Indium-, magnesium-, and zinc-mediated debenzylation of protected 1H-tetrazoles: A comparative study

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A B S T R A C T

5-Substituted 1-benzyltetrazoles (**1**) are easily debenzylated to give the corresponding deprotected tetrazoles (**2**) using dissolved metals under protic conditions: Mg/MeOH, In/MeOH or Zn/$MeCO_2H$ are the procedures of choice for this transformation.

Dedicated to Professor Vicente Gotor on occasion of his retirement

Keywords:

Debenzylation

Magnesium

Indium

Zinc

Tetrazoles

1. Introduction

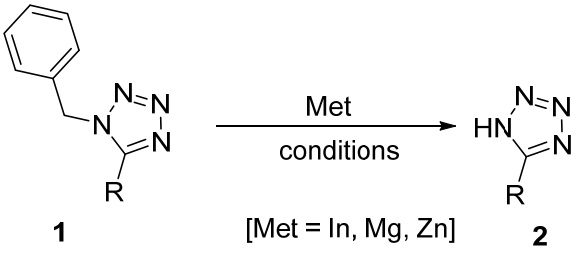
The benzyl moiety is commonly used in synthetic organic chemistry as protecting group for heteroatoms (O, S, N), mainly due its easy introduction and inherent stability.[1] Concerning the corresponding deprotection, the hydrogenolysis has been widely used in multistep organic synthesis, particularly for the debenzylation of *N*-benzyl amines,[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] depivaloilations,[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, so the corresponding 5-substituted tetrazoles are easily liberated under mild reaction conditions.

2. Results

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

The benzylation of tetrazoles **2** was performed by treatment of 1H-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.



a: R = Ph
b: R = CH_2Ph
c: R = 4-$O_2NC_6H_4$
d: R = $CHPh_2$
e: R = 2-pyridyl
f: R = (*E*)-C(CN)=CH(4-HOC_6H_4)
g: R = (*E*)-C(CN)=CHPh
h: R = (*E*)-C(CN)=CH(4-ClC_6H_4)
i: R = (*E*)-C(CN)=CH(4-$MeOC_6H_4$)
j: R = (*E*)-C(CN)=CH(3-MeO-4-HOC_6H_3)

Scheme 1. Debenzylation of compounds **1**.

2.1. 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] so we decided to apply this metal to the debenzylation of compounds **1**.

When we treated the tetrazole **1a** with indium metal (1:0.5 molar ratio) in a mixture of methanol and THF at 0 ºC for 24 h no reaction was observed. However, total conversion occurred when the same reaction mixture was refluxed for 20 h (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**; Table 1, entry 3), pyridyl (**1e**; Table 1, entry 5), a conjugate cyano group (**2g-j**; Table 1, entries 7-10), chlorine (**2h**; Table 1, entry 8)

or phenolic OH (**2j**; Table 1, entry 10), so indicating that this methodology tolerates several functionalities.

2.2. 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 are shown the results coming from the deprotection of tetrazoles **1** with magnesium in methanol. 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 h. However, after refluxing the former mixture (MeOH/THF: 2/1) for 22 h 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 2, entry 1). As it can be seen in Table 1, this methodology is also compatible with the same functionalities shown in Table 1.

2,3. 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, 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 h. Also in this case several functionalities were compatible with the reaction conditions used in the deprotection, as it can be seen in Table 1.

