Detritylation of Protected Tetrazoles by Naphthalene-Catalyzed Lithiation

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Dedicated to the honor of Prof. Francisco Foubelo García

Abstract: Treatment of N-tritylated tetrazoles bearing aliphatic, aromatic, or heteroaromatic substituents (including functionalized ones) with lithium powder and a catalytic amount of naphthalene led to reductive removal of the trityl group to give excellent yields of the corresponding free tetrazoles without decomposition of the tetrazole ring. The detritylation process was successfully extended to several tetrazoles that are components of sartans, an interesting class of drugs. The chemoselectivity between trityl–tetrazole and trityl–amine bond-cleavage reactions was also studied. This method represents an efficient technique for deprotection of tritylated tetrazoles under non-acidic conditions.

Key words: tetrazoles, deprotection, reductions

Sartans are a group of drugs that are effective in treating hypertension and heart failure. They block the renin–angiotensin system and they are among the most effective treatments for hypertension.[1] Of the seven sartans that are used in clinical practice, five contain tetrazole moieties within their structures. The protection and deprotection of the nitrogen atom of the tetrazole ring is a crucial operation during the synthesis of these sartans.[2] One group that can be used to protect the tetrazole nitrogen is the triphenylmethyl (trityl) group, a very efficient protecting group for amines[3] and amino acids,[4] because its bulkiness causes the nitrogen atom to be much less reactive as a nucleophile. Simple treatment with an aqueous acidic solution can be used to remove the trityl protecting group,[3c] but some side-reactions have been observed under these conditions, such as elimination of tritylamine during detritylation of some tritylated amines.[5] Other procedures that have been shown to be efficient in detritylation processes include dissolving-metal reduction,[3c] reactions with molecular hydrogen catalyzed by palladium,[3c] reduction with sodium borohydride in the presence of mercury salts,[6] and reductive cleavage promoted by silanes[7] or low-valent titanium reagents.[8] Palladium catalysts in combination with poly(methylhydrosiloxane) have been shown to permit direct conversion of *N*-trityl amines into *tert*-butyl carbamates.[9]

The arene-catalyzed lithiation method for generating organolithium compounds has been a topic of our research activities for several years.[10,11] By treatment with an excess of lithium powder, some arenes [mainly naphthalene and 4,4′-di-*tert*-butylbiphenyl (DTBB)] generate highly reactive radical anions and dianions that are efficient electron carriers that induce reductive cleavage of various carbon–heteroatom bonds in organic halides,[10,11] nonhalogenated materials,[12] or heterocycles,[13] leading to the corresponding organolithium compounds, including some functionalized examples.[14] This lithiation methodology permits reductive cleavage of C–N bonds in various organic compounds,[15] including detritylation of trityl amines by a naphthalene-catalyzed lithiation process.[16] The application of this lithiation procedure to the reductive removal of the trityl group from the nitrogen atom of several protected tetrazoles under very mild reaction conditions is discussed below.

We chose 5-phenyl-1-trityl-1*H*-tetrazole (**1a**) as a model substrate, and we attempted to detritylate this compound at –78 °C. When a solution of tetrazole **1a** in tetrahydrofuran was added to a green suspension of an excess of lithium powder and a catalytic amount of naphthalene (molar ratio 1:0.2) in tetrahydrofuran at –78 °C, the mixture turned red, possibly indicating the formation of a trityl radical[17] and/or a trityl anion.[18] When the reaction was complete, hydrolysis with 1 M hydrochloric acid at the same temperature gave the corresponding tetrazole **2a**, together with triphenylmethane (Table 1, entry 1). The latter was probably formed by protonation of the generated tritylllithium in the final hydrolysis step. The yield of the isolated 5-phenyl-1*H*-tetrazole was 97%.

Detritylation of two other protected tetrazoles bearing aromatic substituents (**1b** and **1l**) under the optimized reaction conditions gave the expected free tetrazoles **2b** and **2l** in 99 and 75% yield, respectively (Table 1, entries 2 and 12). A tritylated tetrazole bearing a heteroaromatic 2-pyridyl substituent was also deprotected with very good results (entry 6). The detritylation procedure was also effectively applied to tetrazoles **1d**, **1e**, and **1i**, which were substituted on the carbon atom of the ring with aliphatic chains, including a sterically hindered *tert*-butyl group (entries 4, 5, and 9). The benzylic substituents of protected tetrazoles **1c** and **1k** were unaffected by these reaction conditions, leading to the expected deprotected tetrazoles **2c** and **2k** in 82 and 84% yield, respectively (entries 3 and 11).

