Generation and Reactions of *N*-(α-Lithioalkyl)tetrazoles

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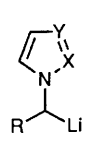
Treatment of 1-alkyl-**4** and 2-alkyl-5-phenyltetrazoles **10** with t-butyllithium in tetrahydrofuran at −78 °C gives 'dipole-stabilised' α-lithioalkyl derivatives **2** and **3** which are readily converted into the corresponding deuteriated, silylated, alkylated, hydroxymethylated, acylated and carboxylated derivatives **5** and **11**, mostly in high yield (Tables 1 and 2). Lithiation of 5-phenyl-2-trimethylsilylmethyltetrazole **10c**, prepared in this way, followed by reaction with aldehydes results in Peterson olefination to give 2-alkenyltetrazoles **11g, h** in good yield.

The generation and reactions of 'dipole-stabilised' carbanions, possibly better described as dipole-stabilised organometallics,[1] is a subject of considerable interest, both from the practical and theoretical points of view.[2] In heteroaromatic chemistry, whilst lithiation of *N*-methyl-, ethyl- and benzyl- groups in suitably substituted pyrazoles occurs readily,[3] lithiation of *N*-methylimidazoles occurs on the ring,[4] although *N*-benzylimidazoles can be metallated on the benzylic carbon.[5] Hence the presence of a second pyridine-type nitrogen adjacent to the pyrrole-type nitrogen greatly facilitates the deprotonation of the *N*-alkyl group, *viz* **1**(X = N, Y = CR) *vs.* **1**(X = CR, Y = N). In accord with this, the metallation of simple *N*-methyl-pyrroles or



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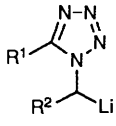

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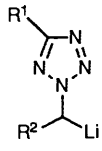


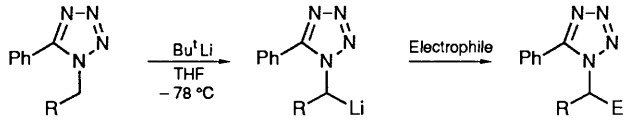
3

-indoles appears to be unknown, although lithiation at the *N*-methyl group does occur with 2-formylindoles condensed, *in situ*, with trimethylethylenediamine.[6] Since we were interested in the preparation and reactions of tetrazoles,[7] we decided to investigate the generation and reactions of simple 1- and 2-lithioalkyltetrazoles **2** and **3**, as a route to more complex, functionalised, derivatives and we now report our results in full.[8]

Results and Discussion

The (patent) literature contains only one example of a lithioalkyltetrazole: treatment of 1-methyltetrazole-5-thiol with an excess of butyllithium followed by quenching with carbon dioxide gave 5-mercaptotetrazol-1-ylacetic acid.[9] With 1-alkyl-5-phenyltetrazoles, prepared by alkylation of 5-phenyltetrazole by standard methods[10] followed by separation of the 2-alkyl isomer, we found that the use of butyllithium as base led to incorporation of a butyl group in the product, presumably as a result of nucleophilic attack on the tetrazole ring. However, treatment of 1-methyl-5-phenyltetrazole **4a** with t-butyllithium at −78 °C in tetrahydrofuran (THF) resulted in an immediate cherry-red coloration, which was discharged by the addition of D_2O to give, after work-up, the deuteriated compound **5a** in excellent yield. One possible concern was that the tetrazole group might direct lithiation to the *ortho*-position of the 5-phenyl ring in preference to the desired metallation of the 1-methyl group. However, we observed no evidence for this since the 1-lithioalkyl species was apparently stable, with no evidence for rearrangement on warming to −23 °C or, briefly, to 0 °C. The

Table 1 Generation and reactions of 1-lithioalkyl-5-phenyltetrazoles



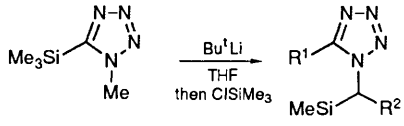
4 **5**

4	R	Electrophile	5	E (in product)	Yield (%)
a	H	D_2O	**a**	D	96
a	H	Me_3SiCl	**b**	Me_3Si	96
a	H	Me_2SO_4	**c**	Me	90
a	H	Ar_2CO	**d**	CAr_2OH	84
b	Ar	Ar_2CO	**e**	CAr_2OH	95
b	Ar	ArCHO	**f**	CH(OH)Ar	87
b	Ar	ArCN	**g**	COAr	80

Ar = *P*-tolyl.

trimethylsilyl derivative **5b** was also prepared in high yield, although inverse addition of the anion to the quench was necessary. The lithioalkyltetrazoles could be methylated, and they reacted readily with aromatic ketones, aldehydes and nitriles to give the corresponding substituted tetrazoles **5** all in very good yield (Table 1). Ketones such as acetophenones did not react because of competing enolisation.

