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Indium-, Magnesium-, and Zinc-Mediated Debenzylation of Protected 1*H*-Tetrazoles: A Comparative Study

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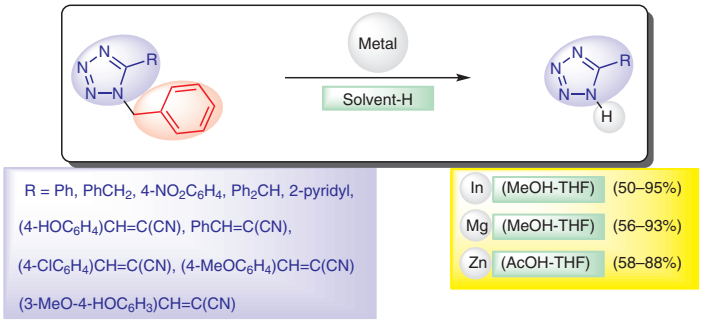
Dedicated to Professor Vicente Gotor on the occasion of his retirement



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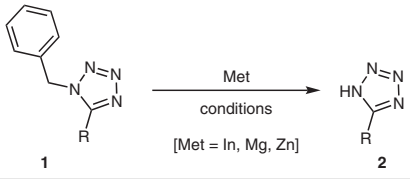
Abstract 5-Substituted 1-benzyltetrazoles are easily debenzylated to give the corresponding deprotected tetrazoles using dissolved metals under protic conditions: Mg/MeOH, In/MeOH, or Zn/$MeCO_2H$ are the procedures of choice for this transformation.

Key words debenzylation, magnesium, indium, zinc, tetrazoles

The benzyl moiety is commonly used in synthetic organic chemistry as protecting group for heteroatoms (O, S, N), mainly due its easy introduction and inherent stability.[1] Concerning the corresponding deprotection, the hydrogenolysis has been widely used in multistep organic synthesis, particularly for the debenzylation of *N*-benzylamines,[2] benzyl ethers,[3] benzyl esters,[4] and benzyl carbamates.[5] This methodology has also been used for the debenzylation of nitrogen-containing heterocycles.[6] Among this group of compounds are tetrazoles, which represent an important structural motif as an aromatic carboxylic acid surrogate in medicinal chemistry since many pharmaceuticals contain this unit.[7] On the other hand, in the last few years we have been interested in developing new methodologies based on dissolved metals (lithium, zinc, and indium). Thus, we have reported detritilations,[8] depivaloylations,[9] deacylations,[10] desilylations,[11] deallyloxy- and debenzyloxycarbonylations,[12] and the reductive removal of the Boc group.[13] In this article, we report the use of indium, magnesium, and zinc metals for the debenzylation of protected tetrazoles under protic conditions to the corresponding 5-substituted tetrazoles under mild reaction conditions.

Tetrazoles **2a–e**, precursors of the starting materials **1a–e**, were prepared by the standard procedure[14] by reacting the corresponding nitrile with sodium azide under reflux in toluene. For tetrazoles **2f–j** the corresponding carbonyl compound, malononitrile, and sodium azide were reacted in water at 50 °C.[15]

The benzylation of tetrazoles **2** was performed by treatment of 1*H*-tetrazoles with benzyl bromide in DMF and using potassium carbonate as base.[16] Once compounds **1** were prepared, the corresponding debenzylation was carried out using indium, magnesium, or zinc as the metallic component according to the general Scheme 1.

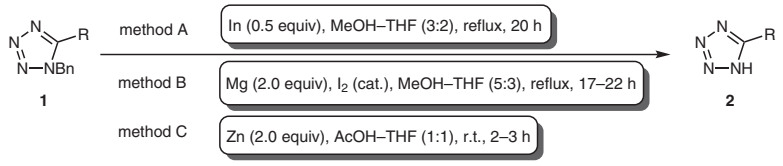


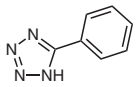
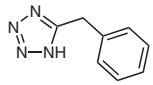
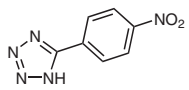
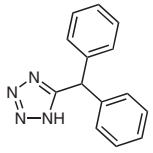
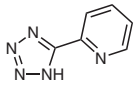
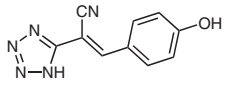
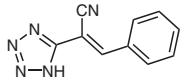
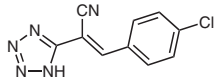
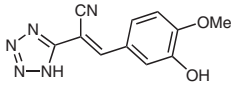
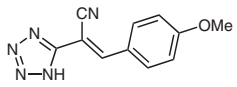
Scheme 1 Debenzylation of compounds **1**; for R groups, see Table 1