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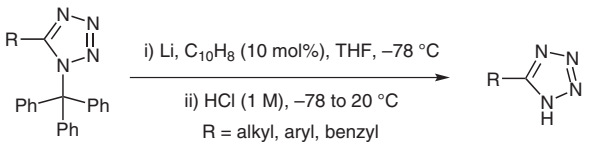
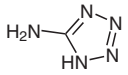
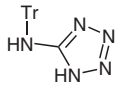
Table 1 Reductive Detritylation of Protected Tetrazoles **1** by a Naphthalene-Catalyzed Lithiation Process[a]



1 **2**

Entry	R	Time (h)	Product	Yield[b] (%)
1	Ph	3.0	**2a**	97
2	2-(4-MeC$_6$H$_4$)C$_6$H$_4$	4.0	**2b**	99
3	Bn	3.0	**2c**	82
4	*t*-Bu	4.0	**2d**	97
5	(CH$_2$)$_{10}$Me	3.0	**2e**	81
6	2-pyridyl	4.0	**2f**	86
7[c]	TrNH	4.0	 **2g**	93
8[d]	TrNH	2.5	 **2h**	94
9	Me	2.5	**2i**	93
10	CH$_2$CO*t*-Bu	4.0	**2j**	80
11	CHPh$_2$	2.0	**2k**	84
12	9-anthryl	6.5	**2l**	75

[a] All reactions were performed at –78 °C.
[b] Yield of isolated product after purification by column chromatography (basic Al_2O_3, hexane–EtOAc), based on starting material **1**.
[c] Compound **1g** was deprotonated with BuLi and treated with TMSCl before performing the naphthalene-catalyzed lithiation step.
[d] Compound **1g** was deprotonated with BuLi before performing the naphthalene-catalyzed lithiation step.

Our method could also be applied to the chemoselective deprotection of a trityl tetrazole in the presence of a trityl amine group. The starting material **1g** has an NH proton that is acidic enough to decompose the naphthalene radical-anion and dianion that act as lithiation agents in this process. To prevent this decomposition, substrate **1g** was deprotonated with butyllithium and treated with chloro(trimethyl)silane before performing the naphthalene-catalyzed lithiation step. This operation led to double detritylation of the starting material to give 1*H*-tetrazol-5-amine (**2g**) in 93% yield (Table 1, entry 7). However, when deprotonated **1g** was directly submitted to the lithiation step without previous treatment with chloro(trimethyl)silane, the trityl group on the tetrazole ring was selectively removed (entry 8). Therefore, the negative charge that appears on the tritylamino substituent after deprotonation with butyllithium effectively protects this group against reductive cleavage of the Tr–N bond.

Interestingly, compound **1j**, which contains a keto-functionalized substituent, could be detritylated under our mild reaction conditions without affecting the carbonyl group, which might have been expected to be reduced by the naphthalene radical-anion or dianion. As a result, 1-(1*H*-tetrazol-5-yl)acetone (**2j**) was isolated in 80% yield (Table 1, entry 10).[19]

In all cases, triphenylmethane, formed by protonation of tritylithium in the final hydrolysis process, was easily separated from the deprotected tetrazoles by column chromatography.

The starting tritylated tetrazoles **1** were prepared by treatment of the corresponding tetrazoles with trityl chloride in the presence of triethylamine and a catalytic amount of 4-(dimethylamino)pyridine.

In summary, we have developed an efficient method for detritylation of protected tetrazoles by a naphthalene-catalyzed lithiation process. The method proved to be useful for the removal of trityl groups from *N*-trityltetrazoles containing aromatic, heteroaromatic, benzylic groups or optionally functionalized aliphatic groups. *N*-Tritytetrazoles containing a secondary *C*-tritylamino group can be selectively detritylated. This method represents a good alternative to the commonly used detritylation procedures, which require acidic conditions.

