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Functionalization of Tetrazoles Bearing the Electrochemically Cleavable 1*N*-(6-Methylpyridyl-2-methyl) Protecting Group

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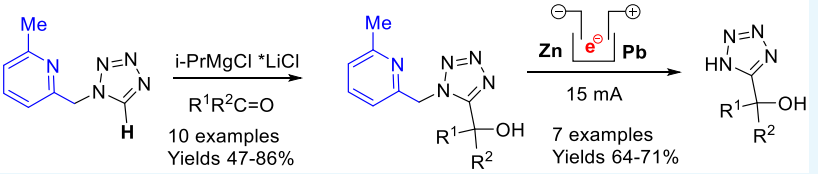

ABSTRACT: 6-Methylpyridyl-2-methyl protected tetrazoles can be C−H deprotonated using the turbo-Grignard reagent and involved in the reactions with aldehydes and ketones. The protecting group can be cleaved under reductive electrochemical conditions using Pb bronze as a cathode and Zn as a sacrificial anode.

INTRODUCTION

Tetrazoles do not exist in nature; however, the tetrazole motif is found in a number of useful compounds with an application in pharmacology,[1] catalysis,[2] and material science.[3] Representative examples of pharmacologically relevant tetrazole derivatives are the antihypertensive drug losartan,[4] antiasthmatic drug tomelukast (LY171883),[5] antibiotic tedizolid,[6] the multidrug resistance efflux pump inhibitor encequidar,[7] and an experimental antitumor agent BMS-317180[8] (Figure 1).

The importance of tetrazole containing compounds has motivated researchers to develop numerous methods for their synthesis.[9] Among them, C−H functionalization of tetrazoles via metalation is an attractive approach to install substituents at the fifth position. It should be noted, however, that lithiated tetrazoles suffer from low stability due to a rapid retro [2 + 3] cycloaddition forming the cyanamide even at −78 °C.[9a−c] Organomagnesiun intermediates are considerably more stable ($t_{1/2}$ = 3 h at −20 °C), which enables the use of routine lab operations for their derivatization.[9c] Recently, we have reported generation organomagnesiun intermediates by C−H deprotonation of 1*N*-PMB protected tetrazole (**1**, PG = PMB), which was subsequently subjected to the reaction with electrophiles (Scheme 1).[10] To extend the utility of this approach, 1*N*-pyridyl-2-methyl protected tetrazoles **1a** and **1b** were investigated as substrates to give C−H functionalization products, which can be deprotected by the electrochemical reduction (Scheme 1).

RESULTS AND DISCUSSION

Methylpyridylmethyl protected tetrazole **1a** was obtained according to a known method.[11] The 6-methyl analogue **1b** was prepared by the alkylation of tetrazole (**4**) with the bromomethylpyridine derivative **3** (Scheme 2). The reaction provided 1*N* alkylation product **1b** as the major isomer together with 2*N* alkylation product **5**, which was separated by chromatography.

The deprotonation efficiency of substrates **1a** and **1b** was determined by the deuterium quench of the metalated intermediates generated by the reaction with the turbo-Grignard reagent (Table 1).

Pyridylmethyl protected tetrazole **1a** gave moderate deuterium incorporation at the fifth position according to the NMR spectra of a reaction mixture (Table 1, entries 1 and 2). A high recovery of tetrazole **1a** as well as product deuterated at the CH_2 group were observed. Imidazopyridine **6a** was isolated from the reaction mixture as a minor impurity resulting from cyanamide **7a**, a product of metalated tetrazole decomposition. Considerable improvement in a deuterium quench experiment was observed using methylpyridylmethyl protected tetrazole **1b** as a substrate. High deuterium incorporation at the fifth position was observed after deprotonation with turbo-Grignard reagent at −60 °C (Table 1, entries 3−5). An increase of the temperature after the metalation step led to the formation of imidazopyridine **6b**. This formed as a major product if the reaction mixture was warmed to room temperature. Better performance of methylpyridylmethyl protected tetrazole **1b** compared to that of substrate **1a** can be explained by blocking the relatively acidic C−H at the sixth position of pyridine, which could cause an equilibrium mixture of several metalated species.

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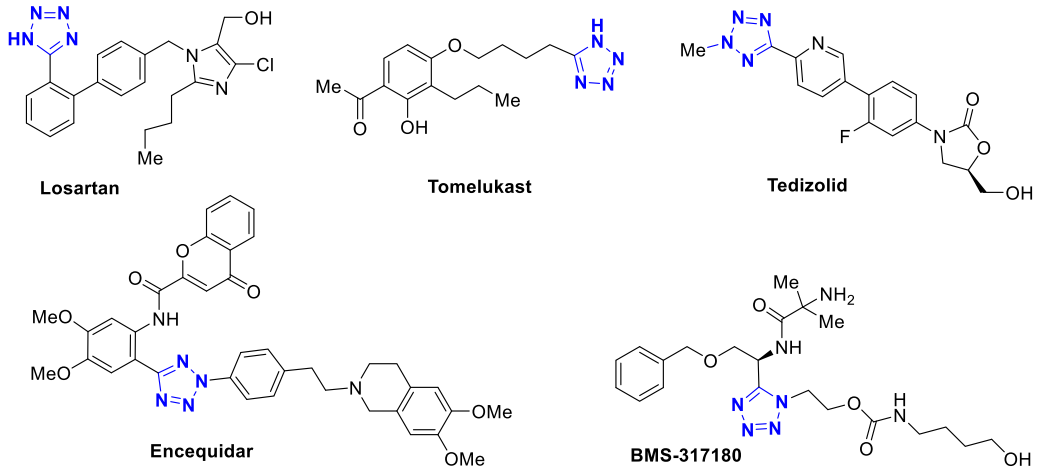
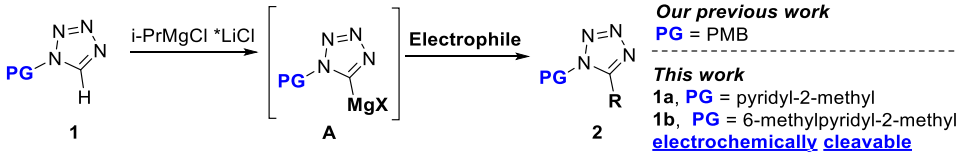


Figure 1. Representative examples of pharmacologically relevant tetrazole derivatives.