Indium-Promoted Debenzylation of Tetrazoles 1 (Method A)

Synthetic methodologies based on indium metal have shown to be very versatile and productive,[17] especially concerning electron transfer processes,[8d,f] which led us to apply this metal to the debenzylation of compounds **1**. When the tetrazole **1a** was treated with indium metal (1:0.5 molar ratio) in a mixture of methanol and THF at 0 °C for 24 hours no reaction was observed. However, total conversion occurred when the same reaction mixture was refluxed for 20 hours (Table 1, entry 1). These conditions were applied to a series of tetrazoles **1b–j**, some of them bearing functional groups such as nitro (**1c**; entry 3), pyridyl (**1e**; entry 5), a

Table 1 Debenzylation of Tetrazoles **1** with Indium, Magnesium, or Zinc



Entry	Starting material	R	Tetrazole product	Structure	A (In)	B (Mg)	C (Zn)
1	**1a**	Ph	**2a**		95	93	88
2	**1b**	$PhCH_2$	**2b**		80	85	87
3	**1c**	4-$O_2NC_6H_4$	**2c**		76	80	80
4	**1d**	Ph_2CH	**2d**		80	84	84
5	**1e**	2-pyridyl	**2e**		88	90	88
6	**1f**	(*E*)-C(CN)=CH(4-HOC_6H_4)	**2f**		50	56	60
7	**1g**	(*E*)-C(CN)=CHPh	**2g**		60	69	64
8	**1h**	(*E*)-C(CN)=CH(4-ClC_6H_4)	**2h**		51	58	68
9	**1i**	(*E*)-C(CN)=CH(4-$MeOC_6H_4$)	**2i**		55	60	58
10	**1j**	(*E*)-C(CN)=CH(3-MeO-4-HOC_6H_3)	**2j**		53	59	61

[a] Isolated yield after recrystallization based on the starting material **1**.

conjugate cyano group (**2g–j**; entries 7–10), chlorine (**2h**; entry 8), or phenolic OH (**2j**; entry 10), thus indicating that this methodology tolerates several functionalities.

Magnesium-Promoted Debenzylation of Tetrazoles 1 (Method B)

Although the mixture of magnesium and methanol has been used for the hydrogenation of double bonds,[18] as far as we know it has been reported to be useful only for the debenzylation of benzyl ethers.[19] In Table 1, the results from the deprotection of tetrazoles **1** with magnesium in methanol are shown. Treatment of the starting material **1a** with

magnesium in methanol or in mixture of methanol and THF at room temperature did not produce the expected debenzylated tetrazoles **2a** after 24 hour. However, after refluxing the former mixture (MeOH–THF 2:1) for 22 hours, a 40% yield of **2a** was obtained. An important increase in the yield was obtained (93%) when a flake of iodine was added to the reaction mixture (Table 1, entry 1). As it can be seen from Table 1, this methodology is also compatible with the same functionalities shown in Table 1.

Zinc-Promoted Debenzylation of Tetrazoles 1 (Method C)

Zinc metal in combination with a proton source can also be useful as dissolving metal for electron transfer reactions.[8e] Thus, by treating protected tetrazoles **1** with zinc metal and acetic acid in THF at room temperature, the corresponding debenzylated products **2** were isolated after 2–3 hours. Also in this case several functionalities were compatible with the reaction conditions used in the deprotection, as it can be seen in Table 1.

Discussion

In general, debenzylation of substituted tetrazoles with indium, magnesium, or zinc metals works properly, especially for non-functionalized compounds **1**, giving the expected deprotected tetrazoles in isolated yields over 80%. However, for highly functionalized tetrazoles **1f–j** containing a conjugate nitrile, isolated yields decrease to 50–70% due to secondary reactions and/or partial decomposition of the starting material/product under the assayed reaction conditions. Concerning the reaction conditions, whereas Zn works at room temperature, In and Mg need refluxing in THF–MeOH for the reaction to proceed. The reaction times for Zn reductions (2–3 h) were significantly shorter than those for In and Mg deprotections (17–22 h).

