydroxy-4-methylpyrazole **8c**. In addition, debenzylation of **7** produced 1-hydroxy-4-methylpyrazole **9**.



7 9

Scheme 6

Treatment of 5-methyl-2-phenyl-1,2,3-triazole 1-oxide **10** (R_4 = H, R_5 = Me) with iodotrimethylsilane and PMP produced 4-iodomethyl-2-phenyl-1,2,3-triazole **11b** (R_4 = H). In addition, 2-phenyl-4-trimethylsilyloxymethyl-1,2,3-triazole **11c** (R_4 = H) was formed. The methyl group of 4-methyl-2-phenyl-1,2,3-triazole 1-oxide **10** (R_4 = Me, R_5 = H) and 5-chloro-4-methyl-2-phenyl-1,2,3-triazole 1-oxide **10** (R_4 = Me, R_5 = Cl) remained intact under similar conditions. The former compound reacted with loss of 5-H followed by addition of electrophile and formation of a *C*-silylated *N*-oxide (path d_2)[11] while the latter compound did not react at all.



Scheme 7

When 4,5-dimethyl-2-phenyl-1,2,3-triazole 1-oxide **10** (R_4 = R_5 = Me) was subjected to the conditions above, 4-iodomethyl-5-methyl-2-phenyl-1,2,3-triazole **11b** (R_4 = Me) and the 4-trimethylsilyloxymethyl compound **11c** (R_4 = Me) were formed together with small amounts of 4,5-di(iodomethyl)-2-phenyl-1,2,3-triazole **12** and 4,5-dimethyl-2-phenyl-1,2,3-triazole **11a** (R_4 = Me). The formation of the trimethylsilyloxymethyl compound **11c** (R_4 = Me) does not affect the value of the reaction in a preparative sense since it readily can be converted into the iodomethyltriazole **11b** (R_4 = Me) by treatment with hydrogen iodide.

Due to the above-mentioned inactivity of 4-methyl groups of 2-substituted triazole 1-oxides it is most likely that it is the 5-methyl group of the dimethyltriazole 1-oxide **10** (R_4 = R_5 = Me) which is transformed by the formation of the iodomethyl **11b** (R_4 = Me) and the trimethylsilyloxymethyl compound **11c** (R_4 = Me). The mechanism responsible for the formation of the di(iodomethyl)-1,2,3-triazole **12** is obscure. It is striking, however, that the product mixture contains a 1:1 mixture of 4,5-di(iodomethyl)-2-phenyl-1,2,3-triazole **12** and 4,5-dimethyl-2-phenyl-1,2,3-triazole **11a** (R_4 = Me). This ratio suggests that the initially formed 4-iodomethyl-5-methyl-2-phenyl-1,2,3-triazole **11b** (R_4 = Me) is oxidized to its *N*-oxide by unchanged starting material **10** (R_4 = R_5 = Me). Then the 5-methyl group of the 4-iodomethyl-5-methyl-2-phenyl-1,2,3-triazole 1-oxide **10** (R_4 = CH_2I, R_5 = Me) is transformed into an iodomethyl group in the usual way.

The fact that only 5-methyl groups in 2-substituted 1,2,3-triazole 1-oxides **10** react is in keeping with predictions based on the donor–acceptor analysis. 4- and 5-methyl groups in 3-substituted 1,2,3-triazole 1-oxides **13**, were also inactive in the a_5 type reactions as predicted by the donor–acceptor analysis. 3-Substituted 1,2,3-triazole 1-oxides **13** reacted exclusively with abstraction of ring protons followed by addition of electrophile in the d_2 fashion to give *C*-silylated *N*-oxides.[11]

The iodomethyl pyrazoles and triazoles are excellent starting materials for the preparation of side-chain substituted derivatives through classical nucleophilic substitution reactions. The reactivity was similar to that of benzyl iodide as shown by the reaction with the weak nucleophile potassium acetate in methanol solution.[12] Both **3d** and **11b** (R_4 = Me) reacted at 60 °C in 2.5 h producing good yields of the acetoxymethyl compounds **3g** and **11f** (R_4 = Me) together with small amounts of the methoxymethyl compounds **3e** and **11e** (R_4 = Me) formed by competing methanolysis.

Conclusion.—The present experiments demonstrate that iodine can be introduced in exocyclic α-positions attached to the immonium carbon atoms of pyrazole and 1,2,3-triazole *N*-oxides if treated with iodotrimethylsilane and 1,2,2,6,6-pentamethylpiperidine (PMP). The reaction is regioselective; substitution at ring carbon atoms is much slower and exocyclic α-positions attached to enammonium carbon atoms does not react at all. The higher reactivity of exocyclic α-positions attached to immonium carbon atoms than to enammonium carbon atoms agrees with predictions based on an extended donor–acceptor analysis.[1]

The iodomethyl compounds prepared are key intermediates useful for the preparation of heteroarylmethyl derivatives which are otherwise difficult to obtain since the iodine atom can be displaced with even weak nucleophiles such as an acetate ion.

Experimental

General.—Dichloromethane was dried over sodium hydride. Dimethylformamide (DMF) was dried as described in ref. 13. All reactions were performed using syringe techniques and screw cap sealed reaction vessels[14] in an atmosphere of nitrogen dried over phosphorus pentaoxide. For drying of solutions, magnesium sulfate was used unless otherwise stated. Solvents were removed under reduced pressure 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. 15. All new compounds were colourless, unless otherwise stated. The purity of all compounds was confirmed using m.p.s, thin layer chromatography (TLC), ^1H and ^{13}C NMR spectra recorded at 200 and 50.32 MHz, respectively, on a Bruker AC-200 instrument. NMR spectroscopic data are shown in Tables 1–4.