FT-IR spectra were recorded on a Nicolet Impact 400D spectrophotometer using KBr pellets. NMR spectra were recorded on a Bruker AC-300 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C) using $CDCl_3$, DMSO-d_6, or CD_3OD as solvent and TMS (δ = 0.00 ppm, ^{1}H) or $CDCl_3$ (δ = 77.0 ppm, ^{13}C), DMSO-d_6 (δ = 2.50 ppm, ^{1}H; δ = 39.75 ppm, ^{13}C), or CD_3OD (δ = 4.87 ppm, ^{1}H; δ = 49.0 ppm, ^{13}C) as internal standards; chemical shifts are given in δ (ppm) and coupling constants (*J*) in Hz. Elemental analyses were performed by the Technical Services of the University of Alicante. Column chromatography was performed on silica gel 60 (35–70 mesh) or basic aluminum oxide (50–160 μm particle size). Deactivated silica gel was treated with 5% Et_3N in hexane, and the column was eluted with the same solvent mixture until the eluent was basic, as shown by pH paper. Naphthalene, TMSCl, and all the reagents used in the syntheses of the *N*-tritytetrazoles **1** were commercially available (Acros or Aldrich) and were used without further purification. Li powder was prepared according to a previously described procedure.[20] Commercially available BuLi was titrated with a 1 M solution of *s*-BuOH in xylene, with 1,10-phenanthroline as indicator.[21] Commercially available anhyd THF (99.9%, H_2O content ≤ 0.006%; Acros) was used as the solvent for all the lithiation reactions.

Tetrazoles 2a–l; General Procedure[22]
The mixture of the appropriate nitrile (50 mmol), NaN_3 (65 mmol), and Et_3N·HCl (150 mmol) in toluene (100 mL) was stirred at 110 °C for 17–30 h (**2b**, **2f**, **2k**, and **2l** for 24 h; **2c** and **2d** for 17 h; **2e** and **2j** for 30 h). The mixture was cooled to r.t. and extracted with H_2O (100 mL). The aqueous layer was acidified with 36% aq HCl and filtered. The resultant solid was washed with H_2O and dried under reduced pressure.

5-Phenyl-1*H*-tetrazole (2a)[23]
White solid; yield: 1.39 g (95%); mp 215–216 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.55–7.62 (m, 3 H), 8.01–8.10 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 124.1 (2 × CH), 127.0 (C), 129.4 (CH), 131.3 (2 × CH), 155.3 (C).

5-(4′-Methylbiphenyl-2-yl)-1*H*-tetrazole (2b)[24]
Brown solid; yield: 1.84 g (78%); mp 149–151 °C.

IR (KBr): 3336, 2974, 2900, 1080, 1046, 879, 755 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.28 (s, 3 H), 6.98 (d, *J* = 8.1 Hz, 2 H), 7.12 (d, *J* = 7.9 Hz, 2 H), 7.55 (ddd, *J* = 10.3, 5.8, 1.9 Hz, 2 H), 7.63–7.69 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.7 (CH_3), 123.4 (CH), 127.6 (CH), 128.7 (2 × CH), 128.9 (CH), 130.5 (2 × CH), 130.6 (CH), 131.1 (C), 136.3 (C), 136.8 (C), 141.5 (C), 155.1 (C).

5-Benzyl-1*H*-tetrazole (2c)[25]
White solid; yield: 1.01 g (63%); mp 123–124 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.28 (s, 2 H), 7.24–7.35 (m, 5 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 29.0 (CH_2), 127.1 (CH), 128.7 (2 × CH), 128.8 (2 × CH), 136.0 (C), 155.3 (C).

5-*tert*-Butyl-1*H*-tetrazole (2d)[24]
White solid; yield: 1.14 g (90%); mp 208–210 °C.

IR (KBr): 2986, 2977, 2869, 1717, 1558, 1366, 1066, 1045, 1008 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.35 (s, 9 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.9 (3 × CH_3), 30.3 (C), 163.4 (C).

5-Undecyl-1*H*-tetrazole (2e)[26]
Brown solid; yield: 1.28 g (57%); mp 72–73 °C.