Concerning a possible reaction mechanism, we presume that a single electron transfer (SET) takes place from the metal to the starting tetrazole **1** cleaving the benzyl–nitrogen bond to give a benzyl radical **I** and the heterocyclic anion **II**, both stabilized by delocalization (Figure 1). Benzyl radical **I** decomposes by a hydrogen atom abstraction to give toluene,[20] meanwhile the hydrolysis of heterocyclic anion **II** leads to the formation of deprotected tetrazole **2**. A similar mechanism could be also involved in the detritylation of protected tetrazoles.[8]

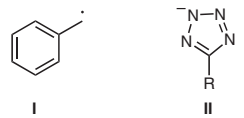


Figure 1 Proposed radical intermediates in the metal debenzylation of tetrazoles **1**

Considering the obtained results, and taking into account reaction conditions and the price of metals,[21] we consider that zinc would be the metal of choice for compounds that are not sensitive to acetic acid. For acid sensitive compounds, probably magnesium would be the best metal to be used in debenzylation of protected tetrazoles due to reaction times, yields, and metal price.

From the results shown here, we can conclude that the debenzylation of 1-benzyl 5-substituted tetrazoles **1** can be performed with indium/methanol, magnesium/methanol, and zinc/acetic acid, in general in good yields to the corresponding tetrazoles **2**. Comparing the three procedures, and taking into account financial aspects, the use of zinc seems to be the most effective for substrates non-sensitive to acidic conditions. For substrates sensitive to acid, magnesium or indium metal can be used, the first one being preferable considering reaction conditions and metal prices.

General Information

FTIR spectra were obtained with a Nicolet Impact 400D spectrophotometer using KBr pellets. NMR spectra were recorded with a Bruker AV400 (400 MHz for 1H and 100 MHz for ^{13}C), DMSO-d_6 as solvent and TMS (δ = 0.00 ppm, 1H) and DMSO-d_6 (δ = 2.50 ppm, ^{1}H and δ = 39.75 ppm, ^{13}C) as internal standards; chemical shifts are given in δ (ppm) and coupling constants (*J*) in Hz. High-resolution mass spectra (HRMS) were carried out in a Agilent 7200, in the electrospray ionization mode (ESI) using a TOF analyzer. All reagents used for the synthesis of tetrazoles **2** and *N*-benzyltetrazoles **1** were commercially available and used without any further purification.

Tetrazoles 2a–e;[14] General Procedure

A mixture of the corresponding nitrile (50 mmol), NaN_3 (65 mmol) and $Et_3N{\cdot}HCl$ (150 mmol) in toluene (100 mL) was stirred at 110 °C for 17–30 h (TLC monitoring). After cooling to r.t., the mixture was extracted with H_2O (100 mL) and the aqueous phase was acidified with aq 36% HCl. The solid formed was filtered, washed with H_2O (3 × 10 mL), and dried under reduced pressure to give the corresponding product **2a–e**.

5-Phenyl-1*H*-tetrazole (2a)[8c]

White solid; yield: 3.0 g (41%); mp 215–216 °C.

IR (KBr): 3333, 2588, 2511, 1055, 925, 789, 643, 619 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.55–7.62 (m, 3 H), 8.01–8.10 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 124.1 (CH), 127.0 (C), 129.4, 131.3 (CH), 155.3 (C).

HRMS (ESI): *m*/*z* calcd for $C_7H_6N_4$ (M^+): 146.0592; found: 146.0598.

5-Benzyl-1*H*-tetrazole (2b)[8c]

White solid; yield: 2.0 g (25%); mp 123–124 °C.

IR (KBr): 2949, 2864, 2709, 1073, 961, 835, 694, 608 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.31 (s, 2 H), 7.25–7.37 (m, 5 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 29.0 (CH_2), 127.1, 128.7, 128.8 (CH), 136.0, 155.3 (C).

HRMS (ESI): *m*/*z* calcd for $C_8H_8N_4$ (M^+): 160.0749; found: 160.0748.

5-(4-Nitrophenyl)-1*H*-tetrazole (2c)[22]

Green solid; yield: 2.9 g (32%); mp 146–147 °C.

IR (KBr): 3453, 2543, 1018, 988, 978, 851, 702, 634 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.29–8.33 (m, 2 H), 8.43–8.46 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 125.0, 128.6 (CH), 131.0, 149.1, 155.8 (C).