We know little about the precise structure of the 1-lithioalkyl-5-phenyltetrazole in solution, and whether the 5-phenyl group plays any role in stabilising the anion. The use of the trimethylsilyl group as an alternative 5-substitutent was briefly

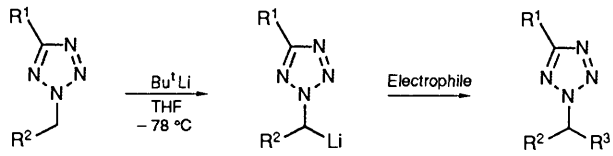


6

7 R^1 = H, R^2 = $SiMe_3$
8 R^1 = $SiMe_3$, R^2 = H
9 R^1 = R^2 = $SiMe_3$

investigated. 1-Methyl-5-trimethylsilyltetrazole **6** was prepared as the major product (43%) by 5-lithiation and trimethylsilylation of 1-methyltetrazole, along with trimethylsilyl-(5-trimethylsilyltetrazol-1-yl)methane **8** and tetrazol-1-yl(bistrimethylsilyl)methane **7**. Lithiation of the tetrazole **6** resulted in the formation of an orange–brown solution of the anion, quenching of which with trimethylsilyl chloride gave bistrimethylsilyl(5-trimethylsilyltetrazol-1-yl)methane **9** as the major product (36%), together with the tetrazoles **8** (5%) and **7** (5%). This product mixture reflects the transmetallation that

Table 2 Generation and reactions of 2-lithioalkyltetrazoles



10 **11**

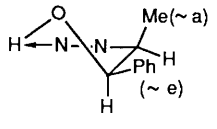
10	R^1	R^2	Electrophile	11	R^2,R^3 in product	Yield (%)
a	Ph	H	Me_3SiCl	**a**	H,$SiMe_3$	70
a	Ph	H	HCHO	**b**	H,CH_2OH	33
a	Ph	H	EtCHO	**c**	H,CH(OH)Et	85
a	Ph	H	ArCHO	**d**	H,CH(OH)Ar	77[a,e]
b	Ph	Me	CO_2	**e**	Me,CO_2H	53
b	Ph	Me	PhCHO	**f**	Me,CH(OH)Ph	98[b]
c	Ph	$SiMe_3$	EtCHO	**g**	=CHEt	68[c]
c	Ph	$SiMe_3$	Bu^tCHO	**h**	=CHBu^t	88[d]
d	PhS	H	ArCHO	**i**	H,CH(OH)Ar	57[a,e]
e	H_2NCH_2	H	ArCHO	**j**	H,CH(OH)Ar	37[a]
f	Me_3Si	Et	Me_3SiCl	**k**	Et,$SiMe_3$	51[e]

Notes: *a* Ar = 4-$MeOC_6H_4$. [b] Mixture of diastereoisomers. [c] *E*/*Z* Mixture. [d] *E*-Alkene. [e] Yield based on NMR.

must occur in the reaction mixture, since presumably the methylene group in **8** is more acidic than the methyl group in the starting tetrazole **6**.

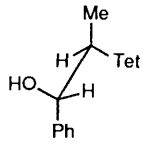
Lithiation of 2-alkyl-5-phenyltetrazoles also proceeded smoothly. Thus addition of t-butyllithium to a THF solution of 2-methyl-5-phenyltetrazole **10a** at −78 °C produced an instantaneous red–orange colour which persisted indefinitely at this temperature. The colour was discharged on adding the solution to trimethylsilyl chloride in THF, and work-up gave the trimethylsilylmethyl derivative **11a** in good yield. Similarly 2-methyl-**10a** and 2-ethyl-5-phenyltetrazole **10b** reacted with a range of electrophiles to give the corresponding substituted derivatives **11b–f** (Table 2). Thus reaction with formaldehyde, propionaldehyde, anisaldehyde and carbon dioxide all proceeded smoothly. Reaction of the anion from 2-ethyl-5-phenyltetrazole **10b** with benzaldehyde leads to a mixture of diastereoisomers, although the reaction shows little selectivity. The major isomer (57:43) is assigned the relative configuration **12** on the basis of its spectroscopic properties.

Product **12** is capable of intramolecular H-bonding between the hydroxy proton and the lone pair of either N-1 or N-3. This arrangement gives a (favoured) 6-membered ring which, however, contains a methyl and a phenyl group in a *cis*-relationship. The twist–boat form of such a ring **12a**, which contains two sp^2 atoms, allows only one of these groups to occupy the preferred pseudo-equatorial position. In the minor



12a

diastereoisomer it is, of course, possible for both groups to occupy pseudo-equatorial positions. These postulates are supported by the greater polarity of the major (*R*,*S*)-/(*S*,*R*)-diastereoisomer during chromatography on silica, the H-bonded OH absorption in the IR [3400 cm^{-1}(br)], and the upfield shift in the NMR spectrum of both the hydroxy proton ($\Delta\delta$ −0.47 ppm) and the methyl protons ($\Delta\delta$ −0.17 ppm) relative to the other diastereoisomer. The NMR effect is attributable to the anisotropy of the aromatic tetrazole and phenyl rings against which the hydroxy and methyl protons lie for a proportion of the NMR time-scale.