IR (KBr): 3225, 2914, 2848, 1545, 1471, 1074, 716 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.84 (t, *J* = 6.8 Hz, 3 H), 1.24 (m, 16 H), 1.65–1.68 (m, 2 H), 2.84 (t, *J* = 7.6 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.9 (CH_3), 22.2, 22.7, 27.0, 28.3, 28.6, 28.7, 28.9, 29.0 (2 C), 31.3 (10 × CH_2), 155.9 (C).

2-(1*H*-Tetrazol-5-yl)pyridine (2f)[24]
Brown solid; yield: 1.25 g (85%); mp 208–210 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.63 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1 H), 8.08 (td, *J* = 7.8, 1.7 Hz, 1 H), 8.22 (dt, *J* = 7.9, 1.0 Hz, 1 H), 8.79 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 122.6 (CH), 126.2 (CH), 138.3 (CH), 143.7 (C), 150.1 (C), 154.8 (CH).

1*H*-Tetrazol-5-amine (2g)[27]
White solid; yield: 0.79 g (93%); mp 212–214 °C.

IR (KBr): 3399, 3192, 1636, 1263, 1044 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 6.56 (s, 2 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 158.2 (C).

***N*-Trityl-1*H*-tetrazol-5-amine (2h)**[28]
Yellow solid; yield: 2.95 g (90%); mp 148–150 °C.

IR (KBr): 3266, 1560, 1445, 757, 695, 633 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14–7.32 (m, 15 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 82.2 (C), 126.9, 127.4, 127.8, 127.9, 128.0, 128.2, 128.4 (6 C), 128.8, 130.0, 130.3 (15 × CH), 141.5 (3 × CH), 162.1 (C).

Anal. Calcd for $C_{20}H_{17}N_5$: C, 73.88; H, 5.61; N, 21.51. Found: C, 73.92; H, 5.21; N, 22.60.

5-Methyl-1*H*-tetrazole (2i)[25]
White solid; yield: 0.78 g (93%); mp 138–140 °C.

IR (KBr): 3005, 2879, 2605, 1578, 1565, 1112, 1052, 899, 683 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.46 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 8.4 (CH_3), 152.2 (C).

3,3-Dimethyl-1-(1*H*-tetrazol-5-yl)butan-2-one (2j)[29]
Orange solid; yield: 1.43 g (85%); mp 152–154 °C.

IR (KBr): 2973, 2322, 1716, 1365, 1048, 1007, 728 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.18 (s, 9 H), 4.41 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.8 (3 × CH_3), 32.2 (CH_2), 44.0 (C–C=O), 128.2 (C), 209.3 (C=O).

5-(Diphenylmethyl)-1*H*-tetrazole (2k)[30]
White solid; yield: 1.70 g (72%); mp 165–166 °C.

IR (KBr): 3264, 2917, 1560, 1446, 743, 695, 632 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 5.85 (s, 1 H), 7.14–7.30 (m, 10 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 40.8 (CH), 128.6 (2 × CH), 129.6 (4 × CH), 129.9 (4 × CH), 140.8 (C), 160.0 (2 × C).

5-(9-Anthryl)-1*H*-tetrazole (2l)[25]
Green solid; yield: 1.85 g (75%); mp 215–216 °C.

IR (KBr): 2987, 2900, 1578, 1053, 735 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.45 (d, *J* = 8.6 Hz, 2 H), 7.56–7.63 (m, 4 H), 8.23–8.31 (m, 2 H), 8.94 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 120.6 (2 × CH), 124.8 (2 × CH), 126.4 (2 × C), 128.2 (CH), 129.2 (C), 130.8 (2 × CH), 131.0 (2 × CH), 138.3 (2 × C), 150.1 (C).

1-Trityl-1*H*-tetrazoles 1a–1l; General Procedure
A solution of the appropriate tetrazole **1** (10.0 mmol) in CH_2Cl_2 (5 mL) was added to a solution of TrCl (3.1 g, 11.0 mmol), Et_3N (2.5 mL, 17.6 mmol), and DMAP (92 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) at r.t., and the mixture was stirred overnight. The reaction was then quenched with H_2O (5 mL) and the mixture was extracted with EtOAc (3 × 15 mL). The organic phases were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated at 15 Torr. The residue was purified by column chromatography (deactivated silica gel, hexane–EtOAc) to give the expected tetrazoles **1a–f** and **1i–l**.

