Detritylation of Protected Tetrazoles by Naphthalene-Catalysed Lithiation

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Abstract: The reaction of N-tritylated tetrazoles (bearing aliphatic, aromatic and heteroaromatic substituents, including a functionalised one) with lithium powder and a catalytic amount of naphthalene led to reductive removal of the trityl group, affording the corresponding free tetrazoles in excellent yields without decomposition of the tetrazole ring. The detritylation process could successfully be extended to several tetrazoles that are components of Sartans, which are an interesting kind of drugs. The chemoselectivity between the trityl-tetrazol and the trityl-amine bond cleavages was also studied. This methodology represents an efficient deprotection of tritylated tetrazole under non-acidic reaction conditions.

Keywords: tetrazole, lithium, lithiation, detritylation, reductive cleavage.

Sartans are a type of drugs that are effective to treat hypertension and heart failure. These drugs block the renin-angiotensin system and represent one of the most effective treatments for hypertension.¹ Among the seven sartans that are used in clinical practice, five of them possess a tetrazole moiety in their structure. The protection and deprotection of the nitrogen atom of the tetrazole ring is a crucial operation during the synthesis of these sartan drugs.² One of the groups that can be used to protect the tetrazole nitrogen is the triphenylmethyl (trityl), which has proved to be a very efficient protecting group for amines³ and aminoacids,⁴ because the bulkiness of the trityl substituent causes the nitrogen atom to be much less reactive as a nucleophile. The simple treatment with an aqueous acidic solution to remove this protecting group has been reported,^{3c} but some side reactions have been observed under these conditions, like the elimination of triphenylmethanamine when the detritylation of some tritylated amines was attempted.⁵ Other procedures that have been shown to be efficient to perform the detritylation process involve dissolving metal reduction,^{3c} reaction with molecular hydrogen catalysed by palladium,^{3c} reduction with sodium borohydride in the presence of mercury salts⁶ and reductive cleavage promoted by silanes⁷ or low-valent titanium reagents.⁸ Palladium catalysts in combination with polymethylhydrosiloxane have been shown to allow the direct conversion of N-trityl amines to *t*-butylcarbamates.⁹

The arene-catalysed lithiation methodology as a tool to generate organolithium compounds has been the topic of our research activities for several years.^{10,11} By reaction with an excess of lithium powder, some arenes [mainly naphthalene and 4,4'-di-*tert*-butylbiphenyl (DTBB)] generate highly reactive radical anions and dianions

which are very efficient electron carriers that allow the reductive cleavage of different carbon heteroatom bonds in organic halides,^{10,11} non-halogenated materials¹² and heterocycles,¹³ leading to the corresponding organolithium compounds, including functionalised examples.¹⁴ This lithiation methodology allowed us to perform the reductive cleavage of carbon-nitrogen bonds in different organic compounds,¹⁵ including the detritylation of trityl amines by a naphthalene-catalysed 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 presented herein.

We chose 5-phenyl-1-trityl-1*H*-tetrazole **1a** (Table 1, entry 1) as a model substrate and we first tried to perform its detritylation at -78 °C. When a solution of **1a** in THF was added to a green suspension of an excess of lithium powder and a catalytic amount of naphthalene (1:0.2 molar ratio) in the same solvent at -78 °C, the reaction mixture turned into a red colour, which could indicate the formation of the trityl radical¹⁷ and/or the trityl anion.¹⁸ When the reaction was complete, the hydrolysis with 1M HCl at the same temperature gave the corresponding tetrazole **2a**, together with triphenylmethane (Equation 1, Table 1, entry 1). The latter was probably formed by protonation of the generated triphenylmethyl lithium in the final hydrolysis step. The yield of the isolated 5-phenyl-1*H*-tetrazole was 97%.