HRMS (ESI): *m*/*z* calcd for $C_7H_5N_5O_2$ (M^+): 191.0443; found: 191.0452.

5-Benzhydryl-1*H*-tetrazole (2d)[8c]

White solid; yield: 3.0 g (27%); mp 165–166 °C.

IR (KBr): 3360, 2680, 1082, 990, 845, 695, 617 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.97 (s, 1 H), 7.11–7.48 (m, 10 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 46.2 (CH), 127.65, 128.9, 129.15 (CH), 140.5, 158.5 (C).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{12}N$ ($M^+ - N_3$): 194.0970; found: 194.0954.

2-(1*H*-Tetrazol-5-yl)pyridine (2e)[22]

Brown solid; yield: 3.0 g (27%); mp 208–210 °C.

IR (KBr): 3091, 2650, 1539, 1114, 975, 899, 695, 615 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.54–7.75 (m, 1 H), 8.04–8.19 (m, 1 H), 8.27 (dd, *J* = 7.4, 3.8 Hz, 1 H), 8.84 (t, *J* = 4.3 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 123.0, 126.5, 138.65 (CH), 144.1 (C), 150.5 (CH), 155.3 (C).

HRMS (ESI): *m*/*z* calcd for $C_6H_5N_3$ ($M^+ - N_2$): 119.0483; found: 119.0491.

Tetrazoles 2f–j;[15] General Procedure

A mixture of the corresponding carbonyl compound (1 mmol), malononitrile (1 mmol), and NaN_3 (2 mmol) in H_2O (5 mL) was stirred at 50 °C until the starting materials were consumed (TLC monitoring). The reaction mixture was filtered and to the filtrate was added aq 2 N HCl (30 mL) until a precipitate was formed. The solid was filtered and dried in a drying oven to furnish the expected tetrazoles **2f–j**.

(*E*)-3-(4-Hydroxyphenyl)-2-(1*H*-tetrazol-5-yl)acrylonitrile (2f)[23]

White solid; yield: 0.20 g (94%); mp 159–161 °C.

IR (KBr): 3330, 2642, 1509, 1411, 988, 821, 653, 604 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.99 (d, *J* = 8.3 Hz, 2 H), 7.96 (d, *J* = 8.3 Hz, 2 H), 8.23 (s, 1 H), 10.68 (br s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 91.9 (CN), 116.3 (C), 116.75 (CH), 123.7 (C), 133.1 (CH), 148.8, 155.6, 162.2 (C).

HRMS (ESI): *m*/*z* calcd for $C_{10}H_6NO$ ($M^+ - HN_4$): 156.0449; found: 156.0452.

(*E*)-3-Phenyl-2-(1*H*-tetrazol-5-yl)acrylonitrile (2g)[23]

Pale yellow solid; yield: 0.10 g (51%); mp 168–170 °C.

IR (KBr): 3310, 2641, 1570, 1477, 982, 848, 669, 608 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.58–7.63 (m, 3 H), 8.00–8.15 (m, 2 H), 8.42 (d, *J* = 3.6 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 97.4 (CN), 115.9 (C), 129.6, 130.0, 130.3, 132.6 (CH), 148.8, 155.9 (C).

HRMS (ESI): *m*/*z* calcd for $C_{10}H_6N_3$ ($M^+ - HN_2$): 168.0562; found: 168.0566.

(*E*)-3-(4-Chlorophenyl)-2-(1*H*-tetrazol-5-yl)acrylonitrile (2h)[24]

White solid; yield: 0.16 g (75%); mp 158–160 °C.

IR (KBr): 3158, 2359, 1585, 1497, 930, 810, 691, 623 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.62–7.72 (m, 2 H), 8.05 (d, *J* = 8.6 Hz, 2 H), 8.41 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 98.1 (CN), 115.8 (C), 129.15, 129.8 (CH), 131.5 (C), 131.9 (CH), 137.3, 147.3 (C).

HRMS (ESI): *m*/*z* calcd for $C_{10}H_5ClN_2$ ($M^+ - HN_3$): 188.0141; found: 188.0140.

(*E*)-3-(4-Methoxyphenyl)-2-(1*H*-tetrazol-5-yl)acrylonitrile (2i)[24]

Green solid; yield: 0.20 g (88%); mp 76–78 °C.