For the preparation of the ditritylated compound **1g**, the amounts of the reagents and solvents used were double those indicated above.

5-Phenyl-1-trityl-1*H*-tetrazole (1a)[23]
White solid; yield: 3.69 g (95%); mp 156–158 °C.

IR (KBr): 1491, 1447, 1189, 1026, 876, 762, 747, 729, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13–7.47 (m, 18 H), 8.12–8.16 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 83.3 (C), 127.2 (2 × CH), 127.7 (3 × CH), 127.9 (6 × CH), 128.9 (C), 130.5 (6 × CH), 141.5 (CH), 145.3 (2 × CH), 150.8 (3 × C), 164.2 (C).

5-(4′-Methylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole (1b)[31]
White solid; yield: 3.21 g (67%); mp 180–184 °C.

IR (KBr): 3056, 1445, 1028, 827, 748, 698, 640 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19 (s, 3 H), 6.82–6.95 (m, 9 H), 7.17–7.40 (m, 13 H), 7.81–7.84 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 83.0 (C), 126.6, 127.4, 127.7, 128.1, 128.2, 128.3 (4 C), 129.2, 129.3 (6 C), 129.4, 130.4, 130.5, 130.8, 136.5 (23 × CH), 138.3 (C), 141.4 (C), 142.4 (C), 147.0 (C), 154.1 (3 × C), 164.3 (C).

5-Benzyl-1-trityl-1*H*-tetrazole (1c)[32]
White solid; yield: 3.54 g (88%); mp 160–164 °C.

IR (KBr): 1530, 1252, 1073, 889, 733, 694 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.28 (s, 2 H), 7.08–7.12 (m, 6 H), 7.23–7.37 (m, 14 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.0 (CH_2), 83.0 (C), 126.8 (CH), 127.8 (3 × CH), 128.1 (6 × CH), 128.8 (2 × CH), 129.1 (2 × CH), 130.0 (6 × CH), 137.0 (C), 141.5 (3 × C), 164.6 (C).

5-*tert*-Butyl-1-trityl-1*H*-tetrazole (1d)[28]
White solid; yield: 2.54 g (69%); mp 132–136 °C.

IR (KBr): 3005, 2605, 1578, 1565, 1386, 1255, 1112, 1052, 899, 683, 632 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 9 H), 7.01–7.26 (m, 15 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.0 (3 × CH_3), 41.7 (C), 82.8 (C), 127.4 (3 × CH), 127.8 (6 × CH), 130.3 (6 × CH), 141.5 (3 × C), 162.1 (C).

Anal. Calcd for $C_{24}H_{24}N_4$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.26; H, 6.55; N, 15.23.

1-Trityl-5-undecyl-1*H*-tetrazole (1e)[28]
Brown solid; yield: 3.87 g (83%); mp 76–80 °C.

IR (KBr): 2922, 2850, 1493, 1444, 747, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.8 Hz, 3 H), 1.27 (m, 16 H), 1.72–1.79 (m, 2 H), 2.90 (t, *J* = 7.6 Hz, 2 H), 7.07–7.36 (m, 15 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (CH_3), 22.8, 29.2, 29.4, 29.7, 29.8, 32.2, 39.7 (C), 82.7 (C), 127.9 (5 × CH), 128.2, 128.4, 128.7, 129.9, 130.3 (6 × CH), 141.6 (3 × C), 166.2 (C).

Anal. Calcd for $C_{31}H_{38}N_4$: C, 79.79; H, 8.21; N, 12.01. Found: C, 79.76; H, 8.22; N, 12.03.

2-(1-Trityl-1*H*-tetrazol-5-yl)pyridine (1f)[28]
Pink solid; yield: 3.31 g (85%); mp 126–128 °C.