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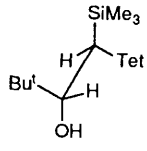

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Lithiation of 5-phenyl-2-trimethylsilylmethyltetrazole, **10c** = **11a**, prepared as above, followed by reaction with aldehydes resulted in Peterson olefination and the formation of the 2-alkenyltetrazoles **11g, h** in good yield. The alkenyltetrazole **11g** was formed as a mixture of *E*- and *Z*-isomers in the ratio of 3:2. Since elimination from the β-hydroxysilanes is thought to be stereospecific in the Peterson reaction,[11] the *E*/*Z* ratio reflects the ratio of diastereoisomers formed in the initial attack of the lithiated tetrazole on the aldehyde. The bulkier pivaldehyde, not surprisingly, results in greater diastereoselectivity, with formation, as the major product, of the intermediate alcohol **13** which was not isolated since under the acidic work-up conditions it immediately gave the alkene **11h** (88%) as a single *E* isomer. A small amount (7%) of the diastereoisomer of **13** was also isolated, but this did not undergo acid-catalysed elimination to the *Z* isomer of **11h** even under forcing conditions.

Lithiations of 2-alkyltetrazoles containing groups other than phenyl at the 5-position were generally less satisfactory, although the 5-phenylthio, -aminomethyl and -trimethylsilyl tetrazoles **10d, e, f** did give some of the desired products (Table 2). When the 5-position was unsubstituted, lithiation occurred on the tetrazole ring itself.

Again, little is known about the structure of the lithiated species, although our limited results suggest that the 2-alkyltetrazoles are more acidic than the 1-isomers. Hence the 1-lithioalkyl species are less stabilised and more nucleophilic. This apparent difference between 1- and 2-alkyltetrazoles is paralleled by the chemical shifts of the methyl groups; the 2-methyl groups resonate at much lower field than the corresponding 1-methyl compounds implying a lower electron density on N-2.

In summary, the α-lithiation of alkyltetrazoles and their subsequent reaction with electrophiles opens up a new route to

substituted tetrazoles which are versatile intermediates in heterocyclic synthesis.[7,10]

Experimental

All solvents were distilled before use. Petroleum refers to light petroleum, b.p. 40–60 °C, and ether refers to diethyl ether. THF and ether were distilled from potassium-benzophenone and sodium-potassium-benzophenone respectively, immediately prior to use. Other solvents were purified and dried by standard procedures.

Lithiations were undertaken in magnetically stirred, oven-dried flasks closed with a rubber septum. The flasks were flushed with dry nitrogen before use and experiments were carried out under positive pressure of nitrogen. Additions and transfers were carried out with oven-dried glass syringes and stainless steel needles as required. Pressure equilibration with dry nitrogen was maintained at all times. Thin layer chromatography (TLC) on commercial plates of silia gel 60 F_{254} on aluminium was used to monitor the progress of reactions. Column chromatography was carried out using silica gel 60H (E. Merck).

IR spectra was recorded on a Perkin-Elmer 298 spectrophotometer in the range 600–4000 cm^{-1} and calibrated against polystyrene. The spectra of solids were recorded as Nujol mulls and of oils as thin films between sodium chloride plates.

UV spectra were recorded in the range 200–450 nm on a Pye Unicam SP800 spectrophotometer in quartz cells of 0.5 path length. Unless otherwise stated the solvent was methanol.

Proton NMR spectra were recorded on one of three instruments as follows: Varian Associates EM-360 (60 MHz), Perkin-Elmer R32 (90 MHz) and Bruker WM 250 (250 MHz) according to the frequency specified. Tetramethylsilane (TMS) was used as an internal reference. Carbon-13 spectra were recorded on the Bruker instrument operating at 62.9 MHz. *J* values are recorded in Hz. Mass spectra were recorded on a VG Micromass 7070B mass spectrometer. An ionising potential of 70 or 12 eV was employed using a direct insertion probe or septum inlet.

N-*Alkyltetrazoles: Lithiation and Condensation with Electrophiles: General Procedure.*—To a solution of the tetrazole **4** or **10** (1.0 equiv.) in THF (4–10 ml per mmol) at −78 °C was added dropwise a 1.85M solution of t-butyllithium in pentane (1.2 equiv.) and the whole stirred 0.5 h at −78 °C. The electrophile (1.2 equiv.) was added neat and the solution allowed to warm to 20 °C (*Peterson reactions:* satd. aq. ammonium chloride was added at −78 °C) when the red colour of the anion had been discharged. Ether (5 volumes) was added and the organic layer washed successively with dil. aq. hydrochloric acid, aq. sodium hydrogen carbonate and water and dried ($MgSO_4$). The solvent was removed and the residue was chromatographed on silica gel with petroleum containing an increasing proportion of ether as eluant. Where necessary ether containing an increasing proportion of methanol was subsequently employed.