Preparation of Pyrazoles.—(*a*) A mixture of 1-benzyl-3-methylpyrazole **3a** and 1-benzyl-5-methylpyrazole **6a** suitable for later conversion to the corresponding *N*-oxides was prepared as follows: Conc. sulfuric acid (5.6 cm^3) was added slowly and cautiously with stirring and cooling in an ice bath to

Table 1 ^{1}H NMR spectroscopic data of 1-benzylpyrazoles, 2-benzylpyrazole 1-oxides and 1-OR substituted pyrazolium salts in $CDCl_3$ with tetramethylsilane as an internal standard

	δ_H						J/Hz	
Compound	3-H	4-H	5-H	C_6H_5	CH_2,[a] CH and OH	CH_3[b]	3-H, 4-H	4-H, 5-H
1	6.75	5.98		7.29–7.37	5.30	2.28	3.74	
2a[c]	7.90	6.52		7.40	5.59	2.52 OCH_3: 4.31	3.51	
2b	7.91	6.53		7.40	5.59	2.52	3.51	
2d	8.40	6.75		3 H: 7.37–7.41 2 H: 7.23–7.28	5.60	2.35 CCH_3: 1.34	3.5	
2e[d]	8.03	6.53		5 H: 7.19–7.33	5.49	2.39 $SiCH_3$: 0.42	3.58	
3a		6.05	7.25	7.20–7.34	5.25	2.30		2.21
3b		6.04	7.25	7.17–7.33	5.24	2.28 J_{HD}/Hz: 2.2		2.2
3c		6.54	7.51	3 H: 7.30–7.36 2 H: 7.19–7.24	5.29 CCH_2: 4.46 (s), 3.54 (q) CH: 4.05 (sept)	CCH_3: 1.43 (d), 1.43 (t)		2.3
3d		6.28	7.25	3 H: 7.28–7.33 2 H: 7.15–7.19	5.22 CCH_2: 4.41			2.3
3e		6.29	7.32	7.18–7.34	5.30 OCH_2: 4.49	OCH_3: 3.41		2.25
3f		6.29	7.32	7.18–7.34	5.29 OCH_2: 4.48			2.3
3g		6.31	7.32	3 H: 7.29–7.35 2 H: 7.18–7.23	5.29 OCH_2: 5.12			2.2
5		5.88	7.17	3 H: 7.29–7.33 2 H: 7.20–7.23	5.38	2.17		2.39
6a	7.46	6.07		3 H: 7.25–7.35 2 H: 7.06–7.11	5.30	2.21	1.80	
6b	7.46	6.31		3 H: 7.26–7.34 2 H: 7.13–7.18	5.41 CCH_2: 4.23		1.92	
6d	7.42	6.20		3 H: 7.23–7.31 2 H: 7.08–7.13	5.35 OCH_2: 4.52		1.84	
7	6.58		7.09	7.27–7.38	5.27	2.00		1.35
8a	7.33		7.12	3 H: 7.25–7.31 2 H: 7.16–7.19	5.21	2.04		*ca.* 0
8b			7.02	3 H: 7.30–7.36 2 H: 7.19–7.25	5.25	1.96		$J_{H\text{-}3,H\text{-}5}$: 0.8
8c			6.92	3 H: 7.30–7.35 2 H: 7.22–7.27	5.06 OH: 10.0 (br)	1.91		$J_{H\text{-}3,H\text{-}5}$: 0.8
9	7.19		7.00		OH: 8.8 (br)	CCH_3: 2.05		

[a] *N*-CH_2 when not otherwise stated. [b] CH_3 at the pyrazole ring when not otherwise stated. [c] As the tetrafluoroborate. [d] Prepared *in situ* from compound **1** and trimethylsilyltriflate.

a mixture of benzylhydrazine (12.2 g), ethanol (10 cm^3) and water (5 cm^3). 4,4-Dimethoxybutan-2-one (13.3 cm^3) was then added and the mixture heated to reflux for 2 h. Addition of sodium carbonate (12 g) and water (10 cm^3), stirring for 1 h, extraction with dichloromethane (3 × 15 cm^3), drying, and removal of the dichloromethane gave a residue which upon distillation afforded 13.4 g (78%) of a 1.6:1 mixture of 1-benzyl-3-methylpyrazole **3a** and 1-benzyl-5-methylpyrazole **6a**, b.p. 100–111 °C/1.5–2.0 mmHg.

(*b*) 1-Benzyl-3-methylpyrazole **3a** and 1-benzyl-5-methylpyrazole **6a** were prepared individually as follows. Benzylhydrazine (12.2 g) and conc. sulfuric acid (7.8 cm^3) were mixed slowly and

Table 2 ^{13}C NMR spectroscopic data of 1-benzylpyrazoles, 2-benzylpyrazole 1-oxides and 1-OR substituted pyrazolium salts in $CDCl_3$ with the solvent peak (δ 76.90) as an internal standard