IR (KBr): 3120, 2773, 1589, 1462, 954, 864, 651, 604 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.85 (s, 3 H), 7.14 (d, *J* = 8.6 Hz, 2 H), 8.01 (d, *J* = 8.6 Hz, 2 H), 8.25 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 56.1 (CH_3), 93.9 (CN), 115.35 (CH), 116.6 (C), 125.3, 132.6 (CH), 148.05, 155.9, 163.0 (C).

HRMS (ESI): *m*/*z* calcd for $C_{10}H_9N_3O$ ($M^+ - CN_2$): 187.0746; found: 187.0733.

(*E*)-3-(4-Hydroxy-3-methoxyphenyl)-2-(1*H*-tetrazol-5-yl)acrylonitrile (2j)[24]

Green solid; yield: 0.16 g (75%); mp 88–89 °C.

IR (KBr): 3121, 2225, 1574, 1458, 998, 844, 644, 620 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.88 (s, 3 H), 7.00 (d, *J* = 8.3 Hz, 1 H), 7.53 (d, *J* = 8.4 Hz, 1 H), 7.75 (s, 1 H), 8.22 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 56.0 (CH_3), 91.9 (CN), 113.2, 116.4 (CH), 116.8 (C), 124.0, 126.3, (CH), 148.2, 148.9, 151.9, 155.75 (C).

HRMS (ESI): *m*/*z* calcd for $C_{10}H_6N_3O$ ($M^+ - N_2CH_3O$): 184.0511; found: 184.0537.

Benzylation of Tetrazoles 2;[16] General Procedure

A mixture of the corresponding tetrazole **2** (1 mmol), benzyl bromide (1 mmol), and K_2CO_3 (2 mmol) in DMF (5 mL) was stirred a 0 °C until the conversion was complete (TLC monitoring). The reaction mixture was filtered and to the filtrate was added H_2O (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), and after evaporation of the solvent (15 Torr) the resulting residue was purified by recrystallization (EtOH) to yield tetrazoles **1**.

1-Benzyl-5-phenyl-1*H*-tetrazole (1a)[25]

White solid; yield: 0.18 g (77%); mp 78–80 °C.

IR (KBr): 1651, 1274, 979, 854, 773, 615 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.80 (s, 2 H), 7.32–7.50 (m, 8 H), 8.13 (dd, *J* = 7.5, 2.3 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 56.8 (CH_2), 126.9, 128.4, 128.8, 128.9, 129.0, 130.3 (CH), 133.4, 162.7, 165.4 (C).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{12}N_4$ (M^+): 236.1062; found: 236.1051.

1,5-Dibenzyl-1*H*-tetrazole (1b)[26]

White solid; yield: 0.2 g (80%); mp 140–142 °C.

IR (KBr): 1604, 1278, 976, 854, 693, 601 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.21 (s, 2 H), 5.68 (s, 2 H), 7.18–7.37 (m, 10 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 31.9, 56.6 (CH_2), 126.9, 128.4, 128.6, 128.8, 128.9, 129.0 (CH), 133.35, 136.7, 165.9 (C).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{12}N_3$ ($M^+ - CH_2N$): 222.1031; found: 222.1027.

1-Benzyl-5-(4-nitrophenyl)-1*H*-tetrazole (1c)[25]

Green solid; yield: 0.18 g (66%); mp 76–78 °C.

IR (KBr): 1604, 1282, 965, 852, 651, 601 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 5.84 (s, 2 H), 7.33–7.52 (m, 5 H), 8.30–8.33 (m, 4 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 57.2 (CH_2), 124.2, 127.7 128.5, 129.1, 129.2 (CH), 132.9, 133.2, 148.85, 163.6 (C).

HRMS (ESI): *m*/*z* calcd for $C_7H_5N_5O_2$ (M^+): 191.0443; found: 191.0452.

5-Benzhydryl-1-benzyl-1*H*-tetrazole (1d)

White solid; yield: 0.27 g (84%); mp 133–135 °C.

IR (KBr): 1598, 1254, 953, 890, 688, 608 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 5.35–5.37 (m, 3 H), 7.00–7.18 (m, 9 H), 7.19–7.38 (m, 6 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 46.55 (CH), 51.1 (CH_2), 127.5, 127.8, 128.6, 128.9, 129.2 (CH), 133.15, 138.1, 156.2 (C);

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{18}N_4$ (M^+): 326.1531; found: 326.1522.