Scheme 1. Functionalization of Tetrazoles Bearing an Electrochemically Cleavable Protecting Group



Scheme 2. Synthesis of Methylpyridylmethyl Protected Tetrazole 1b

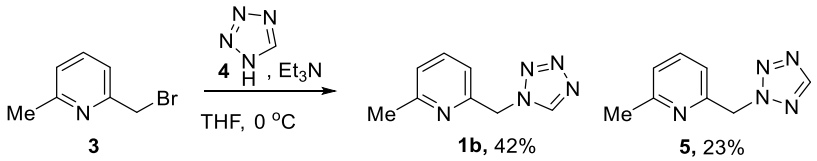
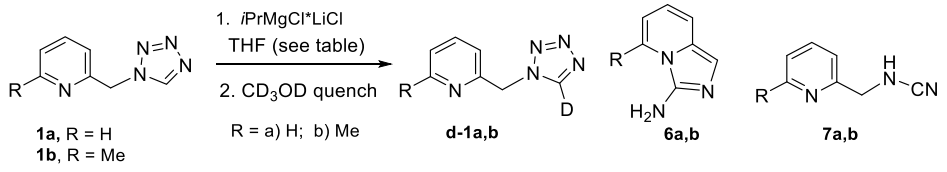


Table 1. Deprotonation Studies of Pyridyl Protected Tetrazoles 1a and 1b with Turbo-Grignard Reagent[a]



entry	temp.	time (min)	d-**1**, yield[b]	**6**, yield[b]
1	−60 °C	15	d-**1a**, ∼40%	**6a**, trace
2	−60 °C	60	d-**1a**, ∼60%	**6a**, trace
3	−60 °C	15	d-**1b**, 90%	**6a**, trace
4	−60 °C	30	d-**1b**, 97%	**6b**, n.d.
5	−60 °C	60	d-**1b**, 98%	**6b**, n.d.
6	0 °C[c]	30	d-**1b**, 55%	**6b**, ∼30%
7	r.t.[c]	30	d-**1b**, 0%	**6b**, 98%

[a]0.7 mmol of tetrazole and 1.2 equiv of turbo-Grignard reagent at −60 °C for the indicated time; quench with 3 equiv of MeOD, add 3 equiv of AcOH, and warm to r.t. [b]Yields were calculated on the basis of the weight of the crude material and the reduction of the integral intensity of the 5-CH group in the NMR spectra. [c]Deprotonation was performed at −60 °C, and then, the reaction was cooled to reach the indicated temperature.

Methylpyridylmethyl protected tetrazole **1b**, after metalation, was subjected to the reaction with aldehydes **8a**−**e** and ketones **8f**−**j** (Scheme 3). The addition of the metalated intermediate to aromatic aldehydes **8a** and **8b**, aliphatic aldehyde **8c**, and heteroaromatic aldehydes **8d** and **8e** was very productive, providing alcohols **9a**−**i**. The reaction with ketones **8f**−**j** was also successful to give alcohols **9f**−**9j** in moderate to good yields.

The pyridylmethyl group has been demonstrated to have electrochemically cleavable protection for thiols,[12,13] carboxylic acids,[14] and alcohols.[13,15] Similar electrochemical conditions were applied for the reductive cleavage of the methylpyridylmethyl group from tetrazole using compound **9a** as the model substrate. A range of electrodes and electrolytes was investigated at the fixed current and electric charge (Table 2). The best result was achieved using leaded bronze electrode as cathode, sacrificial zinc as anode, and TBA·BF_4 (tetrabutyla-

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Scheme 3. Synthesis of Alcohols 9a–j by the Addition of Tetrazole 1b to Carbonyl Compounds

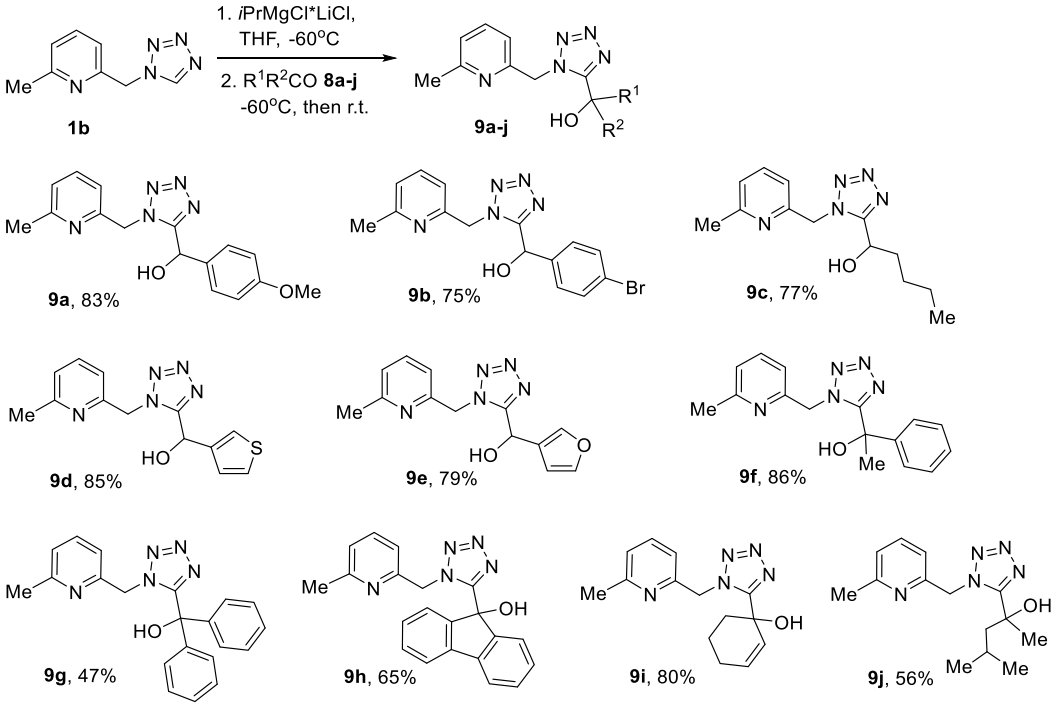
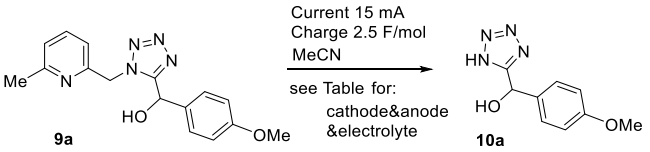