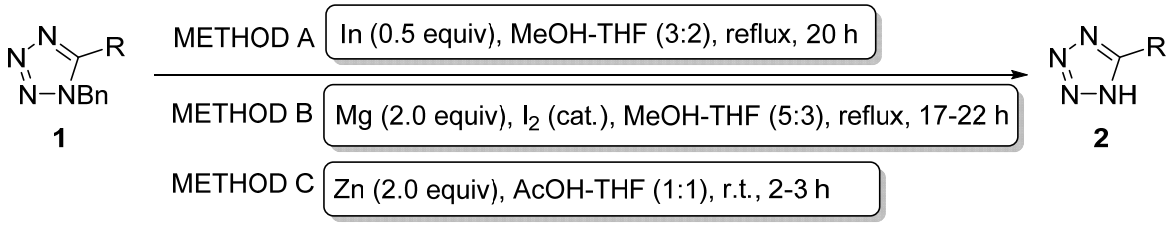
3. Discussion

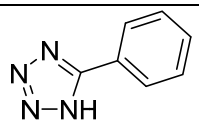
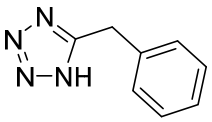
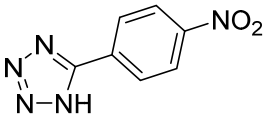
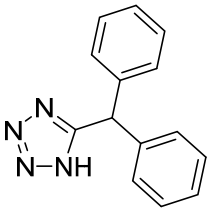
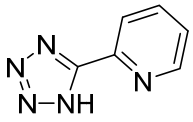
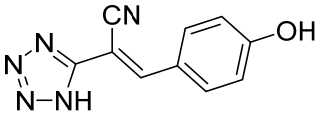
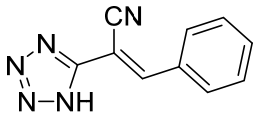
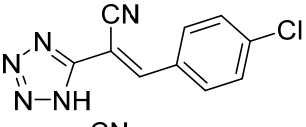
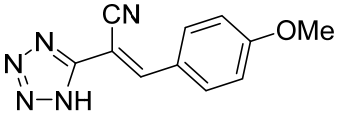
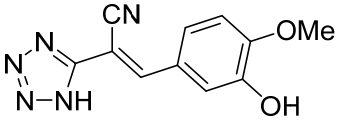
In general, debenzylation of substituted tetrazoles with indium, magnesium or zinc metals works properly, especially for non-functionalized compounds **1**, giving the expected deprotected tetrazoles with isolated yields over 80%. However, for highly functionalized tetrazoles containing a conjugate nitrile **1f-j** isolated, yields decrease until 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 THF/MeOH reflux for the reaction to proceed. Finally, short reaction times (2-3 h) were needs for Zn compare to In and Mg (17-22 h).

Concerning a possible reaction mechanism, we think 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. A second SET would transform the radical into the benzyl anion **III**, which after the final hydrolysis gave toluene and the deprotected tetrazole **2**. The same mechanistic proposal was accepted for the corresponding detritylation of protected tetrazoles.[8]

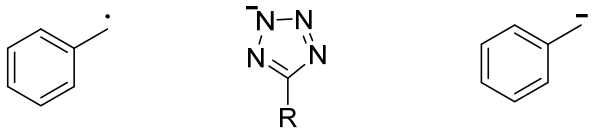
Table 1

Debenzylation of tetrazoles **1** with indium, magnesium or zinc



Entry	Starting material No.	R	Tetrazole **2**, method and yield (%)[a] No.	Structure	A (In)	B (Mg)	C (Zn)
1	**1a**	Ph	**2a**		95	93	88
2	**1b**	$PhCH_2$	**2b**		80	85	87
3	**1c**	$4\text{-}NO_2C_6H_4$	**2c**		76	80	80
4	**1d**	Ph_2CH	**2d**		80	84	84
5	**1e**	2-pyridyl	**2e**		88	90	88
6	**1f**	$(4\text{-}HOC_6H_4)CH{=}C(CN)$	**2f**		50	56	60
7	**1g**	$PhCH{=}C(CN)$	**2g**		60	69	64
8	**1h**	$(4\text{-}ClC_6H_4)CH{=}C(CN)$	**2h**		51	58	68
9	**1i**	$(4\text{-}MeOC_6H_4)CH{=}C(CN)$	**2i**		55	60	58
10	**1j**	$(3\text{-}MeO,4\text{-}HOC_6H_3)CH{=}C(CN)$	**2j**		53	59	61

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



I II III

Considering the obtained results, and taking into account reaction conditions and the price of metals,[20] we consider that zinc would be the metal of choice for compounds that are not sensitive to acetic acid. For these compounds, probably magnesium would be the best metal to be used in debenzylation of protected tetrazoles due to reaction times, yields and metal price.

4. Conclusions

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 with good yields in 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. If this is the case, magnesium or indium metal can be used, the first one being preferable considering reaction conditions and metal prices.

5. Experimental

5.1. General

For general information see reference 8f.

5.2. General procedure for the preparation of tetrazoles 2a-e[14]

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 ºC for 17-30 h (TLC monitoring). After cooling at r.t. the mixture was extracted with water (100 mL) and the aqueous phase was acidified with 36% HCl. The solid formed was filtered, washed with water (3 × 10 mL) and dried under reduced pressure to give products **2a-e**. Yields, physical and spectroscopic data follow.

5.2.1. 5-Phenyl-1H-tetrazole (**2a**).[8c] White solid; yield: 3.0 g (41%), mp 215−216 ºC; IR ν(KBr): 3333, 2588, 2511, 1055, 925, 789, 643, 619 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.55−7.62 (m, 3H), 8.01−8.10 (m, 2H); ^{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): calculated for $C_7H_6N_4$ (M^+) 146.0592, found 146.0598.