2-(1-Benzyl-1*H*-tetrazol-5-yl)pyridine (1e)[27]

Green solid; yield: 0.20 g (88%); mp 75–77 °C.

IR (KBr): 1589, 1263, 999, 876, 690, 601 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 6.25 (s, 2 H), 7.19–7.52 (m, 6 H), 7.82–7.92 (m, 1 H), 8.33 (d, *J* = 7.9 Hz, 1 H), 8.74 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 52.6 (CH_2), 124.5, 125.5, 128.3, 128.4, 128.7 (CH), 134.8 (C), 137.5 (CH), 144.7 (C), 149.3 (CH), 151.6 (C).

HRMS (ESI): *m*/*z* calcd for $C_{13}H_9N_3$ ($M^+ - N_2H_2$): 207.0796; found: 207.0792.

(*E*)-2-(1-Benzyl-1*H*-tetrazol-5-yl)-3-(4-hydroxyphenyl)acrylonitrile (1f)[28]

Orange solid; yield: 0.23 g (77%); mp 160–162 °C.

IR (KBr): 2360, 1511, 1439, 1261, 997, 895, 672, 614 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 5.13 (s, 2 H), 5.78 (s, 1 H), 7.05 (d, *J* = 8.9 Hz, 2 H), 7.33–7.46 (m, 5 H), 7.97 (d, *J* = 8.8 Hz, 2 H), 8.20 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 52.6 (CH_2), 95.3 (CN), 115.5 (CH), 116.2, 125.45 (C), 127.5, 128.5, 129.1, 132.4 (CH), 132.8, 136.0 (C), 146.7 (CH), 161.8 (C).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{11}NO$ ($M^+ - N_4H_2$): 245.0841; found: 245.0829.

(*E*)-2-(1-Benzyl-1*H*-tetrazol-5-yl)-3-phenylacrylonitrile (1g)[29]

Green solid; yield: 0.19 g (67%); mp 190–192 °C.

IR (KBr): 2332, 1596, 1443, 1211, 973, 856, 697, 605 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 5.80 (s, 2 H), 7.33–7.51 (m, 8 H), 7.91–8.02 (m, 2 H), 8.29 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 57.2 (CH_2), 98.6 (CN), 115.6 (C), 128.6, 129.1, 129.2, 129.3, 130.1, 132.1 (CH), 132.2 (C), 147.3 (CH), 161.8 (C).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{13}N_5$ (M^+): 287.1171; found: 287.1148.

(*E*)-2-(1-Benzyl-1*H*-tetrazol-5-yl)-3-(4-chlorophenyl)acrylonitrile (1h)

Green solid; yield: 0.14 g (45%); mp 170–172 °C.

IR (KBr): 2224, 1588, 1474, 1211, 962, 833, 687, 616 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 5.80 (s, 2 H), 7.32–7.53 (m, 7 H), 7.91 (d, *J* = 8.6 Hz, 2 H), 8.24 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 57.3 (CH_2), 99.1 (CN), 115.3 (C), 128.6, 129.1, 129.25, 129.5 (CH), 130.8 (C), 131.3 (CH), 132.7, 138.2 (C), 145.7 (CH), 161.6 (C).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{12}ClN_5$ (M^+): 321.0781; found: 321.0775.

(*E*)-2-(1-Benzyl-1*H*-tetrazol-5-yl)-3-(4-methoxyphenyl)acrylonitrile (1i)

Green solid; yield: 0.19 g (60%); mp 76–78 °C.

IR (KBr): 2221, 1594, 1497, 1217, 970, 825, 683, 613 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.87 (s, 3 H), 5.79 (s, 2 H), 6.98 (d, *J* = 8.9 Hz, 2 H), 7.36–7.47 (m, 5 H), 7.97 (d, *J* = 8.8 Hz, 2 H), 8.20 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 55.6 (CH_3), 57.4 (CH_2), 95.2 (CN), 114.6, 116.2, 125.2 (C), 127.9, 128.5, 129.1, 129.2, 132.3 (CH), 132.9 (C), 146.8 (CH), 162.25, 162.7 (C).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{15}N_5O$ (M^+): 317.1277; found: 317.1268.