Equation 1

Two other protected tetrazoles bearing aromatic R groups, **1b** and **1l**, were submitted to the above mentioned detritylation process under the optimum reaction conditions yielding the expected free tetrazoles **2b** and **2l** in 84% and 75 % yield respectively (Table 1, entries 2 and 12). A tritylated tetrazole bearing the heteroaromatic 2-pyridyl substituent could also be deprotected with very good results (Table 1, entry 6). This detritylation procedure could be effectively applied to tetrazoles **1d**, **1e** and **1i**, substituted on the carbon atom of the ring with sever-

al aliphatic chains, including sterically hindered cases (Table 1, entries 4, 5 and 9). The benzylic substituents of protected tetrazoles **1c** and **1k** were not affected under

these reaction conditions, leading to the expected deprotected tetrazoles **2c** and **2k** in 82 and 84% yields (Table 1, entries 3 and 11).

Table 1 Reductive detritylation of protected tetrazoles **1** by a naphthalene-catalysed lithiation process

Entry	Substrate	T (°C)	t (h)	Product	Yield (%) ^a
1		-78	3.0		97
2		-78	4.0		99
3		-78	3.0		82
4		-78	4.0		97
5		-78	3.0		81
6		-78	4.0		86
7 ^b		-78	4.0		93

8 ^c		-78	2.5		94
9		-78	2.5		93
10		-78	4.0		80
11		-78	2.0		84
12		-78	6.5		75

^a Yield of isolated product after purification by column chromatography (basic aluminium oxide, hexane/ethyl acetate), based on the starting material **1**.

^b Compound **1g** was deprotonated with *n*-BuLi and treated with TMSCl before performing the naphthalene-catalysed lithiation step.

^c Compound **1g** was deprotonated with *n*-BuLi before performing the naphthalene-catalysed lithiation step.

Our methodology could also be applied to the chemoselective deprotection of a trityl tetrazole in the presence of a trityl amine. The starting material **1g** has an NH proton which is acidic enough to decompose the naphthalene radical-anion and dianion that act as lithiation agents in this process. In order to avoid this decomposition, substrate **1g** was deprotonated with *n*-butyllithium and treated with trimethylsilyl chloride before performing the naphthalene-catalysed lithiation step. This operation led to the double detritylation of the starting material, affording 5-amino-1*H*-tetrazole **2g** in 93% yield (Table 1, entry 7). However, when deprotonated **1g** was directly submitted to the lithiation step (without previous treatment with trimethylsilyl chloride), a selective removal of the trityl group on the tetrazole ring was achieved (Table 1, entry 8). Therefore, the negative charge that appears on the TrN substituent after deprotonation with *n*-butyllithium effectively protects this group against the reductive cleavage of its Tr-N bond.

Interestingly, under our mild reaction conditions, the detritylation of compound **1j**, possessing an R substituent functionalized with a ketone, could be carried out without affecting the carbonyl group, which could have been reduced by reaction with the naphthalene radical-anion or dianion. Thus, 1-(1*H*-tetrazol-5-yl)propan-2-one **2j** was isolated in 80% yield (Table 1, entry 10).¹⁹

In all cases, triphenylmethane, which is formed by protonation of the generated triphenylmethyl lithium in the final hydrolysis process, could easily be separated from the deprotected tetrazoles by column chromatography.

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

In summary, in this paper we have presented a very efficient method for the detritylation of protected tetrazoles

via a naphthalene-catalysed lithiation process. The methodology has proved to be useful for the removal of the trityl group from Tr-tetrazoles substituted on the carbon atom of the ring by aromatic, heteroaromatic, aliphatic or benzylic carbon chains, including cases of functionalized substituents. The chemoselective detritylation of a Tr-tetrazole in the presence of a secondary Tr-amine can also be achieved. This method represents a good alternative to the commonly used detritylation procedures which use acidic reaction conditions.