	δ_C					J/Hz		
Compound	C-3 (C-1′)	C-4 (C-2′)	C-5 (C-3′)	CH_2[a] (C-4′)	CH_3[b] (CH)	C-3[c]	C-4[c]	C-5[c]
1	117.2 (134.4)	101.6 (128.2)	127.5 (128.8)	48.6 (128.2)	10.4	194.3 (4-H: 5.9) (CH_2: 3.0)	181.3 (3-H: 5.4) (CH_3: 3.5)	(3-H or 4-H: 6.9 and 5.3) (CH_3: 6.9)
2a[d]	132.3 (130.9)	105.7 (128.8)	141.7 (129.4)	53.3 (129.7)	10.2 OCH_3: 70.0	202.2 (4-H: 6.1) (CH_2: 3.1)	190.9 (3-H: 5.6) (CH_3: 3.8)	(3-H: 5.3) (4-H: 7.0) (CH_3: 7.0)
2b[d]	132.3 (130.9)	105.7 (128.8)	(129.4)	53.3 (129.7)	10.2			
2e[e]	131.1 (131.0)	105.3 (127.8)	140.4 (128.9)	52.4 (129.1)	10.8 $SiCH_3$: −0.7	202.1	190.2 (3-H: 5.5) (CH_3: 3.7)	(3-H: 5.4) (4-H: 6.9) (CH_3: 6.9)
3a	148.2 (136.5)	105.1 (127.1)	129.6 (128.3)	55.1 4.5 (127.4)	13.2	(5-H: 8.3) (4-H: 5.2) (CH_3: 6.5)	174.3 (5-H: 8.3) (CH_3: 3.3)	184.4 (4-H: 9.1) (2-H: 2.9)
3b	148.5 (136.8)	105.4 (127.4)	129.9 (128.6)	55.5 CH_2D: 13.2[f] (127.7)				
3c	140.4 (135.5)	109.4 (127.6)	131.3 (128.7)	56.2 53.7 52.3 (128.2)	16.4 16.2 10.2 (62.6)			
3d	149.7 (135.9)	105.7 (127.4)	130.4 (128.6)	55.8 CCH_2: −3.9 (127.9)		(4-H: 4.5) (5-H: 8.7) (CH_2: 4.3)	176.6 (5-H: 8.4) (CH_2: 3.8)	186.4 (3-H: 8.7) (NCH_2: 2.9)
3f	149.6 (136.4)	105.3 (127.5)	130.1 (128.7)	55.8 CCH_2: 68.0 (127.9)				
3g	147.3 (136.0) C=O: 170.7	106.1 (127.6)	130.2 (128.7)	55.8 OCH_2: 60.0 (128.0)	20.8	(4-H: 4.4) (5-H: 8.4)	176.9 (5-H: 8.6)	186.1 (4-H: 9.0)
5	128.2 (134.9)	99.5 (126.9)	118.5 (128.6)	45.2 (127.7)	12.0		181.1 (5-H: 7.3) (CH_3: 4.3)	195.4 (4-H: 7.5)
6a	137.9 (136.5)	105.2 (126.1)	137.6 128.1	52.2 4.5 (126.9)	10.5	183.7 (5-H: 5.3)	174.4 (3-H: 10.4) (CH_3: 3.5)	
6b	138.5 (136.0)	106.9 (126.8)	138.5 (128.8)	53.6 CCH_2: −9.3 (127.8)		186.2 4-H: 5.3	176.3 3-H: 10.4 CCH_2: 3.8	
6d	138.4 (136.8)	106.0 (126.8)	141.4 (128.6)	53.2 OCH_2: 55.2 (127.6)		185.4 4-H: 5.5	175.7 3-H: 10.3 OCH_2: 3.1	
7	116.6 (134.4)	111.7 (128.2)	119.8 (128.8)	48.2 (128.3)	9.6	192.7 (4-H or 5-H: 5.8 and 5.6) (CH_2: 2.9)	(3-H or 5-H: 6.7 and 4.8) (CH_3: 6.7)	193.9 (3-H: 4.7) (CH_3: 5.0)
8a	139.6 (136.7)	116.2 (127.3)	127.6 (128.5)	55.5 (127.8)	8.6	182.2 (5-H: 7.9) (CH_3: 4.5)	(3-H: 9.6) (5-H: 7.9) (CH_3: 6.4)	
8b	99.7 (135.9)	121.9 (127.7)	128.2 (128.7)	56.3 (128.1)	10.9	(5-H: 10.8) (CH_3: 5.4)	(5-H: 7.8) (CH_3: 6.8)	
8c	160.0 (135.7)	100.9 (127.9)	130.1 (128.7)	55.0 (128.1)	6.7			
9	130.3[g]	113.9	122.2[g]		9.0	185.8		191.1

[a] N-CH_2 when not otherwise stated. [b] C-CH_3 when not otherwise stated. [c] One bond couplings. Other couplings are given in parentheses indicating the proton to which the coupling takes place. [d] As the tetrafluoroborate. [e] Prepared *in situ* from compound **1** and trimethylsilyl triflate. [f] J_{CD} = 19.4 Hz. [g] The signal was assigned by comparison with those of 1-hydroxypyrazole, its 5-methyl- and its 5-chloromethyl derivative.[11]

Table 3 ^{1}H NMR spectroscopic data of 2-phenyl-1,2,3-triazoles in $CDCl_3$ with tetramethylsilane as an internal standard

Compound	δ_H 5-H	C_6H_5	CH_2 and OH	CH_3	J_{CH_3}/Hz
11b; R_4 = H	7.79	2 H: 8.01–8.07 2 H: 7.43–7.51 1 H: 7.30–7.38	4.51		5-H, CH_2: 0.3
11b; R_4 = Me		2 H: 7.94–8.00 2 H: 7.39–7.47 1 H: 7.25–7.33	4.45	2.34	
11d; R_4 = H	7.79	2 H: 8.00–8.06 2 H: 7.43–7.51 1 H: 7.30–7.38	4.87 OH: 2.35 (br)		
11d; R_4 = Me		2 H: 7.98–8.04 2 H: 7.42–7.50 1 H: 7.29–7.37	4.82 OH: 2.0 (br)	2.43	
11e; R_4 = Me		2 H: 7.99–8.06 2 H: 7.41–7.49 1 H: 7.27–7.35	4.59	2.42 OCH_3: 3.42	
11f; R_4 = Me		2 H: 7.98–8.04 2 H: 7.42–7.48 1 H: 7.25–7.33	5.22	2.40 $COCH_3$: 2.10	
12		2 H: 7.98–8.04 3 H: 7.30–7.52	4.53		