1-*Alkyltetrazoles.*—*Reaction of tetrazole* **4a** *with deuterium oxide.* To a solution of tetrazole **4a** (136.7 mg, 0.85 mmol) in THF (3 ml) at −100 °C (CO_2–ether bath) was added t-butyllithium in pentane (0.94 mmol, 1.1 equiv.) to give a dark red colour. After 0.2 h a solution of deuterium oxide (0.3 ml, 16.6 mmol, 20 equiv.) in THF (3 ml) was added to leave a pale yellow solution with a faint white precipitate; warming of this to 20 °C and work-up gave 5-phenyltetrazol-1-yldeuteriomethane **5a** (131.7 mg, 96%); δ(60 MHz, $CDCl_3$) 4.19 (2 H, ≃t, *J* ≃1.5) and 7.63 (5 H, m).

Reaction of the tetrazole **4a** *with chlorotrimethylsilane.* To a solution of the tetrazole **4a** (1.467 g, 9.16 mmol) in THF (45 ml) was added t-butyllithium in pentane (9.34 mmol, 1.02 equiv.). After 1.5 h the dark red suspension (there was some precipitation at this concentration) was added to a solution of chlorotrimethylsilane (5.81 ml, 45.8 mmol, 5.0 equiv.) in THF (5 ml) and stirred 0.3 h. The mixture was allowed to warm to 20 °C and the solvent largely removed by evaporation, when addition of ether (40 ml) caused the product to crystallise. Filtration gave 5-phenyltetrazol-1-yl(trimethylsilyl)methane **5b** (2.034 g, 96%), m.p. 66–68 °C (chloroform–petroleum) (Found: C, 57.1; H, 6.9; N, 24.1. $C_{11}H_{16}N_4Si$ requires C, 56.9; H, 6.9; N, 24.1%); ν_{max}/cm^{-1} 3060, 1530, 1295, 1250s, 865s, 785, 735 and 700; δ(60 MHz, $CDCl_3$) 0.10 (9 H, s), 3.86 (2 H, s) and 7.82–7.49 (5 H, m); *m/z* 232 (M^+), 217, 176, 161, 145, 103, 86, 73 (base) and 59.

Reaction of the tetrazole **4a** *with dimethyl sulphate.* To a solution of the tetrazole **4a** (682 mg, 4.26 mmol) in THF (40 ml) was added t-butyllithium in pentane (4.68 mmol). Dimethyl sulphate (0.444 ml, 4.68 mmol) was added and after 0.75 h the mixture was warmed to −23 °C and stirred for 0.5 h. Work-up and recrystallisation from ethanol gave 5-phenyltetrazol-1-ylethane **5c** (668 mg, 90%), m.p. 70–71 °C (lit.,[12] m.p. 70–71 °C).

Reaction of the tetrazole **4a** *with* 4,4′-*dimethylbenzophenone.* To a solution of the tetrazole **4a** (55.5 mg, 0.35 mmol) in THF (3 ml) at −98 °C were added t-butyllithium in pentane (0.38 mmol) and after 0.2 h a solution of 4,4′-dimethylbenzophenone (80.0 mg, 0.38 mmol) in THF (3 ml). The mixture was stirred 0.75 h and allowed to warm to 20 °C at which temperature it was stirred for 16 h. Work-up and chromatography gave 1,1-bis(*p*-tolyl)-2-(5-phenyltetrazol-1-yl)ethanol **5d** (108 mg, 84%); δ(60 MHz, $CDCl_3$) 2.24 (6 H, s), 4.46 (1 H, s), 5.07 (2 H, s), 7.02 (8 H, m) and 7.48 (5 H, m) which was characterised after dehydration.[13]

Reaction of the tetrazole **4b** *with* 4,4′-*dimethylbenzophenone.* To a solution of the tetrazole **4b** (495.3 mg, 1.98 mmol) in THF (10 ml) were added t-butyllithium in pentane (2.37 mmol. 1.2 equiv.) to give a purple–black solution and after 0.75 h a solution of 4,4′-dimethylbenzophenone (499.3 mg, 2.37 mmol) in THF (8 ml). The mixture was warmed to −23 °C, stirred for 4 h, and allowed to warm to 20 °C over 15 h to give a colourless solution. Work-up and recrystallisation from chloroform–petroleum gave 1,1,2-*tris*(p-*tolyl*)-2-(5-*phenyltetrazol*-1-*yl*)*ethanol* **5e** (864 mg, 95%), m.p. 245–246 °C (Found: C, 78.1; H, 6.1; N, 12.1. $C_{30}H_{20}N_4O$ requires C, 78.2; H, 6.1; N, 12.2%); ν_{max}/cm^{-1} 3525, 1610w, 1535w, 1510, 1400, 765 and 700; δ(60 MHz, $CDCl_3$) 2.23 (6 H, s), 2.32 (3 H, s), 3.50 (1 H, s) (exch. D_2O), 6.27 (1 H, s), 6.80–7.30 (12 H, m) and 7.40–7.80 (5 H, m); *m/z* 352, 312, 296, 283, 266, 248, 233, 219, 209, 193, 163, 117 (base), 103, 101, 91, and 65.