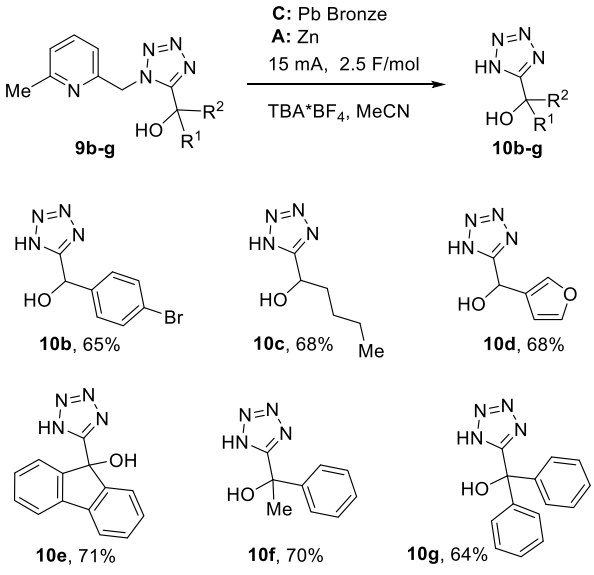
Table 2. Conditions for the Electrochemical Cleavage of the Methylpiridylmethyl Group in Tetrazole 9a



entry	cathode	anode	electrolyte	conversion of **9a** to **10a**, %[a]
1	Pb/bronze	Mg	$TBABF_4$	57
2	Pb	Mg	$TBABF_4$	24
4	Pb	Mg	$LiClO_4$	0
5	BDD	Mg	$TBABF_4$	24
6	Pb/bronze	Zn	$TBABF_4$	87 (67)[b]
7	Pb/bronze	Zn	$TBAClO_4$	42
8	Pb/bronze	Zn	$TBAPF_6$	6
9	Pb	Zn	$TBABF_4$	45
10	BDD	Zn	$TBABF_4$	76 (50)[b]

[a]Determined by the ratio of **10a** and **9a** in HPLC of the reaction mixture. [b]Isolated yield, %.

Scheme 4. Electrochemical Deprotection of the Methylpiridylmethyl Group in Tetrazoles 9b–g



monium tetrafluoroborate) as electrolyte, providing deprotected tetrazole **10a** in good isolated yield (Table 2, entry 6). A good conversion of the starting material **9a** to deprotected tetrazole **10a** was also observed using boron-doped diamond (BDD) as cathode and sacrificial zinc as anode (Table 2, entry 10).

The best electrochemical conditions found for the substrate **9a** deprotection with Pb bronze cathode and the sacrificial Zn anode were applied for the deprotection of tetrazoles **9b–g** (Scheme 4). The resulting free tetrazoles **10b–g** were obtained in fair isolated yields despite high conversion of the starting materials **9b–g**. The major loss of the product was due to the very polar nature of tetrazoles **10b–g**, which complicated the isolation.

The proposed mechanism for the electrochemical cleavage of the 6-methyl-pyridylmethyl group from tetrazole **9** is provided in Scheme 5 in analogy to the cleavage of the *O*-(4-nitro)benzyl group.[16] The reduction of the pyridylmethyl group at the cathode by sacrificing the Zn anode leads to an anion radical **A**, which fragments to pyridylmethyl radical **B** and tetrazole anion $[\mathbf{10}]^-$. The pyridyl radical **B** undergoes further reactions, like hydrogen abstraction, dimerization, oxidation, and/or reduction to give a mixture of byproducts. The formation of pyridylmethyl radical **B** is supported by the observation of 2,6-lutidine by LC/MS analysis of the crude reaction mixture, which can form by either hydrogen abstraction or a reduction followed by a protonation.

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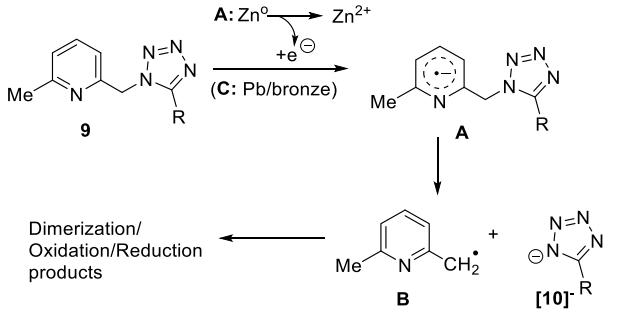
Scheme 5. Proposed Mechanism for Electrochemical Cleavage of the Methylpyridylmethyl Group



CONCLUSIONS

6-Methylpyridyl-2-methyl protected tetrazoles can be C−H deprotonated using the turbo-Grignard reagent and involved in the reactions with aldehydes and ketones. The protecting group can be cleaved in reductive electrochemical conditions using Pb bronze as a cathode and Zn as a sacrificial anode. This expands the utility of tetrazole functionalization via C−H deprotonation, particularly for the cases where selective protecting group cleavage should be achieved. To our knowledge, this is the first example for the protection of tetrazole with an electrochemically cleavable protecting group.