FT-IR spectra were obtained on a Nicolet Impact 400D spectrophotometer using KBr pellets. NMR spectra were recorded on a Bruker AC-300 (300 MHz for ^1H and 75 MHz for ^{13}C) using CDCl_3 , DMSO-d_6 , MeOD-d_4 as solvents and TMS (0.00 ppm, ^1H) and CDCl_3 (77.0 ppm, ^{13}C), DMSO-d_6 (2.50 ppm, ^1H and 39.75 ppm, ^{13}C), MeOD-d_4 (4.87 ppm, ^1H and 49.0 ppm, ^{13}C) as internal standards; chemical shifts are given in δ (ppm) and coupling constants (J) in Hz. Elemental analysis were measured by the Technical Services of the University of Alicante. Column chromatography was performed using silica gel 60 (35-70 mesh) or basic aluminium oxide (50-160 μm particle size). When mentioned, deactivated silica gel means that it was treated with 5% triethylamine in hexane and the column was eluted with the same solvent mixture until the coming eluent was basic according to pH paper. All reagents used for the synthesis of *N*-trityltetrazoles **1**, naphthalene and trimethylsilyl chloride were commercially available (Acros, Aldrich) and were used without further purification. Lithium powder was prepared according to the procedure described in reference 20. Commercially available *n*-butyllithium was titrated with a 1M solution of *sec*-butanol in xylene using 1,10-phenanthroline as indicator.²¹ Commercially available anhydrous THF (99.9%, water content $\leq 0.006\%$, Acros) was used as solvent in all the lithiation reactions.

Synthesis of all Tetrazoles. General Procedure²²

The mixture of a nitrile (50 mmol), NaN_3 (65 mmol) and $\text{Et}_3\text{N}\cdot\text{HCl}$ (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). After cooling to room temperature, the mixture was extracted with water (100 mL). To the aqueous layer, 36% HCl was added dropwise till pH was acidic. After filtration, the solid was washed with water and dried under reduced pressure, yielding the expected tetrazoles **2**. The corresponding physical and spectroscopic data for all tetrazoles **2** follow.

5-Phenyl-1*H*-tetrazole (**2a**)

White solid; yield: 1.39 g (95%); mp: $215\text{--}216^\circ\text{C}$.

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

^{13}C NMR: (75 MHz, DMSO-d_6): $\delta = 124.1$ ($2\times\text{CH}$), 127.0 (C), 129.4 (CH), 131.3 ($2\times\text{CH}$), 155.3 (C).

5-(4'-Methyl-[1,1'-biphenyl]-2-yl)-1*H*-tetrazole (2b**)²³**
Brown solid; yield: 1.84 g (78%); mp: $149\text{--}151^\circ\text{C}$.

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

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

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

Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_4$: C, 71.17; H, 5.12; N, 23.71. Found: C, 70.86; H, 5.17; N, 24.07.

5-Benzyl-1*H*-tetrazole (**2c**)²⁴

White solid; yield: 1.01 g (63%); mp: $123\text{--}124^\circ\text{C}$.

^1H NMR: (300 MHz, DMSO-d_6): $\delta = 4.28$ (s, 2H), 7.24-7.35 (m, 5H).

^{13}C NMR: (75 MHz, DMSO-d_6): $\delta = 29.0$ (CH_2), 127.1 (CH), 128.7 ($2\times\text{CH}$), 128.8 ($2\times\text{CH}$), 136.0 (C), 155.3 (C).

Anal. Calcd for $\text{C}_8\text{H}_8\text{N}_4$: C, 59.99; H, 5.03; N, 34.98. Found: C, 60.05; H, 4.80; N, 36.21.

5-(*tert*-Butyl)-1*H*-tetrazole (**2d**)²⁴

White solid; yield: 1.14 g (90%); mp: $208\text{--}210^\circ\text{C}$.

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

^1H NMR: (300 MHz, DMSO-d_6): $\delta = 1.35$ (s, 9H).

^{13}C NMR: (75 MHz, DMSO-d_6): $\delta = 28.9$ ($3\times\text{CH}_3$), 30.3 (C), 163.4 (C).

5-Undecyl-1*H*-tetrazole (**2e**)

Brown solid; yield: 1.28 g (57%); mp: $72\text{--}73^\circ\text{C}$.