Reaction of the tetrazole **4b** *with* p-*tolualdehyde.* To a solution of the tetrazole **4b** (509 mg, 2.03 mmol) in THF (20 ml) were added t-butyllithium in pentane (2.24 mmol) and then *p*-tolualdehyde (0.264 ml, 2.24 mmol). After 0.5 h the mixture was warmed to −23 °C and stirred for 1 h when the colour had been discharged. Work-up and chromatography gave 1,2-*bis*(p-*tolyl*)-2-(5-*phenyltetrazol*-1-*yl*)*ethanol* **5f** (660 mg, 87%)), m.p. 123–125 °C (Found: C, 74.75; H, 6.0; N, 15.1. $C_{23}H_{22}N_4O$ requires C, 74.6; H, 6.0; N, 15.1%); ν_{max}/cm^{-1} 3350br, 1610, 1510, 1180, 1070, 1030, 775, 755 and 700; δ(250 MHz, $CDCl_3$) 2.27 (3 H, s), 2.36 (3 H, s), 2.90 (1 H, br s) (exch. D_2O), 5.32 (1 H, d, *J* 6), 5.51 (1 H, br d, *J* 6), 6.93 (4 H, m), 7.03 (2 H, m), 7.22 (2 H, m) and 7.36–7.56 (5 H, m); *m/z* 354, 307, 251, 250 (base), 222, 221, 207, 121, 119, 104, 91, 77 and 65.

Reaction of the tetrazole **4b** *with* p-*toluonitrile.* To a solution of the tetrazole **4b** (371 mg, 1.48 mmol) in THF (15 ml) were added t-butyllithium in pentane (1.63 mmol) and then a solution of *p*-toluonitrile (191 mg, 1.63 mmol) in THF (5 ml). After 0.5 h the mixture was warmed to −23 °C and stirred for 0.3 h. Work-up with dil. aq. sulphuric acid at 30 °C for 0.5 h and chromatography gave 1,2-bis(*p*-tolyl)-2-(5-phenyltetrazol-1-yl)-

ethanone **5g** (440 mg, 80%); δ(60 MHz, $CDCl_3$) 2.33 (6 H, m), 5.65 (≃1 H, s), 7.16 (4 H, m), 7.35–7.65 (7 H, m) and 8.10–8.27 (2 H, m), which was present partly (*ca.* 60%; NMR) in the enol form.

Reaction of the tetrazole **4b** *with* 4-*methylacetophenone.* To a solution of the tetrazole **4b** (634.5 mg, 2.54 mmol) in THF (20 ml) were added t-butyllithium in pentane (2.79 mmol) and then 4-methylacetophenone (0.372 ml, 2.79 mmol). No colour change was apparent and the mixture was allowed to warm to 20 °C when the colour was mostly discharged. Work-up and examination of the residue by TLC and NMR showed it to consist largely of the two starting materials.

Reaction of 1-*Methyltetrazole with Chlorotrimethylsilane.*— To a solution of 1-methyltetrazole (688 mg, 8.18 mmol) in THF (25 ml) at −98 °C were added t-butyllithium in pentane (10.64 mmol, 1.3 equiv.) and then chlorotrimethylsilane (1.35 ml, 10.64 mmol). Work-up and chromatography gave (i) 5- trimethylsilyltetrazol-1-ylmethane **6** (555 mg, 43%), δ(60 MHz, $CDCl_3$) 0.33 (9 H, s) and 4.32 (3 H, s); and (ii) an inseparable mixture of trimethylsilyl-(5-trimethylsilyltetrazol-1-yl)methane **8** (295 mg, 16%), δ(60 MHz, $CDCl_3$) 0.13 (9 H, s), 0.33 (9 H, s) and 4.25 (2 H, s); and tetrazol-1-yl(bistrimethylsilyl)methane **7** (243 mg, 13%), δ(60 MHz, $CDCl_3$) 0.07 (18 H, s), 4.30 (1 H, s) and 8.48 (1 H, s) the relative yields of which were estimated by NMR.

Reaction of the tetrazole **6** *with chlorotrimethylsilane.* To a solution of the tetrazole **6** (555 mg, 3.55 mmol) in THF (25 ml) at −78 °C was added t-butyllithium in pentane (4.26 mmol, 1.2 equiv.) to give an orange–brown solution. After 0.25 h the solution was added to a solution of chlorotrimethylsilane (4.51 ml, 35.5 mmol, 10.0 equiv.) in THF (50 ml) also at −78 °C and the mixture was allowed to warm to 20 °C over 15 h. Work-up and chromatography gave (i) *bis(trimethylsilyl)(5-trimethylsilyltetrazol-1-yl)methane* **9** (380 mg, 36%) as an oil (Found: C, 44.2; H, 9.4; N, 18.7. $C_{11}H_{26}N_4Si_3$ requires C, 43.95; H, 9.4; N, 18.6%); ν_{max}/cm^{-1} 2960, 2905, 1420br, 1255, 1020, 870–820 and 700; δ(60 MHz, $CDCl_3$) 0.05 (18 H, s), 0.35 (9 H, s) and 4.19 (1 H, s); *m/z* 301 ($M^+ + 1$), 285, 228, 213, 183, 172, 158, 130, 100, 84, 73 (base), 59 and 45; (ii) an inseparable mixture of isomeric bis-silyl compounds **8** (42 mg, 5%) and **7** (42 mg, 5%) by NMR and (iii) starting tetrazole **6** (89 mg, 13%) by NMR.