Table 4 ^{13}C NMR spectroscopic data of 2-phenyl-1,2,3-triazoles in $CDCl_3$ with the solvent signal (δ 76.90) as an internal standard

Compound	C-4 (C-1′)	C-5 (C-2′)	C-3′	CH_2 (C-4′)	CH_3
11b; R_4 = H	147.1 139.4	134.7 (118.7)	129.1	−9.7 (127.5)	
11b; R_4 = Me	144.5[a] (139.3)	143.8[a] (118.3)	129.1	−9.0 (127.0)	10.17
11d; R_4 = H	148.9 (139.6)	133.9 (118.7)	129.2	56.6 (127.4)	
11f; R_4 = Me	142.0 (139.4)	144.7 (118.3)	129.0	56.5 (127.0)	9.8 $COCH_3$: 20.6
12	144.7 (139.1)	144.7 (118.6)	129.2	−10.5 (127.7)	

[a] The assignments may have to be interchanged.

cautiously with stirring and cooling in an ice–salt bath. Methyl acetylpyruvate sodium salt (16.6 g),[16] methanol (10 cm^3) and water (5 cm^3) were then added, the mixture swirled regularly for 1 h and then heated to reflux with stirring for 2.5 h. Cooling to 20 °C, neutralization with 33% aqueous sodium hydroxide, removal of the methanol, addition of water (30 cm^3), extraction with dichloromethane (3 × 30 cm^3), drying, removal of the dichloromethane, and distillation gave 20.9 g (90%) of a 1:1.2 mixture (^{1}H NMR) of methyl 1-benzyl-3-methylpyrazole-5-carboxylate and methyl 1-benzyl-5-methylpyrazole-3-carboxylate, b.p. 125–200 °C/1 mmHg.

Redistillation using a Podbielniak Column[17] gave 8.0 g (34%) of methyl 1-benzyl-3-methyl-pyrazole-5-carboxylate, b.p. 135–149 °C/1 mmHg, δ_H($CDCl_3$) 7.34–7.35 (5 H, m, Ph), 6.64 (1 H, s, 4-H), 5.69 (2 H, s, N-CH_2), 3.82 (3 H, s, OMe) and 2.30 (3 H, s, CMe). The second fraction contained 8.9 g (38%) of methyl 1-benzyl-5-methylpyrazole-3-carboxylate, b.p. 168–171 °C/1 mmHg, δ_H($CDCl_3$) 7.28–7.32 and 7.09–7.12 (3 H + 2 H, m, Ph), 6.62 (1 H, s, 4-H), 5.38 (2 H, s N-CH_2), 3.92 (3 H, s, OMe) and 2.19 (3 H, s, CMe). In addition, 3.6 g of a 1:1.8 mixture of methyl 1-benzyl-3-methylpyrazole-5-carboxylate and methyl 1-benzyl-5-methylpyrazole-3-carboxylate, b.p. 150–167 °C/1 mmHg was collected.

Methyl 1-benzyl-3-methylpyrazole-5-carboxylate (8.0 g) was heated to reflux for 15 min with 33% aqueous sodium hydroxide (10 equiv.). Neutralization with conc. hydrochloric acid, extraction with dichloromethane (3 × 20 cm^3), drying and evaporation to dryness gave 1-benzyl-3-methylpyrazole-5-carboxylic acid which was heated in a bath to 250 °C for 2 h. The residue was ball tube-distilled at 14 mmHg (oven temperature 175 °C) to give 5.6 g (93%) of 1-benzyl-3-methylpyrazole[18] as an oil (Found: C, 76.5; H, 7.2; N, 16.0. $C_{11}H_{12}N_2$ requires C, 76.7; H, 7.0; N, 16.3%).

Similarly, methyl 1-benzyl-5-methylpyrazole-3-carboxylate produced (98%) of 1-benzyl-5-methylpyrazole[18] as an oil (Found: C, 76.7; H, 7.1; N, 16.3%).

Preparation of Pyrazole 1-Oxides.—Since the *N*-oxides **1** and **5** are easier to separate than the parent pyrazoles **3a** and **6a**. The *N*-oxides were best obtained as follows. A 1.6:1 mixture of 1-benzyl-3-methylpyrazole **3a** and 1-benzyl-5-methylpyrazole **6a** (12.0 g) was oxidized as described for the preparation of 2-benzylpyrazole 1-oxide.[19] The crude product (three batches) was flash chromatographed (3 cm column, ethyl acetate). The first fraction (R_f 0.76) contained 26.85 g (75%) of unchanged slightly impure starting material. Subsequent elution with ethyl acetate–methanol (1:1) gave 3.54 g (9%) of a 6:1 mixture of 2-benzyl-5-methylpyrazole 1-oxide **1** and 2-benzyl-3-methylpyrazole 1-oxide **5** (R_f 0.66) which was dissolved in boiling ethyl acetate (3.2 cm^3). Cooling and seeding with 2-benzyl-5-methylpyrazole 1-oxide **1** (obtained by oxidation of pure 1-benzyl-3-methylpyrazole **3a**), filtration, and washing with 0 °C ethyl acetate (2 × 1.1 cm^3) gave 2.47 g (6.3%) of 2-benzyl-5-methylpyrazole 1-oxide **1**, m.p. 115–116 °C (Found: C, 70.2; H, 6.5; N, 14.75. $C_{11}H_{12}N_2O$ requires C, 70.15; H, 6.4; N, 14.95%). The