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

^1H NMR: (300 MHz, DMSO-d_6): $\delta = 0.84$ (t, $J = 6.8$ Hz, 3H), 1.24 (m, 16H), 1.65-1.68 (m, 2H), 2.84 (t, $J = 7.6$ Hz, 2H).

^{13}C NMR: (75 MHz, DMSO-d_6): $\delta = 13.9$ (CH_3), 22.2, 22.7, 27.0, 28.3, 28.6, 28.7, 28.9, 29.0 (2C), 31.3 ($10\times\text{CH}_2$), 155.9 (C).

Anal. Calcd for $\text{C}_{12}\text{H}_{24}\text{N}_4$: C, 64.24; H, 10.78; N, 24.97. Found: C, 63.97; H, 10.50; N, 26.51.

2-(1*H*-Tetrazol-5-yl)pyridine (**2f**)²³

Brown solid; yield: 1.25 g (85%); mp: $208\text{--}210^\circ\text{C}$.

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

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

1*H*-Tetrazol-5-amine (**2g**)

White solid; yield: 0.79 g (93%); mp: 212–214°C.
IR (KBr): 3399, 3192, 1636, 1263, 1044 cm⁻¹.

¹H NMR: (300 MHz, MeOD-d₄): δ = 6.56 (s, 2H).

¹³C NMR: (75 MHz, MeOD-d₄): δ = 158.2 (C).

Anal. Calcd for CH₃N₅: C, 14.12; H, 3.55; N, 82.33.
Found: C, 14.59; H, 3.92; N, 79.46.

N-Trityl-1*H*-tetrazol-5-amine (2h)

Yellow solid; yield: 2.95 g (90%); mp: 148–150°C.

IR (KBr): 3266, 1560, 1445, 757, 695, 633 cm⁻¹.

¹H NMR: (300 MHz, CDCl₃): δ = 7.14–7.32 (m, 15H).

¹³C NMR: (75 MHz, CDCl₃): δ = 82.2 (C), 126.9, 127.4, 127.8, 127.9, 128.0, 128.2, 128.4 (6C), 128.8, 130.0, 130.3 (15×CH), 141.5 (3×CH), 162.1 (C).

Anal. Calcd for C₂₀H₁₇N₅: 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)

White solid; yield: 0.78 g (93%); mp: 138–140°C.

IR (KBr): 3005, 2879, 2605, 1578, 1565, 1112, 1052, 899, 683 cm⁻¹.

¹H NMR: (300 MHz, DMSO-d₆): δ = 2.46 (s, 3H).

¹³C NMR: (75 MHz, DMSO-d₆): δ = 8.4 (CH₃), 152.2 (C).

Anal. Calcd for C₂H₄N₄: C, 28.57; H, 4.80; N, 66.64.
Found: C, 28.77; H, 4.70; N, 71.13.

3,3-Dimethyl-1-(1*H*-tetrazol-5-yl)butan-2-one (2j)

Orange solid; yield: 1.43 g (85%); mp: 152–154°C.

IR (KBr): 2973, 2322, 1716, 1365, 1048, 1007, 728 cm⁻¹.

¹H NMR: (300 MHz, DMSO-d₆): δ = 1.18 (s, 9H), 4.41 (s, 2H).

¹³C NMR: (75 MHz, DMSO-d₆): δ = 25.8 (3×CH₃), 32.2 (CH₂), 44.0 (C–C=O), 128.2 (C), 209.3 (C=O).

Anal. Calcd for C₇H₁₂N₄O: C, 49.99; H, 7.19; N, 33.31.
Found: C, 49.96; H, 6.61; N, 31.52.

5-Benzhydryl-1*H*-tetrazole (2k)

White solid; yield: 1.70 g (72%); mp: 165–166°C.

IR (KBr): 3264, 2917, 1560, 1446, 743, 695, 632 cm⁻¹.

¹H NMR: (300 MHz, MeOD-d₄): δ = 5.85 (s, 1H), 7.14–7.30 (m, 10H).