EXPERIMENTAL SECTION

General Information. Commercially available reagents were used without further purification. All air- or moisture-sensitive reactions were carried out under an argon atmosphere using oven-dried glassware. Flash chromatography was carried out using Merck Kieselgel 60 (230−400 mesh). Thin layer chromatography was performed on silica gel and was visualized by staining with $KMnO_4$. NMR spectra were recorded on a *Varian Mercury* spectrometer (400 MHz) and a *Bruker Fourier* spectrometer (300 MHz) with chemical shift values (δ) in ppm relative to TMS using the residual chloroform signal as an internal standard. Elemental analyses were performed using a Carlo-Erba EA1108 Elemental Analyzer. HRMS spectra were obtained using a Q-TOF micro high resolution mass spectrometer with ESI (ESI+/ESI−).

Synthesis of Starting Materials. *1H-Tetrazole (**4**).* **4** (11.4 g, 73%) was synthesized according to a literature procedure.[17]

*2-(Bromomethyl)-6-methylpyridine (**3**).* **3** (13.1 g, 68%) was synthesized according to a known method.[18]

*2-(1H-Tetrazol-1-ylmethyl)pyridine (**1a**).* **1a** was synthesized according to a known method.[11]

*2-Methyl-6-(1H-tetrazol-1-ylmethyl)pyridine (**1b**).* A mixture of 1*H*-tetrazole (**4**) (2.9 g, 1.2 equiv), dry THF (150 mL), and 2-(bromomethyl)-6-methylpyridine (**3**) (6.5 g, 1 equiv) was cooled at 0 °C. Triethylamine (19.47 mL, 2.5 equiv) was added, and the mixture was left stirring overnight. Brine (450 mL) was added to quench the reaction, and the mixture was transferred to a separatory funnel and then extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated by a rotary evaporator. Concentration of the extract gave two isomers **1b** and **5**, which were separated by column chromatography on silica gel. The desired isomer **1b** was obtained in high purity (>96%) as an off-white solid.

General Protocol for the Reaction of Tetrazole 1b with Electrophiles. The tetrazole (**1b**, 1.1. equiv) was dissolved in THF (0.12 M) and cooled to −60 °C. An isopropyl magnesium chloride−lithium chloride complex (1.2 equiv) was added dropwise and, after 30 min, at the same temperature, the corresponding electrophile (1 equiv), dissolved in THF (0.7 M), was added dropwise. The reaction mixture was slowly left to reach room temperature and stirring continued for 24−72 h. NH_4Cl was added to quench the reaction; the aqueous phase was extracted with EtOAc (3×), and the combined organics were washed with brine, dried, and evaporated. The crude was purified with column chromatography on silica.

General Protocol for Electrolytic Removal of the 6-Methyl-pyridylmethyl Protecting Group. A single cell with leaded bronze as a cathode and zinc as an anode was charged with 0.28−0.3 mmol of the corresponding tetrazole **9** and supporting electrolyte $TBABF_4$ (1 equiv) under an inert atmosphere. Dry MeCN (7.5 mL) was added, and the reaction was started by applying constant current (15 mA, total charge of 2.5 F/mol). After the end of the reaction, AcOH (1 equiv) was added and the mixture was diluted with EtOAc and water. The aqueous phase was extracted with EtOAc, and the combined organics were washed with 1 N aqueous HCl and brine, dried, and evaporated; product **10** was purified by column chromatography eluted with a mixture of petroleum ether/ethyl acetae/acetic acid (1:1:0.04).

Characterization of the Products. *2-(1H-Tetrazol-1-ylmethyl)pyridine (**1a**).* **1a**, 1.2 g, 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H, −C<u>H</u>−), 8.58 (ddd, J = 4.8, 1.9, 1.0 Hz, 1H, Ar), 7.73 (td, J = 7.7, 1.8 Hz, 1H, Ar), 7.36−7.26 (m, 2H, Ar), 5.71 (s, 2H, −C<u>H</u>$_2$−). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.46, 150.13, 143.11, 137.59, 123.95, 122.74, 53.30.

*2-Methyl-6-(1H-tetrazol-1-ylmethyl)pyridine (**1b**).* **1b**, off-white solid (2.55 g, 42%), mp 53−55 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H, −C<u>H</u>−), 7.59 (t, J = 7.7 Hz, 1H, Ar), 7.10 (dd, J = 17.0, 7.7 Hz, 2H, Ar), 5.64 (s, 2H, −C<u>H</u>$_2$−), 2.51 (s, 3H, −C<u>H</u>$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.40, 151.78, 143.15, 137.78, 123.66, 119.75, 53.52, 24.46. Element. Anal. for $C_8H_9N_5$: N, 39.98; C, 54.85; H, 5.18. Found: N, 39.99; C, 54.85; H, 5.11. HR-MS (ESI-TOF) m/z: Calcd for $C_8H_9N_5Na$ 198.0756; Found $[M + Na]^+$ 198.0758.

*4-(Methoxyphenyl)(1-((6-methylpyridin-2-yl)methyl)-1H-tetrazol-5-yl)methanol (**9a**).* **9a**, white solid (83%), mp 91−95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (t, J = 7.7 Hz, 1H, pyr.), 7.28 (dd, J = 8.9, 0.8 Hz, 1H, Ar), 7.19 (d, J = 7.1 Hz, 1H, pyr.), 7.11 (d, J = 7.8 Hz, 1H, pyr.), 6.82 (d, J = 8.8 Hz, 2H, Ar), 6.38 (s, 1H, −C<u>H</u>−OH), 5.45 (d, J = 14.8 Hz, 1H, −C<u>H</u>$_2$−), 5.34 (d, J = 14.8 Hz, 1H, −C<u>H</u>$_2$−), 3.73 (s, 3H, −OC<u>H</u>$_3$), 2.44 (s, 3H, −C<u>H</u>$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.55, 158.87, 156.90, 151.36, 138.83, 131.38, 127.21, 124.26, 120.87, 114.13, 66.12, 55.33, 52.14, 23.54. HR-MS (ESI-TOF) m/z: Calcd for $C_{16}H_{17}N_5O_2Na$ 334.1280; Found $[M + Na]^+$ 334.1279.