volume of the combined mother liquor and washing phases was reduced to 0.80 cm^3. Cooling and seeding with 2-benzyl-3-methylpyrazole 1-oxide **5** (obtained by oxidation of pure 1-benzyl-5-methylpyrazole **6a**), filtration, and washing with 0 °C ethyl acetate (2 × 0.3 cm^3) gave 0.34 g (0.9%) of 2-benzyl-3-methylpyrazole 1-oxide **5**, m.p. 101 °C (Found: C, 70.45, H, 6.5; N, 14.7).

Similar oxidation of 1-benzyl-4-methylpyrazole **8a** (12.5 g) gave crude product which was flash chromatographed (column diameter 2 cm, ethyl acetate) to give 10.8 g (86%) of unchanged starting material. Subsequent elution with ethyl acetate–methanol (4:1, 100 cm^3) gave 0.58 g (4%) of 2-benzyl-4-methylpyrazole 1-oxide **7**, m.p. 47–52 °C (ethyl acetate). (The compound is hygroscopic and a correct elemental analysis could not be obtained. Found: C, 68.65; H, 6.55; N, 14.75. Calc. for $C_{11}H_{12}N_2O$: C, 70.15; H, 6.4; N, 14.95%).

Preparation of N-*Methoxy- and* N-*Acyloxy-azolium Salts.*—2-Benzyl-5-methylpyrazole 1-oxide **1** (632 mg), trimethyloxonium tetrafluoroborate (636 mg), and nitromethane (2.4 cm^3) were stirred for 2 h. Addition of methanol (0.1 cm^3), stirring for 1 h, removal of the solvents, washing with diethyl ether (5 × 5 cm^3) and with ethyl acetate (3 × 5 cm^3) afforded 780 mg (80%) of 2-benzyl-1-methoxy-5-methylpyrazolium tetrafluoroborate **2a**, m.p. 107–109 °C (Found: C, 49.55; H, 5.15; N, 9.6. $C_{12}H_{15}BF_4N_2O$ requires C, 49.7; H, 5.2; N, 9.65%).

[$^2H_3$]Methyl iodide (0.10 cm^3) was added with stirring at −50 °C to a mixture of 2-benzyl-5-methylpyrazole 1-oxide **1** (250 mg), silver tetrafluoroborate (254 mg), and nitromethane (1.5 cm^3). Stirring at −50 °C for 15 min and at 20 °C for 2 h, filtration through Celite 545, extracting the Celite with further nitromethane (5 × 1 cm^3), and evaporation to dryness gave 381 mg (99%) of 2-benzyl-1-trideuteriomethoxy-5-methylpyrazolium tetrafluoroborate **2b**, m.p. 108–110 °C. The ^1H and ^{13}C NMR spectroscopic data (Tables 1 and 2) corresponded to those of the protio analogue described above.

2,2-Dimethylpropanoyl chloride (0.175 cm^3) was added with stirring at −80 °C to a suspension of 2-benzyl-5-methylpyrazole 1-oxide **1** (219 mg), silver triflate (326 mg), and dichloromethane (3.0 cm^3). After stirring at −40 °C for 0.5 h and at 0 °C for 0.5 h the mixture was centrifuged. Decantation, extraction of the residue with further dichloromethane (3 × 2 cm^3), and removal of the dichloromethane afforded 490 mg (100%) of 2-benzyl-1-(2,2-dimethylpropanoyloxy)-5-methylpyrazolium triflate **2d**, m.p. 97–103 °C. The compound is unstable and a correct elemental analysis could not be obtained.

Deformylation of N-*Methoxyazolium Salts.*—2-Benzyl-3-trideuteriomethoxy-5-methylpyrazolium tetrafluoroborate **2b** (30 mg), DMF (0.6 cm^3), and diisopropylethylamine (0.020 cm^3) were stirred for 3 d. Evaporation to dryness, filtration through silica gel (5 g, column diameter 1 cm) eluting with 15 cm^3 of ethyl acetate–hexane (2:1), and evaporation to dryness gave 18 mg of a 33:1:1.3 mixture* (^1H NMR) of 1-benzyl-3-monodeuteriomethylpyrazole **3b**, 1-benzyl-3-methylpyrazole **3a**, and 1-benzyl-3-trideuteriomethoxymethylpyrazole **3f**. Preparative TLC [dichloromethane–diethyl ether–hexane (1:1:1)] afforded 1-benzyl-3-trideuteriomethoxymethylpyrazole **3f** (R_f 0.41) as an oil; *m/z* 205 (M^+, 3%), 173 (51, $M^+ - CD_2O$) and 91 (100). The ^1H and ^{13}C NMR spectroscopic data (Tables 1 and 2) corresponded to those of the protio analogue described below. The next fraction (R_f 0.73) contained a 33:1 mixture (^1H NMR) of 1-benzyl-3-monodeuteriomethylpyrazole **3b** and 1-benzyl-3-methylpyrazole **3a**. NMR spectroscopic data are given in Tables 1 and 2.

