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Metal-Free Tandem Oxidative Coupling of Primary Alcohols with Azoles for the Synthesis of Hemiaminal Ethers

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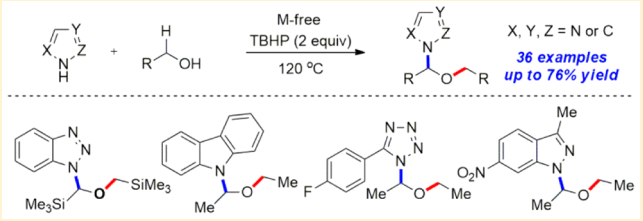
Supporting Information

ABSTRACT: A novel metal-free tandem oxidative coupling process for the synthesis of hemiaminal ethers has been developed. This protocol could be applied for the C−N bond formation of electron-deficient trizoles, tetrazoles, carbazoles and indazoles with primary alcohols.



N-Alkylated azoles represent an important class of compounds because of their common occurrence in medicinally useful products.[1] The development of new synthetic methods for the functionalization of azoles is of great interest.[2−4] Conventionally, *N*-alkylated azoles have been synthesized by coupling of azoles with electrophiles.[5−9] In the past decade, there has been many efforts in the exploration of metal-catalyzed and metal-free C−H bond activation/functionalization strategies for the construction of C−N bond. Highly controlled amination of oxygen-adjacent sp^3 carbons generally occur with cyclic ethers (Figure 1).[10−25] The reports of C−H bond functionalization for primary alcohols were rather limited.[26−30]

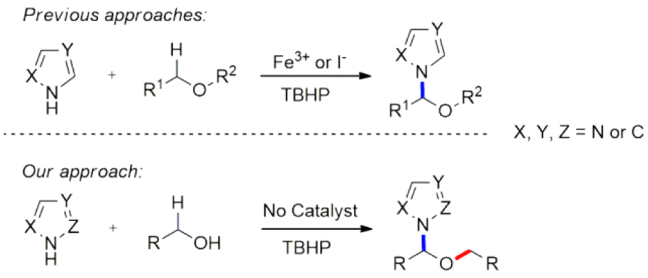


Figure 1. Different approaches to functionalized hemiaminal ethers.

The C−H bond activation of primary alcohols with hydroperoxides has proven to be a challenging task due to the poor chemoselectivity of the oxidant. Contrary to ethers, when applying the typical oxidative coupling conditions with alcohols and azoles, the expected result would be the C−C bond coupling of nucleophilic carbon in azoles with the sp^3-hybridized carbon in alcohols at α-position.[27] When azoles without sp^2 C−H at 2-positon are employed, the dehydrogenative C−C coupling pathway would be unattainable and the C−N bond could form instead. Indeed, our preliminary study indicated that when benzotriazole was mixed with hydroperoxide in excessive amount of ethanol as the solvent under high temperature, the *N*-alkylation occurred and overreacted hemiaminal ether was isolated as the final product. To the best of our knowledge, there has been no such example of 2A+B tandem oxidative C−N coupling transformation reported up to date. Therefore, an investigation has been initiated to find out the scope and pathway of this novel process that could potentially be applied for the construction of a range of azole functionalized hemiaminal ethers.

Our study began with a model reaction of benzotriazole and ethanol in the presence of different oxidants. We first examined DTBP in ethanol at 120 °C for 12 h, no *N*-alkylation product was obtained (entry 1). When using BPO, TBPB, $K_2S_2O_8$, NIS, H_2O_2 or benzoquinone, similar result was observed (entry 2−7). Other oxidants such as DDQ and DCP afforded trace amount of product (entry 8 and 9). CAN afforded a product in moderate yield which proven to be the hemiaminal ether 3a (28%, entry 10). In other words, a second equivalent of ethanol reacted with the triazole after heating to a high temperature. To our delight, **3a** was obtained in high yield when using TBHP as the oxidant (76%, entry 11). Lower conversions were achieved with metal salt additives (entry 12−15).

With the optimized conditions in hand (Table 1, entry 11), we investigated the scope of this tandem oxidative coupling reaction. Benzotriazoles with both electron-withdrawing and electron-donating substituents could react with various primary alcohols to give hemiaminal ethers in good yields (Scheme 1). The reaction efficacy decreased when bulky substrates were used (**3a**−**3e**). High yields were obtained with silyl-substituted alcohols (**3g** and **3l**). The unsymmetrical benzotriazoles afforded 1:1 mixture of isomers that could be identified on