5.2.2. 5-Benzyl-1H-tetrazole (**2b**).[8c] White solid; yield: 2.0 g (25%), mp 123−124 ºC; IR ν(KBr): 2949, 2864, 2709, 1073, 961, 835, 694, 608 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.31 (s, 2H), 7.25−7.37 (m, 5H); ^{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): calculated for $C_8H_8N_4$ (M^+) 160.0749, found 160.0748.

5.2.3. 5-(4-Nitrophenyl)-1H-tetrazole (**2c**).[21] Green solid; yield: 2.9 g (32%), mp 146−147 ºC; IR ν (KBr): 3453, 2543, 1018, 988, 978, 851, 702, 634 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.29−8.33 (m, 2H), 8.43−8.46 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 125.0, 128.6 (CH), 131.0, 149.1, 155.8 (C); HRMS (ESI): calculated for $C_7H_5N_5O_2$ (M^+) 191.0443, found 191.0452.

5.2.4. 5-Benzhydryl-1H-tetrazole (**2d**).[8c] White solid; yield: 3.0 g (27%), mp 165−166 ºC; IR ν (KBr): 3360, 2680, 1082, 990, 845, 695, 617 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.97 (s, 1H), 7.11−7.48 (m, 10H); ^{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): calculated for $C_{14}H_{12}N$ (M^+-N_3) 194.0970, found 194.0954.

5.2.5. 2-(1H-Tetrazol-5-yl)pyridine (**2e**).[21] Brown solid; yield: 3.0 g (27%), mp 208−210 ºC; IR ν (KBr): 3091, 2650, 1539, 1114, 975, 899, 695, 615 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.54−7.75 (m, 1H), 8.04−8.19 (m, 1H), 8.27 (dd, J = 7.4, 3.8 Hz, 1H), 8.84 (t, J = 4.3 Hz, 1H); ^{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): calculated for $C_6H_5N_3$ (M^+-N_2) 119.0483, found 119.0491.

5.3. General procedure for the preparation of tetrazoles 2f-j[15]

A mixture of the corresponding carbonyl compound (1 mmol), malononitrile (1 mmol) and NaN_3 (2 mmol) in water (5 mL) was stirred at 50 ºC until the starting materials were consumed (TLC monitoring). The reaction mixture was filtered and to the filtrate was added 2N HCl (30 mL) so a precipitate was formed. The solid was filtered and dried in a drying oven to furnish the expected tetrazoles **2f-j**. Yields, physical and spectroscopic data follow.

*5.3.1. (*E*)-3-(4-Hydroxyphenyl)-2-(1H-tetrazol-5-yl)acrylonitrile* (**2f**).[22] White solid; yield: 0.20 g (94%), mp 159−161 ºC; IR ν (KBr): 3330, 2642, 1509, 1411, 988, 821, 653, 604 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 6.99 (d, J = 8.3 Hz, 2H), 7.96 (d, J = 8.3 Hz, 2H), 8.23 (s, 1H), 10.68 (br s, 1H); ^{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): calculated for $C_{10}H_6NO$ (M^+-HN_4) 156.0449, found 156.0452.

*5.3.2. (*E*)-3-Phenyl-2-(1H-tetrazol-5-yl)acrylonitrile* (**2g**).[22] Pale yellow solid; yield: 0.10 g (51%), mp 168−170 ºC; IR ν (KBr): 3310, 2641, 1570, 1477, 982, 848, 669, 608 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.58−7.63 (m, 3H), 8.00−8.15 (m, 2H), 8.42 (d, J = 3.6 Hz, 1H); ^{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): calculated for $C_{10}H_6N_3$ (M^+-HN_2) 168.0562, found 168.0566.

*5.3.3. (*E*)-3-(4-Chlorophenyl)-2-(1H-tetrazol-5-yl)acrylonitrile* (**2h**).[23] White solid; yield: 0.16 g (75%), mp 158−160 ºC; IR ν (KBr): 3158, 2359, 1585, 1497, 930, 810, 691, 623 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.62−7.72 (m, 2H), 8.05 (d, J = 8.6 Hz, 2H), 8.41 (s, 1H); ^{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): calculated for $C_{10}H_5ClN_2$ (M^+-HN_3) 188.0141, found 188.0140.