Reactions of Azole N-*Oxides with Iodotrimethylsilane.*—2-Benzyl-5-methylpyrazole 1-oxide **1** (56 mg), chloroform (1.4 cm^3), iodotrimethylsilane (0.16 cm^3) and 1,2,2,6,6-pentamethylpiperidine (0.17 cm^3) were heated to 50 °C for 4 h. Evaporation to dryness and filtration through silica gel (5 g, column diameter 1.5 cm), eluting with dichloromethane–diethyl ether–hexane (1:1:1; 45 cm^3), and removal of the solvents produced 66 mg (75%) of 1-benzyl-3-iodomethylpyrazole **3d**, m.p. 51–59 °C. Recrystallization (hexane) gave m.p. 70 °C (Found: C, 44.45; H, 3.7; N, 9.25. $C_{11}H_{11}IN_2$ requires C, 44.3; H, 3.7; N, 9.4%).

By using the same procedure replacing 1,2,2,6,6-pentamethylpiperidine with diisopropylethylamine, 2-benzyl-5-methylpyrazole 1-oxide **1** gave a 3:2 mixture of 1-benzyl-3-iodomethylpyrazole **3d** and ethyl(diisopropyl)(1-benzylpyrazol-3-ylmethyl)ammonium iodide **3c**. Using the same work up procedure, the column was eluted with methanol–ethyl acetate (1:4) (50 cm^3) and then with methanol–formic acid (9:1) (75 cm^3). The latter eluate was evaporated to dryness. Addition of 2 mol dm^{-3} sodium hydroxide (3 cm^3), removal of the water, extraction with dichloromethane (10 × 3 cm^3), removal of the dichloromethane, dissolution in water (2 cm^3), addition of 0.25 mol dm^{-3} sodium tetraphenylboronate (2 cm^3), centrifugation, decantation, washing with water (2 × 3 cm^3), drying, and recrystallization (ethyl acetate–acetone) gave ethyl(diisopropyl)(1-benzylpyrazol-3-ylmethyl)ammonium tetraphenylboronate **3c** ($Y^- = Ph_4B^-$) m.p. 178–179 °C (Found: C, 83.25; H, 8.2; N, 6.7. $C_{43}H_{30}BN_3$ requires C, 83.35; H, 8.15; N, 6.8%).

2-Benzyl-3-methylpyrazole 1-oxide **5** (87 mg), chloroform (1.5 cm^3), iodotrimethylsilane (0.25 cm^3), and 1,2,2,6,6-pentamethylpiperidine (0.25 cm^3) were heated to 50 °C for 1.5 h. Evaporation to dryness, addition of aqueous hydrogen iodide (57%, 0.5 cm^3), stirring at 20 °C for 1 h, addition of 2 mol dm^{-3} aqueous sodium hydroxide to pH 5, extraction with dichloromethane (5 × 3 cm^3), addition of 2 mol dm^{-3} sodium hydroxide to pH 12, extraction with dichloromethane (5 × 3 cm^3), drying of the combined organic solutions, removal of the dichloromethane, filtration through silica gel (5 g, column diameter 1 cm), elution with dichloromethane–diethyl ether–hexane (1:1:1; 35 cm^3), and removal of the solvents afforded 76 mg (56%) of 1-benzyl-5-iodomethylpyrazole **6b** as an oil. Low temperature recrystallization (ether–hexane) gave a product with m.p. *ca.* 5 °C (Found: C, 44.25; H, 3.75. $C_{11}H_{11}IN_2$ requires C, 44.3; H, 3.7%). The compound is unstable and should be kept in a refrigerator. Further elution with dichloromethane–ether (1:1) (50 cm^3) gave 27 mg (31%) of 1-benzyl-5-hydroxymethylpyrazole **6d** as an oil. Low temperature recrystallization (ethyl acetate–hexane) gave m.p. 36 °C (Found: C, 70.05; H, 6.45; N, 15.05. $C_{11}H_{12}NO$ requires C, 70.15; H, 6.4; N, 14.95%).

The ratio between 1-benzyl-5-iodomethylpyrazole **6b** and 1-benzyl-5-hydroxymethylpyrazole **6d** in the crude mixture was 1.37:1 (^1H NMR). This ratio increased to 1.67:1 when the amount of iodotrimethylsilane was increased by 2.5 times.

Competition experiment. 2-Benzyl-3-methylpyrazole 1-oxide **5** (18 mg), 2-benzyl-5-methylpyrazole 1-oxide **1** (18 mg), deuteriochloroform (0.5 cm^3), iodotrimethylsilane (0.025 cm^3) and 1,2,2,6,6-pentamethylpiperidine (0.021 cm^3) were heated to 50 °C for 10 min. An NMR spectrum showed 25% conversion of the 2-benzyl-3-methylpyrazole 1-oxide **5** and 5% conversion of the 2-benzyl-5-methylpyrazole 1-oxide **1**. The products were identical with those formed when **5** and **1** were treated separately with iodotrimethylsilane and PMP (see above).

2-Benzyl-4-methylpyrazole 1-oxide **7** (86 mg), chloroform (1.0 cm^3), iodotrimethylsilane (0.25 cm^3), and 1,2,2,6,6-pentamethylpiperidine (0.25 cm^3) were heated to 70 °C for 5 h. The reaction mixture containing a 1:1.5:1.4 mixture (^1H NMR) of

* If the reaction was performed in dichloromethane the ratio changed to 29:1:33, while in chloroform the ratio was 50:1:29.