*(4-Bromophenyl)(1-((6-methylpyridin-2-yl)methyl)-1H-tetrazol-5-yl)methanol (**9b**).* **9b**, light green solid (75%), mp 131−135 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.71 (t, J = 7.7 Hz, 1H, pyr.), 7.51 (d, J = 8.5 Hz, 2H, Ar), 7.37 (d, J = 7.9 Hz, 2H, Ar), 7.31 (d, J = 7.6 Hz, 1H, pyr.), 7.22 (d, J = 7.8 Hz, 1H, pyr.), 6.46 (s, 1H, −C<u>H</u>−OH), 5.58 (d, J = 14.8 Hz, 1H, −C<u>H</u>$_2$−), 5.45 (d, J = 14.8 Hz, 1H, −C<u>H</u>$_2$−), 2.53 (s, 3H, −C<u>H</u>$_3$). ^{13}C NMR (101 MHz, CDCl3) δ 158.90, 156.34, 151.09, 139.00, 138.39, 131.85, 127.77, 124.43, 122.41, 120.99,

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65.92, 52.19, 23.51. HR-MS (ESI-TOF) m/z: Calcd for $C_{15}H_{15}BrN_5O$ 360.0460; Found $[M + H]^+$ 360.0470.

*1-(1-((6-Methylpyridin-2-yl)methyl)-1H-tetrazol-5-yl)-pentan-1-ol (**9c**).* **9c**, white solid (77%), mp 105−108 °C. ^{1}H NMR (400 MHz, chloroform-d) δ 7.68 (t, J = 7.7 Hz, 1H, pyr.), 7.33 (d, J = 7.6 Hz, 1H, pyr.), 7.18 (d, J = 7.8 Hz, 1H, pyr.), 7.06 (sb, 1H, −OH), 5.80 (d, J = 14.6 Hz, 1H, −CH$_2$−), 5.68 (d, J = 14.6 Hz, 1H, −CH$_2$−), 5.18 (dd, J = 7.9, 5.2 Hz, 1H, −CH−OH), 2.50 (s, 3H, −CH$_3$), 2.21−1.94 (m, 2H, −CH$_2$−), 1.60−1.35 (m, 4H, −CH$_2$−CH$_2$−), 0.92 (t, J = 7.2 Hz, 3H, −CH$_3$). ^{13}C NMR (101 MHz, CDCl3) δ 158.86, 157.26, 151.66, 138.78, 124.21, 121.01, 64.90, 52.27, 35.58, 27.44, 23.73, 22.47, 14.00. HR-MS (ESI-TOF) m/z: Calcd for $C_{13}H_{20}N_5O$ 262.1668; Found $[M + H]^+$ 262.1667.

*(1-((6-Methylpyridin-2-yl)methyl)-1H-tetrazol-5-yl)-(thiophen-3-yl)methanol (**9d**).* **9d**, subwhite solid (85%), mp 76−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (sb, 1H, −OH) 7.62 (t, J = 7.7 Hz, 1H, pyr.), 7.32 (dt, J = 2.7, 1.3 Hz, 1H, thioph.), 7.28 (dd, J = 5.0, 3.1 Hz, 1H, thioph.), 7.20 (d, J = 7.6 Hz, 1H, pyr.), 7.13 (d, J = 7.8 Hz, 1H, pyr.), 6.97 (dd, J = 5.0, 1.3 Hz, 1H, thioph.), 6.47 (d, J = 1.2 Hz, 1H, −CH−OH), 5.55 (d, J = 14.8 Hz, 1H, −CH$_2$−), 5.41 (d, J = 14.8 Hz, 1H, −CH$_2$−), 2.43 (s, 3H, −CH$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.79, 156.24, 151.33, 140.75, 138.80, 126.98, 125.65, 124.22, 122.31, 120.82, 63.80, 52.24, 23.52. HR-MS (ESI-TOF) m/z: Calcd for $C_{13}H_{14}N_5OS$ 288.0919; Found $[M + H]^+$ 288.0909.

*Furan-3-yl(1-((6-methylpyridin-2-yl)methyl)-1H-tetrazol-5-yl)methanol (**9e**).* **9e**, light brown solid (79%), mp 71−75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (t, J = 7.7 Hz, 1H, pyr.), 7.52 (q, J = 1.2 Hz, 1H, furan), 7.42 (t, J = 1.8 Hz, 1H, furan), 7.31 (d, J = 7.6 Hz, 1H, pyr.), 7.18 (d, J = 7.8 Hz, 1H, pyr.), 6.40 (d, J = 1.3 Hz, 2H, furan), 5.64 (s, 2H, −CH$_2$−), 2.48 (s, 3H, −CH$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.92, 156.00, 151.31, 143.92, 140.23, 138.90, 125.18, 124.35, 121.02, 108.84, 61.01, 52.32, 23.54. HR-MS (ESI-TOF) m/z: Calcd for $C_{13}H_{14}N_5O_2$ 272.1147; Found $[M + H]^+$ 272.1151.

*1-(1-((6-Methylpyridin-2-yl)methyl)-1H-tetrazol-5-yl)-1-phenylethan-1-ol (**9f**).* **9f**, yellow crystalline (86%), mp 106−109 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (t, J = 7.7 Hz, 1H, pyr.), 7.48−7.41 (m, 2H, Ar), 7.37−7.25 (m, 3H, Ar), 7.21 (d, J = 7.6 Hz, 1H, pyr.), 7.15 (d, J = 7.8 Hz, 1H, pyr.), 5.38 (d, J = 14.8 Hz, 1H, −CH$_2$−), 5.12 (d, J = 14.8 Hz, 1H, −CH$_2$−), 2.51 (s, 3H, −CH$_3$), 2.16 (s, 3H, −CH$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.48, 158.60, 151.44, 144.76, 138.93, 128.69, 127.85, 124.80, 124.23, 120.92, 71.11, 52.21, 31.99, 23.38. HR-MS (ESI-TOF) m/z: Calcd for $C_{16}H_{18}N_5O$ 296.1511; Found $[M + H]^+$ 296.1516.