IR (KBr): 1489, 1446, 1072, 747, 698 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 6.79–6.94 (m, 15 H), 7.17–7.21 (m, 1 H), 7.64 (td, *J* = 7.8, 1.6 Hz, 1 H), 7.80 (d, *J* = 7.9 Hz, 1 H), 8.36 (d, *J* = 4.4 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 51.6 (C), 86.4 (CH), 122.6 (CH), 126.1 (CH), 127.0 (3 × CH), 127.9 (6 × CH), 128.2 (6 × CH), 137.0 (3 × C), 138.2 (C), 143.6 (C), 150.1 (CH).

Anal. Calcd for $C_{25}H_{19}N_5$: C, 77.10; H, 4.92; N, 17.98. Found: C, 77.08; H, 4.88; N, 18.00.

***N*,1-Ditrityl-1*H*-tetrazol-5-amine (1g)**[28]
White solid; yield: 1.42 g (25%); mp 220–222 °C.

IR (KBr): 1560, 1493, 1446, 1184, 881, 743, 696, 632 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.82 (s, 1 H), 6.84–7.40 (m, 30 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 71.7 (C), 82.1 (C), 125.9, 126.4, 126.8, 127.6, 127.8, 127.9, 128.0 (5 C), 128.4 (6 C), 129.0 (5 C), 129.6 (6 C), 130.1, 141.5 (30 × CH), 144.8 (3 × C), 147.8 (3 × C), 165.1 (C).

Anal. Calcd for $C_{39}H_{31}N_5$: C, 82.22; H, 5.48; N, 12.29. Found: C, 82.22; H, 5.46; N, 12.24.

5-Methyl-1-trityl-1*H*-tetrazole (1i)[28]
White solid; yield: 2.25 g (69%); mp 172–174 °C.

IR (KBr): 1507, 1492, 883, 748, 696, 635 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.56 (s, 3 H), 7.09–7.12 (m, 6 H), 7.21–7.38 (m, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4 (CH_3), 82.8 (C), 126.9 (3 × CH), 128.1 (6 × CH), 130.3 (6 × CH), 141.5 (3 × C), 162.1 (C).

Anal. Calcd for $C_{21}H_{18}N_4$: C, 77.28; H, 5.56; N, 17.17. Found: C, 77.41; H, 5.57; N, 17.41.

3,3-Dimethyl-1-(1-trityl-1*H*-tetrazol-5-yl)butan-2-one (1j)[28]
Pink solid; yield: 2.55 g (62%); mp 190–194 °C.

IR (KBr): 1714, 1445, 1057, 882, 752, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (s, 9 H), 4.17 (s, 2 H), 7.10–7.35 (m, 15 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.8 (3 × CH_3), 32.2 (CH_2), 44.0 (C–C=O), 82.8 (C), 127.4 (3 × CH), 127.8 (6 × CH), 130.3 (6 × CH), 141.5 (3 × C), 162.1 (C), 209.3 (C=O).

Anal. Calcd for $C_{26}H_{26}N_4O$: C, 76.07; H, 6.38; N, 13.65. Found: C, 76.09; H, 6.37; N, 13.68.

5-(Diphenylmethyl)-1-trityl-1*H*-tetrazole (1k)[28]
Yellow solid; yield: 2.92 g (61%); mp 164–166 °C.

IR (KBr): 1492, 1445, 1048, 748, 697, 639 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.88 (s, 1 H), 7.13–7.38 (m, 25 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.9 (CH), 82.1 (C), 125.9, 126.4, 126.8, 127.4 (2 C), 127.6 (4 C), 127.8 (3 C), 127.9, 128.1, 128.4 (6 C), 129.0, 129.6, 130.1, 141.5, 144.0 (25 × CH), 144.8 (C), 147.0 (2 × C), 165.1 (3 × C).

Anal. Calcd for $C_{33}H_{26}N_4$: C, 82.82; H, 5.48; N, 11.71. Found: C, 82.80; H, 5.46; N, 11.69.

5-(9-Anthryl)-1-trityl-1*H*-tetrazole (1l)[28]
Green solid; yield: 3.47 g (71%); mp 170–172 °C.

IR (KBr): 1491, 1447, 1189, 876, 762, 747, 694 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.45 (m, 21 H), 7.70–7.73 (m, 1 H), 8.03 (dd, *J* = 4.8, 4.2 Hz, 1 H), 8.57 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 83.7 (C), 125.6 (2 × CH), 126.8 (2 × C), 127.4 (2 × C), 128.0 (3 × CH), 128.1 (CH), 128.2 (6 × CH), 128.6 (2 × CH), 128.7 (2 × CH), 130.4 (6 × CH), 131.3 (C), 141.6 (2 × C), 147.0 (3 × C), 162.6 (C).