1-benzyl-3-iodo-4-methylpyrazole **8b**, 1-benzyl-4-methylpyrazol-3-ol **8c**, and 4-methylpyrazol-1-ol **9** was filtered through silica gel (5 g, 1 cm column diameter) eluting with dichloromethane–diethyl ether–hexane (1:1:1) (35 cm^3). Removal of the solvents and preparative TLC (dichloromethane–diethyl ether–hexane (1:1:8) gave 31 mg (23%) of 1-benzyl-3-iodo-4-methylpyrazole **8b** (R_f 0.55); *m/z* 298 (M^+, 51%), 91 (100). Elution of the column with dichloromethane–diethyl ether (1:1) gave 1-benzyl-4-methylpyrazol-3-ol **8c** which was crystallized from ethyl acetate–hexane, m.p. 143–147 °C, *m/z* 188 (M^+, 50%) and 91 (100). The mother liquor was evaporated to dryness. Addition of 1 mol dm^{-3} phosphate buffer pH 11 (5 cm^3), washing with chloroform (3 × 1 cm^3), addition of 4 mol dm^{-3} hydrochloric acid to pH 6, and continuous extraction with dichloromethane–diethyl ether (1:2) for 18 h gave 4-methylpyrazol-1-ol **9** as an oil; *m/z* 98 (M^+, 100%).

5-Methyl-2-phenyltriazole 1-oxide **10** (R_4 = H, R_5 = Me) (203 mg), chloroform (2.0 cm^3), iodotrimethylsilane (0.63 cm^3), and PMP (0.63 cm^3) were heated to 70 °C for 3.5 h. Addition of aqueous hydrogen iodide (57%, 2.0 cm^3), stirring for 0.5 h, addition of water (5 cm^3) and 2 mol dm^{-3} aqueous sodium hydroxide to pH 5, extraction with dichloromethane (5 × 5 cm^3), addition of 2 mol dm^{-3} sodium hydroxide to pH 12, extraction with dichloromethane (5 × 5 cm^3), drying of the combined organic solutions, removal of the dichloromethane, filtration through silica gel (5 g, column diameter 1 cm) eluting with dichloromethane–diethyl ether–hexane (1:1:8) (35 cm^3), evaporation to dryness, and preparative TLC gave 129 mg (39%) of 4-iodomethyl-2-phenyl-1,2,3-triazole **11b** (R_4 = H) (R_f 0.55). Low temperature recrystallization (hexane) gave m.p. 71 °C (Found: C, 38.1; H, 2.9; N, 14.75. $C_9H_8IN_3$ requires C, 37.9; H, 2.85; N, 14.75%). Subsequent elution of the column with dichloromethane–diethyl ether–hexane (1:1:1) (40 cm^3), evaporation to dryness, and preparative TLC gave 4-hydroxymethyl-2-phenyl-1,2,3-triazole **11d** (R_4 = H) (R_f 0.50) which was dissolved in ether and filtrated through activated carbon. Yield 39 mg (19%). Recrystallization (ethyl acetate–hexane) gave m.p. 68–69 °C (Found: C, 61.8; H, 5.25; N, 23.85. $C_9H_9N_3O$ requires C, 61.7; H, 5.2; N, 24.0%).

4,5-Dimethyl-2-phenyltriazole 1-oxide **10** (R_4 = R_5 = Me) (55 mg), chloroform (1.2 cm^3), iodotrimethylsilane (0.16 cm^3) and 1,2,2,6,6-pentamethylpiperidine (0.16 cm^3) were heated to 50 °C for 2 h. Evaporation to dryness and filtration through silica gel (5 g, 1.5 cm column), eluting with dichloromethane–diethyl ether–hexane (1:1:1; 50 cm^3), and removal of the solvent afforded 85 mg of a brown oil containing 4-iodomethyl-5-methyl-2-phenyltriazole **11b** (R_4 = Me), 5-methyl-2-phenyl-4-trimethylsilyloxytriazole **11c** (R_4 = Me), 4,5-iodomethyl-2-phenyltriazole **12** and 4,5-methyl-2-phenyltriazole **11a**; (R_4 = Me). To this mixture was added chloroform (2 cm^3), tetrabutylammonium iodide (10 mg) and 67% hydroiodic acid (0.20 cm^3). Heating to 70 °C for 6 h, addition of water (5 cm^3), and extraction with dichloromethane (3 × 5 cm^3), drying, removal of the dichloromethane, filtration through silica gel (5 g, 1.5 cm column), eluting with dichloromethane–diethyl ether–hexane (1:1:1; 40 cm^3), and removal of the solvents gave 87 mg of an oil containing **11b** (R_4 = Me), **12** and **11a** (R_4 = Me) in the ratio 9.1:1:1.1. Preparative TLC (dichloromethane–diethyl ether–hexane (1:1:15) gave 5.0 mg (10%) of 4,5-methyl-2-phenyltriazole **11a** (R_4 = Me) (R_f = 0.56), identical with an authentic sample,[20] and 59 mg (68%) of 4-iodomethyl-5-methyl-2-phenyltriazole **11b** (R_4 = Me) (R_f 0.61), m.p. 80 °C. Recrystallization from hexane gave m.p. 81 °C (Found: C, 40.25; H, 3.4; N, 14.0. $C_{10}H_{10}IN_3$ requires C, 40.15; H, 3.35; N, 14.05%). The third fraction (R_f 0.69) contained 11.1 mg (9%) of 4,5-iodomethyl-2-phenyltriazole **12**, m.p. 104–107 °C; recrystallization (hexane) gave m.p. 122 °C (Found: C, 28.55; H, 1.95; N, 10.05. $C_{10}H_9I_2N_3$ requires C, 28.25; H, 2.15; N, 9.9%).