2-*Alkyltetrazoles.*—*Reaction of the tetrazole* **10a** *with chlorotrimethylsilane.* To a solution of the tetrazole **10a** (2.159 g, 13.48 mmol) in THF (45 ml) was added t-butyllithium in pentane (14.83 mmol) and the solution was added to a solution of chlorotrimethylsilane (8.55 ml, 67.4 mmol, 5.0 equiv.) in THF (30 ml) at −78 °C. Work-up and recrystallisation from methanol gave 5-*phenyltetrazol-2-yl(trimethylsilyl)methane* **11a** (2.204 g, 70%), m.p. 88–89 °C (Found: C, 57.0; H, 6.8; N, 24.2. $C_{11}H_{16}N_4Si$ requires C, 56.9; H, 6.9; N, 24.1%); ν_{max}/cm^{-1} 3070, 3040, 1470, 1245, 865, 730 and 695; δ(60 MHz, $CDCl_3$) 0.08 (9 H, s), 4.11 (2 H, s), 7.31–7.52 (3 H, m) and 7.99–8.23 (2 H, m); *m/z* (10 eV) 232 (M^+), 217, 204, 176, 101, 86 (base) and 73.

Reaction of the tetrazole **10a** *with formaldehyde.* To a solution of the tetrazole **10a** (552 mg, 3.45 mmol) in THF (30 ml) was added t-butyllithium in pentane (4.14 mmol). A stream of dry nitrogen gas carrying the vapour from thermally depolymerised paraformaldehyde was passed over the solution and the 'skin' which formed on the surface of the solution was mechanically removed from time to time. When the orange–red colour of the anion had been discharged work-up and chromatography gave 2-(5-phenyltetrazol-2-yl)ethanol **11b** (212 mg, 33%) identical with authentic material (TLC, NMR).[7]

Reaction of the tetrazole **10a** *with propionaldehyde.* To a solution of tetrazole **10a** (478 mg, 3.0 mmol) in THF (15 ml) was added t-butyllithium in pentane (3.6 mmol) and then propionaldehyde (0.282 ml, 3.9 mmol, 1.3 equiv.). Addition of a 10% v/v solution of water in THF (0.5 ml) at −78 °C, work-up and chromatography gave 1-(5-*phenyltetrazol-2-yl)butan-2-ol* **11c** (553 mg, 85%) as an oil, b.p. 110 °C at 0.5 Torr (Found: C, 60.4; H, 6.6; N, 25.9. $C_{11}H_{14}N_4O$ requires C, 60.5; H, 6.5; N, 25.7%); ν_{max}/cm^{-1} 3400br, 2970, 2930, 2880, 1525, 1465, 1450, 1360, 1190, 730 and 690; δ(400 MHz, $CDCl_3$) 1.08 (3 H, t, *J* 7.5), 1.63 (2 H, quintet, *J* 7.5), 2.3–2.8 (1 H, br s), 4.20 (1 H, m), 4.65 [1 H, d(½ABq), *J* 12.5 and 8], 4.75 [1 H, d(½ABq), *J* 12.5 and 3.5], 7.50 (3 H, m) and 8.13 (2 H, m); *m/z* 218 (M^+), 190, 131 (base), 104, 77, 63, 59 and 51.

Reaction of the tetrazole **10a** *with* 4-*methoxybenzaldehyde.* To a solution of the tetrazole **10a** (278 mg, 1.75 mmol) in THF (20 ml) at −78 °C was added t-butyllithium in pentane (1.90 mmol). This solution was added to a solution of 4-methoxybenzaldehyde (286 mg, 2.1 mmol) in THF (20 ml) also at −78 °C. Work-up and evaporation gave a pale yellow oil (610 mg) containing 1-(4-methoxyphenyl)-2-(5-phenyltetrazol-2-yl)-ethanol **11d** [estimated yield, 77% (NMR)], characterised after dehydration.[14]