*5.3.3. (*E*)-3-(4-Methoxyphenyl)-2-(1H-tetrazol-5-yl)acrylonitrile* (**2i**).[23] Green solid; yield: 0.20 g (88%), mp 76−78 ºC; IR ν (KBr): 3120, 2773, 1589, 1462, 954, 864, 651, 604 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.85 (s, 3H), 7.14 (d, J = 8.6 Hz, 2H), 8.01 (d, J = 8.6 Hz, 2H), 8.25 (s, 1H); ^{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): calculated for $C_{10}H_9N_3O$ (M^+-CN_2) 187.0746, found 187.0733.

*5.3.3. (*E*)-3-(4-Hydroxy-3-methoxyphenyl)-2-(1H-tetrazol-5-yl)acrylonitrile* (**2j**).[23] Green solid; yield: 0.16 g (75%), mp 88−89 ºC; IR ν (KBr): 3121, 2225, 1574, 1458, 998, 844, 644, 620 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.88 (s, 3H), 7.00 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.75 (s, 1H), 8.22 (s, 1H); ^{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): calculated for $C_{10}H_6N_3O$ ($M^+-N_2CH_3O$) 184.0511, found 184.0537.

5.4. General procedure for the benzylation of tetrazoles 2[16]

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 ºC until the conversion was complete (TLC monitoring). The reaction mixture was filtered and to the filtrate was added water (15 mL) and extracted with EtOAc (3 × 10 mL) and dried over Na_2SO_4. After evaporation of the solvent (15 Torr) the resulting residue was purified by recrystallization (EtOH) to yield tetrazoles **1**. Yields and physical and spectroscopic data follow.

5.4.1. 1-Benzyl-5-phenyl-1H-tetrazole (**1a**).[24] White solid; yield: 0.18 g (77%), mp 78−280 ºC; IR ν (KBr): 1651, 1274, 979, 854, 773, 615 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.80 (s, 2H), 7.32−7.50 (m, 8H), 8.13 (dd, J = 7.5, 2.3 Hz, 2H); ^{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): calculated for $C_{14}H_{12}N_4$ (M^+) 236.1062, found 236.1051.

5.4.2. 1,5-Dibenzyl-1H-tetrazole (**1b**).[25] White solid; yield: 0.2 g (80%), mp 140−142 ºC; IR ν (KBr): 1604, 1278, 976, 854, 693, 601 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.21 (s, 2H), 5.68 (s, 2H), 7.18−7.37 (m, 10H); ^{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): calculated for $C_{14}H_{12}N_3$ (M^+-CH_2N) 222.1031, found 222.1027.

5.4.3. 1-Benzyl-5-(4-nitrophenyl)-1H-tetrazole (**1c**).[24] Green solid; yield: 0.18 g (66%), mp 76−78 ºC; IR ν (KBr): 1604, 1282, 965, 852, 651, 601 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.84 (s, 2H), 7.33−7.52 (m, 5H), 8.30−8.33 (m, 4H); ^{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): calculated for $C_7H_5N_5O_2$ (M^+) 191.0443, found 191.0452.

5.4.4. 5-Benzhydryl-1-benzyl-1H-tetrazole (**1d**). White solid; yield: 0.27 g (84%), mp 133−135 ºC; IR ν (KBr): 1598, 1254, 953, 890, 688, 608 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.35−5.37 (m, 3H), 7.00−7.18 (m, 9H), 7.19−7.38 (m, 6H); ^{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): calculated for $C_{21}H_{18}N_4$ (M^+) 326.1531, found 326.1522.

5.4.5. 2-(1-Benzyl-1H-tetrazol-5-yl)pyridine (**1e**).[26] Green solid; yield: 0.20 g (88%), mp 75−77 ºC; IR ν (KBr): 1589, 1263, 999, 876, 690, 601 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 6.25 (s, 2H), 7.19−7.52 (m, 6H), 7.82−7.92 (m, 1H), 8.33 (d, J = 7.9 Hz, 1H), 8.74 (s, 1H); ^{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): calculated for $C_{13}H_9N_3$ ($M^+-N_2H_2$) 207.0796, found 207.0792.

*5.4.6. (*E*)-2-(1-Benzyl-1H-tetrazol-5-yl)-3-(4-hydroxyphenyl)acrylonitrile* (**1f**).[27] Orange solid; yield: 0.23 g (77%); mp 160−162 ºC; IR ν (KBr): 2360, 1511, 1439, 1261, 997, 895, 672, 614 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.13 (s, 2H), 5.78 (s, 1H), 7.05 (d, J = 8.9 Hz, 2H), 7.33−7.46 (m, 5H), 7.97 (d, J = 8.8 Hz, 2H), 8.20 (s, 1H); ^{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): calculated for $C_{17}H_{11}NO$ ($M^+-N_4H_2$) 245.0841, found 245.0829.