*(1-((6-Methylpyridin-2-yl)methyl)-1H-tetrazol-5-yl)-diphenyl Methanol (**9g**).* **9g**, subyellow solid (47%), mp 108−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (t, J = 7.7 Hz, 1H, pyr.), 7.47−7.41 (m, 4H, Ar), 7.38−7.26 (m, 7H, Ar(6H) + pyr.(1H)), 7.12 (d, J = 7.8 Hz, 1H, pyr.), 5.72 (s, 2H, −CH$_2$−), 2.31 (s, 3H, −CH$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.04, 158.58, 151.64, 144.28, 139.09, 128.17, 127.96, 127.11, 124.33, 121.17, 76.65, 52.97, 23.16. HR-MS (ESI-TOF) m/z: Calcd for $C_{21}H_{20}N_5O$ 358.1668; Found $[M + H]^+$ 358.1666.

*9-(1-((6-Methylpyridin-2-yl)methyl)-1H-tetrazol-5-yl)-9H-fluoren-9-ol (**9h**).* **9h**, yellow solid (65%), mp 165−170 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H, −OH), 7.72−7.64 (m, 3H, pyr.(1H) + Ar(2H)), 7.40 (ddd, J = 7.5, 6.9, 1.7 Hz, 2H, Ar), 7.33−7.16 (m, 6H. pyr.(2H) + Ar(4H)), 5.98 (s, 2H, −CH$_2$−), 2.58 (s, 3H, −CH$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.54, 157.81, 151.94, 146.88, 139.84, 138.89, 130.00, 128.44, 124.25, 124.11, 120.78, 120.75, 79.37, 53.03, 23.85. HR-MS (ESI-TOF) m/z: Calcd for $C_{21}H_{18}N_5O$ 356.1511; Found $[M + H]^+$ 356.1508.

*1-(1-((6-Methylpyridin-2-yl)methyl)-1H-tetrazol-5-yl)-cyclohex-2-en-1-ol (**9i**).* **9i**, beige solid (80%), mp 92−95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (t, J = 7.7 Hz, 1H, pyr.), 7.44 (sb, 1H, −OH), 7.29 (d, J = 7.6 Hz, 1H, pyr.), 7.17 (d, J = 7.8 Hz, 1H, pyr.), 6.03 (dt, J = 9.9, 3.7 Hz, 1H, −CH=CH−), 5.95 (d, J = 14.5 Hz, 1H, −CH$_2$−), 5.85 (d, J = 14.5 Hz, 1H, −CH$_2$−), 5.79 (dd, J = 10.0, 1.0 Hz, 1H, −CH=CH−), 2.51 (s, 3H, −CH$_3$), 2.27 (ddd, J = 13.2, 10.3, 3.6 Hz, 1H, −CH$_2$−), 2.18 (dddd, J = 9.3, 5.7, 3.3, 2.2 Hz, 2H, −CH$_2$−), 2.10 (dddd, J = 13.3, 7.2, 3.2, 1.1 Hz, 1H, −CH$_2$−), 2.01−1.83 (m, 2H, −CH$_2$−). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.01, 158.61, 152.27, 138.70, 131.13, 129.20, 124.05, 120.93, 68.58, 53.11, 37.21, 24.62, 23.79, 18.08. HR-MS (ESI-TOF) m/z: Calcd for $C_{14}H_{17}N_5O$ 272.1511; Found $[M + H]^+$ 272.1513.

*4-Methyl-2-(1-((6-methylpyridin-2-yl)methyl)-1H-tetrazol-5-yl)pentan-2-ol (**9j**).* **9j**, thick yellow oil (56%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.69 (t, J = 7.7 Hz, 1H, pyr.), 7.35 (d, J = 7.5 Hz, 1H, pyr.), 7.18 (d, J = 7.8 Hz, 1H, pyr.), 5.99 (d, J = 14.2 Hz, 1H, −CH$_2$−), 5.82 (d, J = 14.3 Hz, 1H, −CH$_2$−), 2.52 (s, 3H, −CH$_3$), 2.05 (dd, J = 14.2, 6.7 Hz, 1H, −CH$_2$−), 1.95 (dd, J = 14.2, 5.5 Hz, 1H, −CH$_2$−), 1.86−1.75 (m, 1H, −CH−), 1.72 (s, 3H, −CH$_3$), 0.98 (d, J = 6.7 Hz, 3H, −CH$_3$), 0.73 (d, J = 6.7 Hz, 3H, −CH$_3$). ^{13}C NMR (101 MHz, CDCl3) δ 160.53, 158.50, 152.28, 138.93, 124.22, 121.35, 72.49, 52.93, 51.62, 31.57, 24.61, 24.41, 23.68, 23.63. HR-MS (ESI-TOF) m/z: Calcd for $C_{14}H_{22}N_5O$ 276.1824; Found $[M + H]^+$ 276.1834.