¹³C NMR: (75 MHz, MeOD-d₄): δ = 40.8 (CH), 128.6 (2×CH), 129.6 (4×CH), 129.9 (4×CH), 140.8 (C), 160.0 (2×C).

Anal. Calcd for C₁₄H₁₂N₄: C, 71.17; H, 5.12; N, 23.71.
Found: C, 70.86; H, 5.17; N, 24.07.

5-(Anthracen-9-yl)-1*H*-tetrazole (2l)

Green solid; yield: 1.85 g (75%); mp: 215–216°C.

IR (KBr): 2987, 2900, 1578, 1053, 735 cm⁻¹.

¹H NMR: (300 MHz, DMSO-d₆): δ = 7.45 (d, *J* = 8.6 Hz, 2H), 7.56–7.63 (m, 4H), 8.23–8.31 (m, 2H), 8.94 (s, 1H).

¹³C NMR: (75 MHz, DMSO-d₆): 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).

Anal. Calcd for C₁₅H₁₀N₄: C, 73.16; H, 4.09; N, 22.75.
Found: C, 72.80; H, 4.18; N, 22.75.

Tritylation of 5-Substituted Tetrazoles. General Procedure

A solution of the corresponding tetrazole (10.0 mmol) in CH₂Cl₂ (5 mL) was added to a solution of trityl chloride (3.1 g, 11.0 mmol), triethylamine (2.5 mL, 17.6 mmol) and 4-(dimethylamino)pyridine (92 mg, 0.4 mmol) in CH₂Cl₂ (10 mL) at room temperature and the mixture was stirred overnight. The reaction was then quenched with water (5 mL) and extracted with ethyl acetate (3 × 15 mL) and the combined organic phases were washed with brine (5 mL) and dried over sodium sulfate. After evaporation of the solvents (15 Torr), the resulting residue was purified by column chromatography (deactivated silica gel, hexane/ethyl acetate) affording the expected tetrazoles **1a–1f** and **1i–1l**.

For the preparation of the double tritylated compound **1g** the amounts of the reagents and solvent used were double the ones indicated above. Compound **1g** was separated by column chromatography [deactivated silica gel, hexane/ethyl acetate]. The corresponding physical, spectroscopic and analytical data for the tritylated tetrazoles follow.

5-Phenyl-1-trityl-1*H*-tetrazole (1a)

White solid; yield: 3.69 g (95%); mp: 156–158°C.

IR (KBr): 1491, 1447, 1189, 1026, 876, 762, 747, 729, 693 cm⁻¹.

¹H NMR: (300 MHz, CDCl₃): δ = 7.13–7.47 (m, 18H), 8.12–8.16 (m, 2H).

¹³C NMR: (75 MHz, CDCl₃): 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).

Anal. Calcd for C₂₆H₂₀N₄: C, 80.39; H, 5.19; N, 14.42.
Found: C, 80.09; H, 5.66; N, 13.92.

5-(4'-Methyl-[1,1'-biphenyl]-2-yl)-1-trityl-1*H*-tetrazole (1b)

White solid; yield: 3.21 g (67%); mp: 180–184°C.

IR (KBr): 3056, 1445, 1028, 827, 748, 698, 640 cm⁻¹.

¹H NMR: (300 MHz, CDCl₃): δ = 2.19 (s, 3H), 6.82–6.95 (m, 9H), 7.17–7.40 (m, 13H), 7.81–7.84 (m, 1H).

¹³C NMR: (75 MHz, CDCl₃): δ = 21.3 (CH₃), 83.0 (C), 126.6, 127.4, 127.7, 128.1, 128.2, 128.3 (4C), 129.2, 129.3 (6C), 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).

Anal. Calcd for $C_{33}H_{26}N_4$: C, 82.82; H, 5.48; N, 11.71. Found: C, 82.37; H, 5.46; N, 11.42.

5-Benzyl-1-trityl-1H-tetrazole (1c)

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, 2H), 7.08–7.12 (m, 6H), 7.23–7.37 (m, 14H).

^{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).