Nucleophilic Displacement.—1-Benzyl-3-iodomethylpyrazole **3d** (64 mg), potassium acetate (69 mg) and methanol (0.5 cm^3) were heated to 60 °C for 2.5 h. This gave a 4:1 mixture of 3-acetoxymethyl-1-benzylpyrazole **3g** and 1-benzyl-3-methoxymethylpyrazole **3e** (^{1}H NMR) which was separated by preparative TLC (dichloromethane–diethyl ether–hexane, 3:3:2) to give 39 mg (79%) of 3-acetoxymethyl-1-benzylpyrazole **3g** (R_f 0.62). Reprecipitation (ethyl acetate–hexane) gave m.p. 41–42 °C (Found: C, 67.95; H, 6.2; N, 12.0. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.15%). The next fraction contained 9 mg (20%) of 1-benzyl-3-methoxymethylpyrazole **3e** (R_f 0.44).

Similarly, 4-iodomethyl-5-methyl-2-phenyltriazole **11b** (R_4 = Me) gave a 10:1.1:1 mixture (^{1}H NMR) of 4-acetoxymethyl-5-methyl-2-phenyltriazole **11f** (R_4 = Me), 4-hydroxymethyl-5-methyl-2-phenyltriazole **11d** (R_4 = Me), and 4-methoxymethyl-5-methyl-2-phenyltriazole **11e** (R_4 = Me). Hydrolysis (1 mol dm^{-3} sodium hydroxide in 50% aqueous methanol, 100 °C, 3 h, removal of the methanol, extraction with dichloromethane) and preparative TLC (dichloromethane–diethyl ether–hexane, 1:1:4) gave 24 mg of (90%) of 4-hydroxymethyl-5-methyl-2-phenyl-1,2,3-triazole **11d** (R_4 = Me) (R_f 0.17), m.p. 78 °C (ethyl acetate–hexane) (Found: C, 63.4; H, 5.85; N, 21.95. $C_{10}H_{11}N_3O$ requires C, 63.5; H, 5.85; N, 22.2%). The next fraction contained 2.4 mg (8%) of 4-methoxymethyl-5-methyl-2-phenyl-1,2,3-triazole **11e** (R_4 = Me) (R_f 0.69) as an oil; *m/z* 203 (93%, M^+) and 172 (100). In order to get the acetoxymethyltriazole **11f** (R_4 = Me) in the pure state, the hydroxymethyltriazole **11e** (R_4 = Me) (55 mg), chloroform (0.5 cm^3), and acetyl chloride (0.042 cm^3) were stirred for 18 h. Evaporation to dryness, filtration through silica gel (5 g, column diameter 1 cm) eluting with dichloromethane–diethyl ether–hexane (1:1:1) (40 cm^3) and removal of the solvents afforded 65 mg (96%) 4-acetoxymethyl-5-methyl-2-phenyl-1,2,3-triazole **11f** (R_4 = Me), m.p. 42 °C (low temperature recrystallization, hexane) (Found: C, 62.3; H, 5.75; N, 18.0. $C_{12}H_{13}N_3O_2$ requires C, 62.35; H, 5.65; N, 18.15%).

Acknowledgements

This work was supported by the Danish Council for Technical and Scientific Research. P. V. thanks the Technical University of Denmark for a grant. The NMR spectrometer is a gift from the Velux Foundation of 1981, The Danish Council for Technical and Scientific Research, The Ib Henriksen Foundation and the Torkil Steenbeck Foundation. Microanalyses were performed by LEO Pharmaceutical Products. Thanks are due to Dr. J. Øgaard Madsen for the mass spectra.

References

1 M. Begtrup, *Heterocycles*, 1992, **33**, 1129.
2 M. Begtrup and J. Holm, *J. Chem. Soc., Perkin Trans. 1*, 1981, 503.
3 M. Begtrup, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2749.
4 W. N. Marmer and D. Swern, *J. Am. Chem. Soc.*, 1971, **93**, 2719.
5 V. J. Traynelis and J. P. Kimball, *J. Org. Chem.*, 1975, **40**, 2365.
6 H. Sliwa and A. Tartar, *Tetrahedron*, 1977, **33**, 3111.
7 R. A. Abramovitch, S. Kato and G. M. Singer, *J. Am. Chem. Soc.*, 1971, **93**, 3074.
8 H. Emde, D. Domsch, H. Feger, U. Frick, A. Götz, H. H. Hergott, K. Hofmann, W. Kober, K. Krägeloh, T. Oesterle, W. Steppan, W. West and G. Simchen, *Synthesis*, 1982, **84**, 1.
9 H. K. Hall, *J. Am. Chem. Soc.*, 1957, **79**, 5444.
10 H. C. Brown and B. Kanner, *J. Am. Chem. Soc.*, 1966, **88**, 986.
11 M. Begtrup and P. Vedsø, to be published.
12 R. G. Pearson, H. Sobel and I. Songstad, *J. Am. Chem. Soc.*, 1968, **90**, 319.
13 D. R. Burfield and R. H. Smithers, *J. Org. Chem.*, 1978, **43**, 3966.
14 M. Begtrup, *J. Chem. Educ.*, 1987, **64**, 974.

15 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
16 E. Berner and S. Laland, *Acta Chem. Scand.*, 1949, **3**, 335.
17 J. Cason and H. Rapoport, *Laboratory Texts in Organic Chemistry*, Prentice-Hall, New York, 1962, p. 237.
18 K. von Auwers and H. Hollmann, *Chem. Ber.*, 1926, **59**, 1282.
19 M. Begtrup, P. Larsen and P. Vedsø, *Acta Chem. Scand.*, in the press.
20 H. von Pechmann, *Chem. Ber.*, 1888, **21**, 2751.

Paper 2/01289H
Received 10*th March* 1992
Accepted 3*rd June* 1992