Reaction of the tetrazole **10b** *with carbon dioxide.* To a solution of the tetrazole **10b** (933 mg, 5.4 mmol) in THF (40 ml) at −78 °C was added t-butyllithium in pentane (5.9 mmol). Addition of solid carbon dioxide (*ca.* 300 mg, 6.8 mmol) and satd. aq. ammonium chloride, warming and work-up using dil. aq. hydrochloric acid gave a colourless oil. The oil was taken up in aq. sodium hydroxide, washed with dichloromethane, acidified to pH 3 (some decarboxylation apparent) and extracted with dichloromethane. Evaporation of the solvent gave 2-(5-*phenyltetrazol-2-yl)propanoic acid* **11e** (618 mg, 53%), m.p. 145–146 °C (Found: C, 54.8; H, 4.5; N, 25.6. $C_{10}H_{10}N_4O_2$ requires C, 55.0; H, 4.6; N, 25.7%); ν_{max}/cm^{-1} 3085, 2555br, 1745(s), 1615, 1530, 1290, 1250, 1185s, 1000, 735 and 690; δ(60 MHz, $CDCl_3$ + [$^2H_6$]acetone) 2.07 (3 H, d, *J* 7), 5.73 (1 H, q, *J* 7), 7.33–7.64 (3 H, m), 8.05–8.32 (2 H, m) and 8.76 (1 H, s); *m/z* 218 (M^+), 190, 145, 104 (base), 77, 63, 56, 51, 45 and 42. Evaporation of the dichloromethane wash gave starting material **10b** (440 mg, 45%).

Reaction of the tetrazole **10b** *with benzaldehyde.* To a solution of the tetrazole **10b** (212 mg, 1.22 mmol) in THF (5 ml) was added t-butyllithium in pentane (1.46 mmol) and then benzaldehyde (0.161 ml, 1.58 mmol), 1.3 equiv.). Work-up and chromatography gave the product (98% yield in total) as (i) a mixture of the diastereoisomers of 1-*phenyl*-2-(5-*phenyltetrazol-2-yl)propanol* **11f** (290 mg, 86%) and (ii) pure (R, S)-/(S,R)-1-*phenyl*-2-(5-*phenyltetrazol-2-yl)propanol* **11f** (39 mg, 12%) as an oil (Found: C, 68.4; H, 5.9; N, 19.6. $C_{16}H_{16}N_4O$ requires C, 68.55; H, 5.75; N, 20.0%); ν_{max}/cm^{-1} 3400br, 3065, 3030, 1530, 1495, 1465, 1450s, 1050, 1015, 735 and 705; δ(250 MHz, $CDCl_3$) 1.49 (3 H, d, *J* 6.1), 2.95 (1 H, d, *J* 3.6), 5.10–5.28 (2 H, br m), 7.30–7.41 (5 H, m), 7.42–7.52 (3 H, m) and 8.10–8.20 (2 H, m); *m/z* 281, 280 (M^+), 252, 210, 199, 174, 145, 107, 104, 79, 51 and 42. The minor diastereoisomer (*R,R*)-/(*S,S*)-(**11f**) has δ(250 MHz, $CDCl_3$) 1.66 (3 H, d, *J* 6.1), 3.42 (1 H, d, *J* 3.6), 5.10–5.28 (2 H, br m), 7.30–7.41 (5 H, m), 7.42–7.52 (3 H, m) and 8.10–8.20 (2 H, m).

Reaction of the tetrazole **10c** *with propionaldehyde.* To a solution of the tetrazole **10c** (334 mg, 1.44 mmol) in THF (6 ml) was added t-butyllithium in pentane (1.58 mmol) and then propionaldehyde (0.125 ml, 1.73 mmol). The reaction was quenched with water at −78 °C and work-up and chromatography gave (E)/(Z)-1-(5-*phenyltetrazol-2-yl)prop-1-ene* **11g** (196.4 mg, 68%) as an oil (Found: C, 65.7; H, 6.3; N, 27.9. $C_{11}H_{12}N_4$ requires C, 66.0; H, 6.0; N, 28.0%); ν_{max}/cm^{-1} 3070, 2970, 2930, 2880, 1530, 1450, 1380, 1210, 1025, 735 and 700; δ(250 MHz, $CDCl_3$) (E)-*isomer*: 0.89 (3 H, t, *J* 7.5), 2.02 (2 H, ddq, *J* 7.5, 6.6 and 1.7), 6.58 (1 H, dt, *J* 13.9 and 6.6), 7.03 (1 H, dt. *J* 13.9 and 1.7), 7.17–7.27 (3 H, m) and 7.90–7.97 (2 H, m); (Z)-

isomer: 0.89 (3 H, t, *J* 7.5), 2.48 (2 H, ddq, *J* 7.5, 7.5 and 1.9), 5.43 (1 H, dt, *J* 9.2 and 7.5), 6.92 (1 H, dt, *J* 9.2 and 1.9), 7.17–7.27 (3 H, m), and 7.90–7.97 (2 H, m); *m/z* (10 eV) 200 (M^+), 172, 157, 130, 104, 69, 54 and 42.