*5.4.7. (*E*)-2-(1-Benzyl-1H-tetrazol-5-yl)-3-phenylacrylonitrile* (**1g**).[28] Green solid; yield: 0.19 g (67%); mp 190−192 ºC; IR ν (KBr): 2332, 1596, 1443, 1211, 973, 856, 697, 605 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.80 (s, 2H), 7.33−7.51 (m, 8H), 7.91−8.02 (m, 2H), 8.29 (s, 1H); ^{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): calculated for $C_{17}H_{13}N_5$ (M^+) 287.1171, found 287.1148.

*5.4.8. (*E*)-2-(1-Benzyl-1H-tetrazol-5-yl)-3-(4-chlorophenyl)acrylonitrile* (**1h**). Green solid; yield: 0.14 g (45%); mp 170−172 ºC; IR ν (KBr): 2224, 1588, 1474, 1211, 962, 833, 687, 616 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 5.80 (s, 2H), 7.32−7.53 (m, 7H), 7.91 (d, J = 8.6 Hz, 2H), 8.24 (s, 1H); ^{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): calculated for $C_{17}H_{12}ClN_5$ (M^+) 321.0781, found 321.0775.

*5.4.9. (*E*)-2-(1-Benzyl-1H-tetrazol-5-yl)-3-(4-methoxyphenyl)acrylonitrile* (**1i**). Green solid; yield: 0.19 g (60%), mp 76−78 ºC; IR ν (KBr): 2221, 1594, 1497, 1217, 970, 825, 683, 613 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.87 (s, 3H), 5.79 (s, 2H), 6.98 (d, J = 8.9 Hz, 2H), 7.36−7.47 (m, 5H), 7.97 (d, J = 8.8 Hz, 2H), 8.20 (s, 1H); ^{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): calculated for $C_{18}H_{15}N_5O$ (M^+) 317.1277, found 317.1268.

*5.4.10. (*E*)-2-(1-Benzyl-1H-tetrazol-5-yl)-3-(4-Hydroxy-3-methoxyphenyl)acrylonitrile* (**1j**). Green solid; yield: 0.20 g (63%); mp 170−172 ºC; IR ν (KBr): 2225, 1512, 1426, 1253, 939, 801, 671, 603 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.96 (s, 3H), 5.23 (s, 2H), 5.78 (s, 1H), 6.94 (d, J = 8.5 Hz, 1H), 7.38−7.43 (m, 6H), 7.79 (s, 1H), 8.17 (s, 1H); ^{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): calculated for $C_{18}H_{15}NO_2$ (M^+-N_4) 277.1103, found 277.1085.

5.5. General procedure for the indium-promoted debenzylation of tetrazoles 1

A mixture of the corresponding tetrazole **2** (0.1 mmol) and indium 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 at r.t. 1M HCl (0.5 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4 and evaporated (15 Torr). The resulting residue was recrystallized to give pure products **2**, which were fully characterized by comparison of their physical and spectroscopic data with pure samples of **2**.

5.6. General procedure for the magnesium-promoted debenzylation of tetrazoles 1

To a solution of the corresponding 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 iodine. The reaction was refluxed until the starting material was consumed (17-22 h) and then the reaction was cooled to 0°C and diluted with ether (5 mL) and 10% aqueous NH_4Cl. The mixture was stirred until it became clear and then separated. The combined ether extracts (2 × 5 mL) were dried over Na_2SO_4 and evaporated (15 Torr) to give a residue that was purified by recrystallization in EtOH, to afford the pure deprotected tetrazoles **2**. They were fully characterized by comparison of their physical and spectroscopic data with pure samples of **2**.

5.7. General procedure for the zinc-promoted debenzylation of tetrazoles 1

To a stirred solution of the corresponding tetrazole **1** (2.5 mmol) in THF (1.0 mL) at r.t. was added zinc dust (5 mmol) and stirring was continued for 30 additional min. The resulting suspension was cooled with an ice-water bath and glacial acetic acid (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 phase was separated, washed with H_2O (2 × 10 mL), sat $NaHCO_3$ (3 × 10 mL) and brine (3 × 15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure (15 Torr). The resulting residue was purified by recrystallization to give pure compounds **2**, which were characterized by comparison of their physical and spectroscopic data with pure samples of **2**.

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