(*E*)-2-(1-Benzyl-1*H*-tetrazol-5-yl)-3-(4-Hydroxy-3-methoxyphenyl)acrylonitrile (1j)

Green solid; yield: 0.20 g (63%); mp 170–172 °C.

IR (KBr): 2225, 1512, 1426, 1253, 939, 801, 671, 603 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.96 (s, 3 H), 5.23 (s, 2 H), 5.78 (s, 1 H), 6.94 (d, *J* = 8.5 Hz, 1 H), 7.38–7.43 (m, 6 H), 7.79 (s, 1 H), 8.17 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 56.1 (CH_3), 57.1 (CH_2), 95.3 (CN), 113.0 (CH), 116.2 (C), 125.7, 127.2, 128.1, 128.5, 128.7 (CH), 132.8, 136.1 (C), 147.0 (CH), 149.6, 151.6, 162.1 (C).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{15}NO_2$ ($M^+ - N_4$) 277.1103; found: 277.1085.

Indium-Promoted Debenzylation of Tetrazoles 1; General Procedure

A mixture of the corresponding benzylated tetrazole **1** (0.1 mmol) and In powder (58 mg, 0.5 mmol) in MeOH (6 mL) and THF (4 mL) was refluxed until the starting material disappeared (20 h). After cooling to r.t., aq 1 M HCl (0.5 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and evaporated (15 Torr). The resulting residue was recrystallized to give the corresponding pure product **2**. All the products were fully characterized by comparison of their physical and spectroscopic data with pure samples of **2** (Table 1).

Magnesium-Promoted Debenzylation of Tetrazoles 1; General Procedure

To a solution of the corresponding benzylated tetrazole **1** (1 mmol) in MeOH (5 mL) and THF (3 mL) was added freshly scratched Mg turnings (48 mg, 2 mmol) and a tiny crystal of I_2. The reaction mixture was refluxed until the starting material was consumed (17–22 h) and

then cooled to 0 °C. The mixture was diluted with Et_2O (5 mL) and 10% aq NH_4Cl was added. The mixture was stirred until it became clear and then separated. The process was repeated once again and the combined Et_2O extracts (2 × 5 mL) were dried (Na_2SO_4) and evaporated (15 Torr) to give a residue that was purified by recrystallization in EtOH, to afford the corresponding pure deprotected tetrazole **2**. All the products were fully characterized by comparison of their physical and spectroscopic data with pure samples of **2** (Table 1).

Zinc-Promoted Debenzylation of Tetrazoles 1; General Procedure

To a stirred solution of the corresponding benzylated tetrazole **1** (2.5 mmol) in THF (1.0 mL) at r.t. was added Zn dust (5 mmol) and stirring was continued for an additional 30 min. The resulting suspension was cooled with an ice-water bath and glacial AcOH (1.0 mL) was added slowly. The cooling bath was removed and the final mixture was stirred for further 1–3 h and then filtered. The collected solids were washed with H_2O (3 × 10 mL) and CH_2Cl_2 (3 × 15 mL). The organic phases were separated, combined, and washed with H_2O (2 × 10 mL), sat. aq $NaHCO_3$ (3 × 10 mL), and brine (3 × 15 mL). After drying (Na_2SO_4), and filtration, the solvent was evaporated under reduced pressure (15 Torr). The resulting residue was purified by recrystallization to give the corresponding pure compound **2**. All the products were characterized by comparison of their physical and spectroscopic data with pure samples of **2** (Table 1).

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610170.