*(4-Methoxyphenyl)(1H-tetrazol-5-yl)methanol (**10a**).* **10a**, 67%. ^{1}H NMR (300 MHz, CD_3OD) δ 7.35 (d, J = 8.7 Hz, 2H, Ar), 6.92 (d, J = 8.7 Hz, 2H, Ar), 6.10 (s, 1H, −CH−OH), 3.77 (s, 3H, −OCH$_3$).[10]

*(4-Bromophenyl)(1H-tetrazol-5-yl)methanol (**10b**).* **10b**, 65%. ^{1}H NMR (300 MHz, CD_3OD) δ 7.54 (d, J = 8.5 Hz, 2H, Ar), 7.39 (d, J = 8.4 Hz, 2H, Ar), 6.14 (s, 1H, −CH−OH).[10]

*1-(1H-Tetrazol-5-yl)pentan-1-ol (**10c**).* **10c**, 68%. ^{1}H NMR (300 MHz, CD_3OD) δ 5.04 (t, J = 6.5 Hz, 1H, −CH−OH), 2.00−1.77 (m, 2H, −CH$_2$−), 1.38 (dd, J = 7.4, 3.9 Hz, 4H, −CH$_2$−CH$_2$−), 1.09−0.81 (m, 3H, −CH$_3$).[11]

*Furan-3-yl(1H-tetrazol-5-yl)methanol (**10d**).* **10d**, white amorphous solid (68%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 (s, 1H, −C=CH−O−), 7.49 (t, J = 1.9 Hz, 1H, =CH−O−), 6.45 (t, J = 1.9 Hz, 1H, C−CH=), 6.14 (s, 1H, −CH−OH). ^{13}C NMR (101 MHz, CD_3OD) δ 159.10, 143.68, 140.15, 125.50, 108.37, 60.22. HR-MS (ESI-TOF) m/z: Calcd for $C_6H_6N_4O_2$ 165.0413; Found $[M - H]^-$ 165.0417.

*9-(1H-Tetrazol-5-yl)-9H-fluoren-9-ol (**10e**).* **10e**, 71%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.79 (dd, J = 7.6, 0.9 Hz, 2H), 7.49−7.39 (m, 4H), 7.32 (td, J = 7.5, 1.1 Hz, 2H).[10]

*1-Phenyl-1-(1H-tetrazol-5-yl)ethan-1-ol (**10f**).* **10f**, white solid (70%), mp 142−146 °C. ^{1}H NMR (400 MHz, MeOD) δ 7.51 (d, J = 7.2 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.3 Hz, 1H), 2.02 (s, 3H, −CH$_3$). ^{13}C NMR (101 MHz, CD_3OD) δ 164.03, 145.86, 129.40, 128.72, 125.99, 72.19, 30.08. HR-MS (ESI-TOF) m/z: Calcd for $C_9H_{10}N_4O$ 189.0776; Found $[M - H]^-$ 189.0780.

*Diphenyl(1H-tetrazol-5-yl)methanol (**10g**).* **10g**, white solid (64%), mp 146−150 °C. ^{1}H NMR (400 MHz,

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CD_3OD) δ 7.43−7.37 (m, 4H), 7.37−7.28 (m, 6H). ^{13}C NMR (101 MHz, CD_3OD) δ 163.45, 145.20, 129.15, 129.09, 128.27, 77.81. HR-MS (ESI-TOF) m/z: Calcd for $C_{14}H_{12}N_4O$ 251.0933; Found $[M - H]^-$ 251.0943.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c01633.

^1H NMR and ^{13}C NMR spectra for compounds **1a**,**b**, **6b**, **9a**−**j**, and **10a**−**g**; ^1H NMR spectra for crude mixtures from the deuterium incorporation experiments in Table 1 (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257−10274. (b) Zou, Y.; Liu, L.; Liu, J.; Liu, G. Bioisosteres in drug discovery: focus on tetrazole. *Future Med. Chem.* **2020**, *12*, 91−93. (c) Myznikov, L. V.; Vorona, S. V.; Zevatskii, Y. E. Biologically active compounds and drugs in the tetrazole series. *Chem. Heterocycl. Compd.* **2021**, *57*, 224−233. (d) Ostrovskii, V. A.; Trifonov, R. E.; Popova, E. A. Medicinal chemistry of tetrazoles. *Russ. Chem. Bull.* **2012**, *61*, 768−780. (e) Ballatore, C.; Huryn, D. M.; Smith, A. B. 3rd. Carboxylic acid (bio)isosteres in drug design. *ChemMedChem.* **2013**, *8*, 385−395. (f) Herr, R. J. 5-Substituted-1H-tetrazoles as carboxylic acid isosteres: medicinal chemistry and synthetic methods. *Bioorg. Med. Chem.* **2002**, *10*, 3379−3393.

(2) (a) Knudsen, K. R.; Mitchell, C. E. T.; Ley, S. V. Asymmetric organocatalytic conjugate addition of malonates to enones using a proline tetrazole catalyst. *Chem. Commun.* **2006**, 66−68. (b) Shmatova, O. I.; Nenajdenko, V. G. Synthesis of Tetrazole-Derived Organocatalysts via Azido-Ugi Reaction with Cyclic Ketimines. *J. Org. Chem.* **2013**, *78*, 9214−9222.

(3) (a) Pinter, T.; Jana, S.; Courtemanche, R. J. M.; Hof, F. Recognition Properties of Carboxylic Acid Bioisosteres: Anion Binding by Tetrazoles, Aryl Sulfonamides, and Acyl Sulfonamides on a Calix[4]arene Scaffold. *J. Org. Chem.* **2011**, *76*, 3733−3741. (b) Pinter, T.; Simhadri, C.; Hof, F. Dissecting the Complex Recognition Interfaces of Potent Tetrazole- and Pyrrole-Based Anion Binders. *J. Org. Chem.* **2013**, *78*, 4642−4648. (c) Yin, P.; Zhang, Q.; Shreeve, J. N. M. Dancing with Energetic Nitrogen Atoms: Versatile *N*-Functionalization Strategies for *N*-Heterocyclic Frameworks in High Energy Density Materials. *Acc. Chem. Res.* **2016**, *49*, 4−16. (d) McKie, A. H.; Friedland, S.; Hof, F. Tetrazoles are Potent Anion Recognition Elements That Emulate the Disfavored Anti Conformations of Carboxylic Acids. *Org. Lett.* **2008**, *10*, 4653−4655. (e) Wurzenberger, M. H. H.; Endraß, S. M. J.; Lommel, M.; Klapötke, T. M.; Stierstorfer, J. Comparison of 1-Propyl-5H-tetrazole and 1-Azidopropyl-5H-tetrazole as Ligands for Laser Ignitable Energetic Materials. *ACS Appl. Energy Mater.* **2020**, *3*, 3798−3806.