Anal. Calcd for $C_{27}H_{22}N_4$: C, 80.57; H, 5.51; N, 13.92. Found: C, 80.30; H, 5.52; N, 14.84.

5-(tert-Butyl)-1-trityl-1H-tetrazole (1d)

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, 9H), 7.01–7.26 (m, 15H).

^{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, 78.58; H, 8.14; N, 13.46.

1-Trityl-5-undecyl-1H-tetrazole (1e)

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, 3H), 1.27 (m, 16H), 1.72–1.79 (m, 2H), 2.90 (t, J = 7.6 Hz, 2H), 7.07–7.36 (m, 15H).

^{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, 80.06; H, 8.14; N, 13.46.

2-(1-Trityl-1H-tetrazol-5-yl)pyridine (1f)

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, 15H), 7.17–7.21 (m, 1H), 7.64 (td, J = 7.8, 1.6 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 8.36 (d, J = 4.4 Hz, 1H).

^{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, 77.00; H, 5.57; N, 17.41.

N,1-Ditrityl-1H-tetrazol-5-amine (1g)

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, 1H), 6.84–7.40 (m, 30H).

^{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 (5C), 128.4 (6C), 129.0 (5C), 129.6 (6C), 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, 12.27. Found: C, 82.22; H, 5.46; N, 11.42.

5-Methyl-1-trityl-1H-tetrazole (1i)

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, 3H), 7.09–7.12 (m, 6H), 7.21–7.38 (m, 9H).

^{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-1H-tetrazol-5-yl)butan-2-one (1j)

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, 9H), 4.17 (s, 2H), 7.10–7.35 (m, 15H).

^{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, 75.09; H, 5.57; N, 17.41.

5-Benzhydryl-1-trityl-1H-tetrazole (1k)

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, 1H), 7.13–7.38 (m, 25H).

^{13}C NMR: (75 MHz, $CDCl_3$): δ = 50.9 (CH), 82.1 (C), 125.9, 126.4, 126.8, 127.4 (2C), 127.6 (4C), 127.8 (3C), 127.9, 128.1, 128.4 (6C), 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, 82.37; H, 5.46; N, 11.42.

5-(Anthracen-9-yl)-1-trityl-1H-tetrazole (1l)

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, 21H), 7.70–7.73 (m, 1H), 8.03 (dd, J = 4.8, 4.2 Hz, 1H), 8.57 (s, 1H).

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

Anal. Calcd for $\text{C}_{34}\text{H}_{24}\text{N}_4$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.05; H, 5.34; N, 8.79.

Reductive Cleavage of Tritylated Tetrazoles **1a–1f** and **1i–1l** via a Naphthalene-Catalysed Lithiation. General Procedure

A solution of N-trityltetrazole **1** (1.0 mmol) in THF (2 mL) was dropwise added to a green suspension of lithium powder (70 mg, 10.0 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL), under Ar, at 0 °C. The reaction mixture turned to a dark red colour after the addition of a few drops of the solution of **1**. After stirring at the same temperature for the time indicated in Table 1, HCl 1M (5 mL) was carefully added, the cooling bath was removed and the reaction was stirred till it reached room temperature. The mixture was extracted with ethyl acetate (3 $\times$ 15 mL) and the combined organic phases were washed with brine (5 mL), being then dried over sodium sulfate. After evaporation of the solvents (15 Torr), the resulting residue was purified by column chromatography (basic aluminium oxide, hexane/ethyl acetate), affording the corresponding free tetrazoles **2** in the yields indicated in Table 1.

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

Reductive Cleavage of the Double Tritylated Amino Tetrazol **1g** by a Naphthalene-Catalysed Lithiation.