Anal. Calcd for $C_{34}H_{24}N_4$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.55; H, 4.91; N, 11.50.

Reductive Cleavage of 1-Trityl-1*H*-tetrazoles 1a–1f and 1i–1l by Naphthalene-Catalyzed Lithiation; General Procedure
A solution of *N*-trityltetrazole **1** (1.0 mmol) in THF (2 mL) was added dropwise to a green suspension of Li powder (70 mg, 10.0 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL) under argon at –78 °C. The mixture, which turned dark red after the addition of a few drops of the solution of tetrazole **1**, was stirred at –78 °C for the time indicated in Table 1. 1 M aq HCl (5 mL) was carefully added, the cooling bath was removed, and the mixture was stirred until it reached r.t. The mixture was then extracted with EtOAc (3 × 15 mL) and the organic phases were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated at 15 Torr. The residue was purified by column chromatography (basic Al_2O_3, hexane–EtOAc), affording the corresponding free tetrazoles **2** in the following yields: **2a** (142 mg, 97%), **2b** (234 mg, 99%), **2c** (131 mg, 82%), **2d** (122 mg, 97%), **2e** (182 mg, 81%), **2f** (127 mg, 86%), **2i** (78 mg, 93%), **2j** (135 mg, 80%), **2k** (198 mg, 84%) and **2l** (185 mg, 75%).

Compounds **2a**, **2g**, and **2i** were commercially available, and compounds **2b**–**f**, **2h**, and **2j**–**l** were prepared by us (see above). All the compounds were characterized by comparison of their physical and spectroscopic properties with those of authentic samples.

Reductive Cleavage of *N*,1-Ditrityl-1*H*-tetrazol-5-amine (1g) by Naphthalene-Catalyzed Lithiation
A 1.6 M solution of BuLi in hexane (0.45 mL, 0.7 mmol) was added dropwise to a solution of tetrazole **1g** (186 mg, 0.5 mmol) in THF (2 mL) at 0 °C under argon until a red color developed. The mixture was stirred for 10 min then TMSCl was added until the red color vanished (0.15 mL, 1.2 mmol). The mixture was stirred for 10 min

and then transferred dropwise by syringe to a green suspension of Li powder (50 mg, 7.2 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL) under argon at –78 °C. The mixture turned dark red and was stirred at –78 °C for the time indicated in Table 1. 1 M aq HCl (5 mL) was carefully added, the cooling bath was removed, and the mixture was stirred until it reached r.t. The mixture was then acidified with 2 M aq HCl (5 mL) and extracted with EtOAc (3 × 15 mL). The organic phases were discarded and the aqueous phase was basified with 2 M NaOH (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated to give the pure tetrazole **2g** [yield: 79 mg (93%)], which was characterized by comparison of its physical and spectroscopic properties with those of an authentic sample.

Monodetritylation of *N*,1-Dityrityl-1*H*-tetrazol-5-amine (1g) by Naphthalene-Catalyzed Lithiation

A 1.6 M solution of BuLi in hexane (0.45 mL, 0.7 mmol) was added dropwise to a solution of tetrazole **1g** (186 mg, 0.5 mmol) in THF (2 mL) under argon at 0 °C until a red color developed. The mixture was stirred for 10 min and then transferred dropwise by syringe to a green suspension of Li powder (50 mg, 7.2 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL) under argon at –78 °C. The mixture turned dark red and was stirred at –78 °C for 2.5 h. 1 M aq HCl (5 mL) was then carefully added, the cooling bath was removed, and the reaction was stirred until it reached r.t. The mixture was acidified with 2 M aq HCl (5 mL) and extracted with EtOAc (3 × 15 mL). The organic phases were discarded and the aqueous phase was basified with 2 M NaOH (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated to give the pure tetrazole **2h** [yield: 308 mg (94%)], which was characterized by comparison of its physical and spectroscopic properties with those of an authentic sample.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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