(4) Belz, G. G.; Butzer, R.; Kober, S.; Mang, C.; Mutschler, E. Time course and extent of angiotensin II antagonism after irbesartan, losartan, and valsartan in humans assessed by angiotensin II dose response and radioligand receptor assay. *Clin. Pharmacol. Ther.* **1999**, *66*, 367−373.

(5) Feinstein, D. L. Contrasting the neuroprotective and gliotoxic effects of PPARγ agonists. *Drug Discovery Today Ther. Strateg.* **2004**, *1*, 29−34.

(6) Gao, F.; Xiao, J.; Huang, G. Current scenario of tetrazole hybrids for antibacterial activity. *Eur. J. Med. Chem.* **2019**, *184*, 111744.

(7) Zhang, J.; Wang, S.; Ba, Y.; Xu, Z. Tetrazole hybrids with potential anticancer activity. *Eur. J. Med. Chem.* **2019**, *178*, 341−351.

(8) Davulcu, A. H.; McLeod, D. D.; Li, J.; Katipally, K.; Littke, A.; Doubleday, W.; Xu, Z.; McConlogue, C. W.; Lai, C. J.; Gleeson, M.; Schwinden, M.; Parsons, R. L. Process Research and Development for a Tetrazole-Based Growth Hormone Secretagogue (GHS) Pharmaceutical Development Candidate. *J. Org. Chem.* **2009**, *74*, 4068−4079.

(9) (a) Raap, R. Reactions of 1-Substituted 5-Tetrazolyllithium Compounds; Preparation of 5-Substituted 1-Methyltetrazoles. *Can. J. Chem.* **1971**, *49*, 2139−2142. (b) Satoh, Y.; Marcopulos, N. Application of 5-Lithiotetrazoles in Organic-Synthesis. *Tetrahedron Lett.* **1995**, *36*, 1759−1762. (c) Wiedemann, S. H.; Bio, M. M.; Brown, L. M.; Hansen, K. B.; Langille, N. F. Some Practical Methods for the Application of 5-Metallo-1-benzyl-1H-tetrazoles in Synthesis. *Synlett* **2012**, *23*, 2231−2236. (d) Roh, J.; Vavrova, K.; Hrabalek, A. Synthesis and Functionalization of 5-Substituted Tetrazoles. *Eur. J. Org. Chem.* **2012**, *2012*, 6101−6118. (e) Alexakos, P. D.; Wardrop, D. J. *N*-Morpholinomethyl-5-lithiotetrazole: A Reagent for the One-Pot Synthesis of 5-(1-Hydroxyalkyl)tetrazoles. *J. Org. Chem.* **2019**, *84*, 12430−12436. (f) Neochoritis, C. G.; Zhao, T.; Domling, A. Tetrazoles via Multicomponent Reactions. *Chem. Rev.* **2019**, *119*, 1970−2042. (g) Tullmann, C. P.; Steiner, S.; Knochel, P. Preparation and Reactions of (1H-Tetrazol-5-yl)zinc Pivalates. *Synthesis-Stuttgart* **2020**, *52*, 2357−2363. (h) Zhang, Y.; Lee, J. C. H.; Reese, M. R.; Boscoe, B. P.; Humphrey, J. M.; Helal, C. J. 5-Aryltetrazoles from Direct C-H Arylation with Aryl Bromides. *J. Org. Chem.* **2020**, *85*, 5718−5723.

(10) Grammatoglou, K.; Jirgensons, A. Functionalization of 1N-Protected Tetrazoles by Deprotonation with the Turbo Grignard Reagent. *J. Org. Chem.* **2022**, *87*, 3810−3816.

(11) Brandão, G. C.; Rocha Missias, F. C.; Arantes, L. M.; Soares, L. F.; Roy, K. K.; Doerksen, R. J.; Braga de Oliveira, A.; Pereira, G. R. Antimalarial naphthoquinones. Synthesis via click chemistry, in vitro activity, docking to PfDHODH and SAR of lapachol-based compounds. *Eur. J. Med. Chem.* **2018**, *145*, 191−205.

(12) Delerue-Matos, C.; Freitas, A. M. B.; Maia, H. L. S.; Medeiros, M. J.; Montenegro, M. I.; Pletcher, D. Electrochemical cleavage of some protecting groups from the sulphydryl function in aprotic solvents. *J. Electroanal. Chem.* **1991**, *315*, 1−8.

(13) Gosden, A.; Stevenson, D.; Young, G. T. Protection of thiol and phenolic hydroxy-groups as their 4-picolyl ethers, cleaved by electrolytic reduction. *Chem. Commun.* **1972**, 1123−1124.

(14) Camble, R.; Garner, R.; Young, G. T. Amino-acids and peptides. Part XXX. Facilitation of peptide synthesis by the use of 4-picolyl esters for carboxy-group protection. *J. Chem. Soc. Section C: Organic* **1969**, 1911−1916.

(15) Wieditz, S.; Schafer, H. J.; Schmidt, W.; Undheim, K.; Enzell, C. R.; Inoue, K. The picolyl group, an electroactive protection group for alcohols. *Acta Chem. Scand.* **1983**, *37b*, 475.

(16) Montenegro, M. I. The electrochemical cleavage of protecting groups. *Electrochim. Acta* **1986**, *31*, 607−620.

(17) Wang, X.; Liu, J.; Wang, D.; Bi, X.; Zhao, W. Synthesis and Characterization of Sodium 5-Chlorotetrazolate Dihydrate by Chlorination of 1H-Tetrazole. *Z. Anorg. Allg. Chem.* **2015**, *641*, 631−635.
(18) Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. Facile Conversion of Alcohols into Esters and Dihydrogen Catalyzed by New Ruthenium Complexes. *J. Am. Chem. Soc.* **2005**, *127*, 10840−10841.

https://doi.org/10.1021/acsomega.2c01633
ACS Omega 2022, 7, 18103−18109