References

(1) See, for instance: Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*; Wiley-Interscience: Hoboken, **2007**, 4th ed..
(2) Babu, S. N. N.; Srinivasa, G. R.; Santhosh, D. C.; Gowda, D. C. *J. Chem. Res.* **2004**, 66.
(3) Felpin, F.-X.; Fouquet, E. *Chem. Eur. J.* **2010**, *16*, 12440.
(4) Sultane, P. R.; Mete, T. B.; Bhat, R. G. *Tetrahedron Lett.* **2015**, *56*, 2067.
(5) Papageorgiou, E. A.; Gaunt, M. J.; Yu, J.-q.; Spencer, J. B. *Org. Lett.* **2000**, *2*, 1049.
(6) Tanielyan, S. K.; Alvez, G.; Marín, N.; Agustine, R. L. *Top. Catal.* **2014**, *57*, 1359.
(7) Popova, E. A.; Protas, A. V.; Trifonov, R. E. *Anticancer Agent Med. Chem.* **2017**, *17*, 1856.
(8) (a) Yus, M.; Behloul, C.; Guijarro, D. *Synthesis* **2003**, 2179. (b) Behloul, C.; Guijarro, D.; Yus, M. *Synthesis* **2004**, 1274. (c) Behloul, C.; Bouchelouche, K.; Guijarro, D.; Nájera, C.; Yus, M. *Synthesis* **2014**, *46*, 2065. (d) Behloul, C.; Bouchelouche, K.; Guijarro, D.; Foubelo, F.; Nájera, C.; Yus, M. *Synlett* **2015**, *26*, 2399. (e) Behloul, C.; Bouchelouche, K.; Hadji, Y.; Benseghir, S.; Guijarro, D.; Nájera, C.; Yus, M. *Synthesis* **2016**, *48*, 2455. (f) Behloul, C.; Chouti, A.; Guijarro, D.; Foubelo, F.; Nájera, C.; Yus, M. *Tetrahedron* **2016**, *72*, 7937. (g) Behloul, C.; Chouti, A.; Chabour, I.; Bey, H. B.; Guijarro, D.; Foubelo, F.; Nájera, C.; Yus, M. *Tetrahedron Lett.* **2016**, *57*, 3526.
(9) Behloul, C.; Chouti, A.; Guijarro, D.; Nájera, C.; Yus, M. *Synthesis* **2015**, *47*, 507.
(10) Behloul, C.; Guijarro, D.; Yus, M. *Synthesis* **2006**, 309.
(11) Behloul, C.; Guijarro, D.; Yus, M. *Tetrahedron* **2005**, *61*, 6908.
(12) Behloul, C.; Guijarro, D.; Yus, M. *Tetrahedron* **2005**, *61*, 9319.
(13) Almansa, R.; Behloul, C.; Guijarro, D.; Yus, M. *ARKIVOC* **2007**, *(vii)*, 41.
(14) Koguro, K.; Oga, T.; Mitsui, S.; Orita, R. *Synthesis* **1998**, 910.
(15) Tisseh, Z. N.; Dabiri, M.; Nobahar, M.; Khavasi, H. R.; Bazgir, A. *Tetrahedron* **2012**, *68*, 1769.
(16) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Organic Synthesis*; Wiley-Interscience: Hoboken, **2007**, 4th ed. 814.
(17) See, for instance: (a) Cintas, P. *Synlett* **1995**, 1087. (b) Auge, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739.
(18) Hutchins, R. O. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, **1995**, 3202–3204.
(19) Huang, W.; Zhang, X.; Liu, H.; Shen, J.; Jiang, H. *Tetrahedron Lett.* **2005**, *46*, 5965.
(20) Boyle, W. J.; Bunnett, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 1418.
(21) Prices for powdered metals from the Aldrich catalogue: In (99.99%), 10 g/115.50 €; Mg (≥99%), 100 g/24.40 €; Zn (≥99%), 500 g/55.80 €.
(22) Rama, V.; Kanagaraj, K.; Pitchumani, K. *J. Org. Chem.* **2011**, *76*, 9090.
(23) Tisseh, Z. N.; Dabiri, M.; Nobahar, M.; Khavasi, H. R.; Bazgir, A. *Tetrahedron* **2012**, *68*, 1769.
(24) Ahmed, N.; Siddiqui, Z. N. *RSC Adv.* **2015**, *5*, 16707.
(25) Katritzky, A. R.; Cai, C.; Meher, N. K. *Synthesis* **2007**, 1204.
(26) Suzuki, H.; Hwang, Y. S.; Nakaya, C.; Matano, Y. *Synthesis* **1993**, 1218.
(27) Kiselyov, A. S. *Tetrahedron Lett.* **2005**, *46*, 4851.
(28) Safaei-Ghomi, J.; Paymard-Samani, S.; Zahedi, S.; Shahbazi-Alavi, H. *Z. Naturforsch. B* **2015**, *70*, 819.
(29) Maddila, S.; Naicker, K.; Momin, M. I. K.; Rana, S.; Gorle, S.; Maddila, S.; Yalagala, K.; Singh, M.; Koorbanally, N. A.; Jonnalagadda, S. B. *Med. Chem. Res.* **2016**, *25*, 283.