Reaction of the tetrazole **10c** *with* 2,2-*dimethylpropanol*. To a solution of the tetrazole **10c** (348 mg, 1.5 mmol) in THF (15 ml) was added t-butyllithium in pentane (1.57 mmol, 1.05 equiv.) and then 2,2-dimethylpropanal (142 mg, 1.64 mmol, 1.1 equiv.). The reaction was quenched with water at −78 °C and work-up and chromatogaphy gave (i) 3,3-*dimethyl*-1-(5-*phenyltetrazol*-2-*yl*)*but*-1-*ene* **11h** (302.5 mg, 88%), m.p. 57–59 °C (Found: C, 68.2; H, 7.05; N, 24.55. $C_{13}H_{16}N_4$ requires C, 68.4; H, 7.1; N, 24.5%); ν_{max}/cm^{-1} 3090, 1530, 1190, 1020, 960, 840, 725s and 690s; δ(60 MHz, $CDCl_3$) 1.21 (9 H, s), 6.93 (1 H, d, *J* 14), 7.38 (1 H, d, *J* 14), 7.41–7.68 (3 H, m) and 8.13–8.40 (2 H, m); *m/z* 228 (M^+), 200, 104, 82, 70 (base) and 55; and (ii) 3,3-dimethyl-1-(5-phenyltetrazol-2-yl)-1-trimethylsilylbutan-2-ol (34 mg, 7%); δ(90 MHz, $CDCl_3$) 0.15 (9 H, s), 0.70 (9 H, s), 3.62 (2 H, br s), 4.90 (1 H, s), 7.45 (3 H, m) and 8.10 (2 H, m) as a mixture with starting material **10c** (*ca.* 5 mg, 1.5%).

Reaction of the tetrazole **10d** *with* 4-*methoxybenzaldehyde*. To a solution of the tetrazole **10d** (75.2 mg, 0.39 mmol) in THF (5 ml) was added t-butyllithium in pentane (0.47 mmol) and after 1.5 h 4-methoxybenzaldehyde (0.06 ml, 0.51 mmol, 1.3 equiv.). Work-up and chromatography gave an oil (135.1 mg) which was a mixture of 4-methoxybenzaldehyde (62.1 mg) and 1-(4-methoxyphenyl)-2-(5-phenylthiotetrazol-2-yl)ethanol **11i** (73 mg, 57%); δ(250 MHz, $CDCl_3$) 3.79 (3 H, s), 4.12 (1 H, br m), 4.60 [2 H, br s (ABq)], 4.69 (1 H, m), 6.88 (2 H, ≃d, *J* 9), 7.29 (2 H, ≃d, *J* 9), 7.34 (3 H, m) and 7.57 (2 H, m).

Reaction of the tetrazole **10e** *with* 4-*methoxybenzaldehyde*. To a solution of the tetrazole **10e** (298 mg, 2.63 mmol) in THF (25 ml) was added t-butyllithium in pentane (5.80 mmol, 2.2 equiv.). A copious precipitate formed, which was redissolved by swirling at *ca.* −40 °C. After recooling to −78 °C 4-methoxybenzaldehyde (0.384 ml, 3.16 mmol) was added and after 0.8 h the mixture was warmed to 20 °C and stirred 30 h. Work-up using dichloromethane extraction from aqueous base gave 2-(5-aminomethyltetrazol-2-yl)-1-(4-methoxyphenyl)ethanol **11j** (240 mg, 37%) as an oil; δ(60 MHz, $CDCl_3$) 3.20 (2 H, br s), 3.79 (3 H, s), 3.92 (1 H, br s), 4.63 [2 H, br s (≃ABq)], 4.73 (1 H, m), 5.22 (2 H, m), 6.89 (2 H, m) and 7.31 (2 H, m).

Reaction of the tetrazole **10f** *with chlorotrimethylsilane*. To a solution of the tetrazole **10f** (227 mg, 1.23 mmol) in THF (10 ml) was added t-butyllithium in pentane (1.35 mmol, 1.1 equiv.). After 0.1 h the solution was added to a solution of chlorotrimethylsilane (1.56 ml, 12.32 mmol, 10 equiv.) in THF (10 ml). Work-up and evaporation gave an oil (280 mg) which contained (NMR) 1-trimethylsilyl-1-(5-trimethylsilyltetrazol-2-yl)-propane **11k** (159 mg, 51%) together with starting material and 1,1-bis-silyl products.

Reaction of 1-(*tetrazol*-2-*yl*)*propane with chlorotrimethylsilane; lithiation at the tetrazole* 5-*position*. To a solution of 1-(tetrazol-2-yl)propane (265 mg, 2.36 mmol) in THF at 98 °C was added t-butyllithium in pentane (2.60 mmol, 1.1 equiv.). After 0.03 h chlorotrimethylsilane (0.363 ml, 2.86 mmol, 1.2 equiv.) was added and after a further 0.25 h the whole was warmed to −78 °C, when quenching and work-up gave a colourless oil. Distillation (120 °C, 10 Torr) gave 1-(5-trimethylsilyltetrazol-2-yl)propane **10f** (355 mg, 82%) as an oil, δ(90 MHz, $CDCl_3$) 0.34 (9 H, s), 0.90 (3 H, t, *J* 7), 1.97 (2 H, m) and 4.52 (2 H, t, *J* 7) which was used directly in the condensation with chlorotrimethylsilane.

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