To a solution of **1g** (186 mg, 0.5 mmol) in THF (2 mL), under Ar, at 0 °C, *n*-BuLi was dropwise added until a red colour developed in the reaction mixture (0.45 mL of a 1.6 M solution of *n*-BuLi in hexane, 0.7 mmol). After stirring for 10 min, trimethylsilyl chloride was added until the red colour vanished (0.15 mL, 1.2 mmol). The reaction mixture was stirred for 10 min and it was then transferred dropwise via syringe to a green suspension of lithium powder (50 mg, 7.2 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL), under Ar, at -78 °C. The reaction mixture turned to a dark red colour. After stirring at the same temperature for the time indicated in Table 1, HCl 1M (5 mL) was carefully added, the cooling bath was removed and the reaction was stirred till it reached room temperature. The mixture was acidified with 2 M HCl (5 mL) and extracted with EtOAc (3 $\times$ 15 mL), the combined organic phases being discarded. The aqueous phase was basified with 2 M NaOH (5 mL) and

extracted with dichloromethane (3 $\times$ 15 mL). The combined organic phases were dried over sodium sulfate. Evaporation of the solvents afforded a 93% yield of the pure expected tetrazole **2g**, which was characterised by comparison of its physical and spectroscopic data with an authentic sample.

Monodetritylation of Compound **1g** by a Naphthalene-Catalysed Lithiation.

To a solution of **1g** (186 mg, 0.5 mmol) in THF (2 mL), under Ar, at 0 °C, *n*-BuLi was dropwise added until a red colour developed in the reaction mixture (0.45 mL of a 1.6 M solution of *n*-BuLi in hexane, 0.7 mmol). The reaction mixture was stirred for 10 min and it was then transferred dropwise via syringe to a green suspension of lithium powder (50 mg, 7.2 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL), under Ar, at -78 °C. The reaction mixture turned to a dark red colour. After stirring at the same temperature for 2.5 h, HCl 1M (5 mL) was carefully added, the cooling bath was removed and the reaction was stirred till it reached room temperature. The mixture was acidified with 2 M HCl (5 mL) and extracted with EtOAc (3 $\times$ 15 mL), the combined organic phases being discarded. The aqueous phase was basified with 2 M NaOH (5 mL) and extracted with dichloromethane (3 $\times$ 15 mL). The combined organic phases were dried over sodium sulfate. Evaporation of the solvents afforded a 94% yield of the pure expected tetrazol **2h**, which was characterised by comparison of its physical and spectroscopic data with an authentic sample.

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References

- (1) See, for instance: Applegate, H. E.; Cimarusti, C. M.; Dolfini, J. E.; Funke, P. T.; Koster, W. H.; Puar, M. S.; Slusarchyk, W. A.; Young, M. G. *J. Org. Chem.* **1979**, *44*, 811.
- (2) Srimurugan, S.; Suresh, P.; Babu, B.; Hiriyanna, S. G.; Pati, H. N. *Chem. Pharm. Bull.* **2008**, *56*, 383.
- (3) (a) Sheppard, R. C. In *Comprehensive Organic Chemistry*, Vol. 5; Barton, D.; Ollis, W. D., Eds.; Pergamon Press: Oxford, **1979**, 323.
(b) Kunz, H.; Waldmann, H. In *Comprehensive Organic Synthesis*, Vol. 6; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, p. 644.
(c) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, **1999**, 583.
- (4) (a) Bodanszky, M.; Onetti, O. A. *Peptide Synthesis*; Interscience: New York, **1966**, 36.
(b) Bodanszky, M. *Principles in Peptide Synthesis*, 2nd Ed.; Springer-Verlag: New York, **1993**, p. 88.

- (5) See, for instance: Sharma, S. K.; Songster, M. F.; Colpitts, T. L.; Hegyes, P.; Barany, G.; Castellino, F. J. *J. Org. Chem.* **1993**, *58*, 4993.
- (6) Maltese, M. *J. Org. Chem.* **2001**, *66*, 7615.
- (7) Vedejs, E.; Klapars, A.; Warner, D. L.; Weiss, A. H. *J. Org. Chem.* **2001**, *66*, 7542.
- (8) Rele, S.; Nayak, S. K. *Synth. Commun.* **2002**, *32*, 3533.
- (9) Chandrasekhar, S.; Nagendra Babu, B.; Reddy, C. R. *Tetrahedron Lett.* **2003**, *44*, 2057.
- (10) For reviews, see: (a) Yus, M. *Chem. Soc. Rev.* **1996**, *25*, 155. (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225. (c) Yus, M. *Synlett* **2001**, 1197. (d) Yus, M.; Ramón, D. J. *Latv. J. Chem.* **2002**, *79*. (e) Ramón, D. J.; Yus, M. *Rev. Cubana Quim.* **2002**, *14*, 76. (f) Yus, M. In *The Chemistry of Organolithium Compounds*; Rappoport, Z.; Mareck, I. Eds.; J. Wiley & Sons: Chichester, **2004**, Chapter 11. For a mechanistic study, see: (g) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2001**, *42*, 3455. (h) Yus, M.; Herrera, R. P.; Guijarro, A. *Chem. Eur. J.* **2002**, *8*, 2574. (i) Herrera, R. P.; Guijarro, A.; Yus, M. *Tetrahedron Lett.* **2003**, *44*, 1309.
- (11) For a polymer-supported version of this reaction, see: (a) Gómez, C.; Ruiz, S.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1397. (b) Gómez, C.; Ruiz, S.; Yus, M. *Tetrahedron* **1999**, *55*, 7017. (c) Yus, M.; Gómez, C.; Candela, P. *Tetrahedron* **2002**, *58*, 6207.
- (12) For reviews, see: (a) Guijarro, D.; Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2011**, *15*, 375. (b) Guijarro, D.; Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2011**, *15*, 2362.
- (13) For reviews, see: (a) Yus, M.; Foubelo, F. *Rev. Heteroatom. Chem.* **1997**, *17*, 73. (b) Yus, M.; Foubelo, F. *Targets in Heterocyclic Systems* **2002**, *6*, 136. (c) Yus, M. *Pure Appl. Chem.* **2003**, *75*, 1453.
- (14) For reviews, see: (a) Nájera, C.; Yus, M. *Trends Org. Chem.* **1991**, *2*, 155. (b) Nájera, C.; Yus, M. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 67. (c) Nájera, C.; Yus, M. *Curr. Org. Chem.* **2003**, *7*, 867. (d) Nájera, C.; Sansano, J. M.; Yus, M. *Tetrahedron* **2003**, *59*, 9255. (e) Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667.
- (15) (a) Almena, J.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1994**, *59*, 3210. (b) Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1994**, *50*, 5775. (c) Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1996**, *52*, 8545. (d) Alonso, E.; Guijarro, D.; Martínez, P.; Ramón, D. J.; Yus, M. *Tetrahedron* **1999**, *55*, 11027. (e) Guijarro, D.; Martínez, P. J.; Nájera, C.; Yus, M. *ARKIVOC* **2004**, Part (iv), 5.
- (16) Yus, M.; Behloul, C.; Guijarro, D. *Synthesis* **2004**, 1274.
- (17) The formation of orange-red solutions of the trityl radical in THF has been described in the literature. See, for instance: Ashby, E. C.; Goel, A. B.; DePriest, R. N. *J. Org. Chem.* **1981**, *46*, 2429.
- (18) Chadwick, D. J.; Hodgson, S. T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 93.
- (19) With the aim of trying to broaden the substrate scope, we tried to prepare some other tetrazoles functionalized with either ester or amide groups but, unfortunately, all our attempts were unsuccessful.
- (20) Yus, M.; Martínez, P.; Guijarro, D. *Tetrahedron* **2001**, *57*, 10119.
- (21) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
- (22) Koguro, K.; Oga, T.; Mitsui, S.; Orita, R. *Synthesis* **1998**, 910.
- (23) Demko, Z. P.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 7945.
- (24) Curran, D. P.; Hadida, S.; Kim, S.-Y. *Tetrahedron* **1999**, *55*, 8997.

Detritylation of Protected Tetrazoles by Naphthalene-Catalysed LithiationKenza Bouchelouche,^a Cherif Behloul,^{*a} David Guijarro,^b Carmen Nájera^b and Miguel Yus^b