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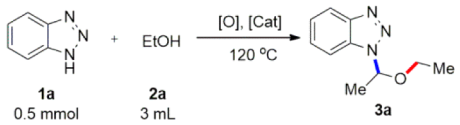
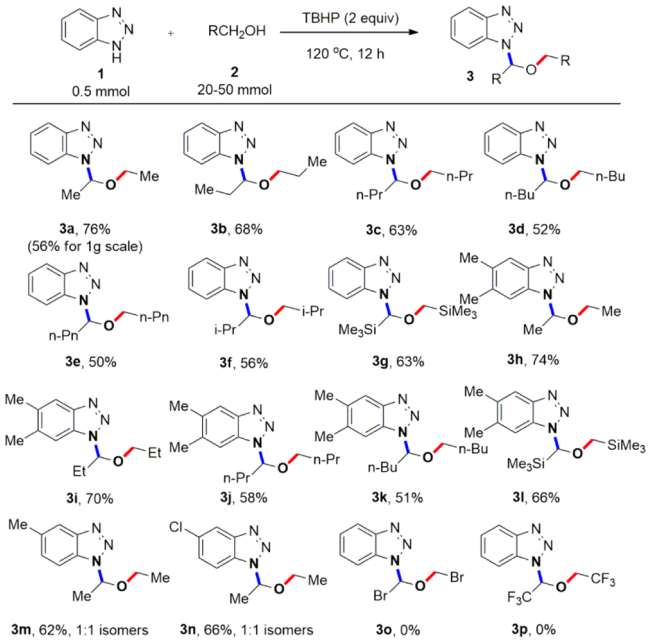
Table 1. Optimization of the Reaction Conditions[a]



entry	oxidant (2 equiv)	catalyst	yield (%)
1	DTBP	–	0
2	BPO	–	0
3	TBPB	–	0
4	$K_2S_2O_8$	–	0
5	NIS	–	0
6	H_2O_2	–	0
7	BQ	–	0
8	DDQ	–	trace
9	DCP	–	trace
10	CAN	–	28
11	TBHP	–	76
12	TBHP	$Fe(acac)_3$	12
13	TBHP	$AgNO_3$	15
14	TBHP	$Pd(OAc)_2$	56
15	TBHP	$Mn(OAc)_3$	trace

[a]DTBP = Di-*tert*-butyl peroxide, BPO = Benzoyl peroxide, TBPB = *tert*-Butyl perbenzoate, BQ = 1,4-Benzoquinone, DDQ = 2,3-Dichloro-5,6-dicyano-1,4-Benzoquinone, DCP = Dicumyl peroxide, CAN = Ceric ammonium nitrate, TBHP = *tert*-Butyl hydroperoxide.

Scheme 1. Reactions of 1*H*-Benzotriazole Derivatives with Aliphatic Primary Alcohols



the NMR spectra (**3m** and **3n**). Bromo- and trifluoromethyl-substituted alcohols did not afford the desired products (**3o** and **3p**).

To explore the generality of this protocol, we also tested the pharmacologically useful 1*H*-tetrazole derivatives (Scheme 2). A variety of alkoxyl sp^3 hydrogens were activated by TBHP. The reactions of halogenated 1*H*-tetrazoles resulted in the formation of **5d**–**5j** in high yields. Also, the reactions of nitrophenyl substrate furnished the corresponding products in similar yields (**5q**, 63%).

The methodology could be applied to *N*-heterocycles such as carbazoles and indazoles, moderate yields were achieved (Scheme 3, **7a**–**7c**). However, no desired product was observed for benzoimidazoles and indoles (**7d** and **7e**). This is due to the competitive sp^2 C–H in azole that being activated primarily under those conditions.

In order to elucidate the reaction mechanism, we carried out a series of control experiments. When the reaction was conducted under various atmospheres, difficult outcomes were observed. In air or under a nitrogen atmosphere, the reaction proceeded uneventfully, however in the presence of oxygen the reaction did not occur; this latter observation is suggestive of a radical pathway (Scheme 4a). The attempt of trapping the alkoxyl radical with TEMPO resulted in no desired hemiaminal ether product, only a proton was captured and detected by GC–MS (Scheme 4b). On the basis of these results, we assumed that the alcohol was first oxidized to aldehyde by TBHP before reacting with the azole substrates. Indeed, when the oxidant TBHP was replaced by acetaldehyde, the hemiaminal ether product was afforded in moderate yield, which indicated the reaction might go through the hemiacetal pathway (Scheme 4c).

A plausible mechanism is proposed based on the control experiments (Scheme 5). According to the previous reports,[13,15] it is believed that active oxonium ion is the crucial intermediate in such amination reaction. Initially ethanol **2** is oxidized by TBHP to form acetaldehyde,[31] which undergoes condensation reaction with another equivalent of ethanol to form the hemiacetal **10**, followed by elimination to give the active oxonium species **11**. Finally, nucleophilic attack of the azole **1** to the oxonium intermediate **11** furnishes the title product **3** (Path A). Alternatively, acetaldehyde first reacts with benzotriazole **1** and goes through similar iminium intermediate **14** to provide the title product **3** (Path B).

In summary, we have demonstrated a novel protocol for the oxidative coupling of azoles with primary alcohols. This metal-free amination pathway presents a direct access to a variety of hemiacetal ethers of electron-deficient trizoles, tetrazoles, carbazoles and indazoles.

EXPERIMENTAL SECTION

General Considerations. Commercially available reagents were used as received without purification. TBHP (5.5 M in decane) was purchased from Sigma-Aldrich. Column chromatography was carried out on silica gel (300–400 mesh). Analytical thin-layer chromatography was performed on glass plates of Silica Gel GF-254 with detection by UV. ^1H and ^{13}C NMR spectra were recorded on a 400 M spectrometer. The chemical shift references were as follows: ^1H NMR (400 MHz, $CDCl_3$) 7.26 ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 77.0 ppm. HRMS spectra were carried out on TOF MS ESI. Melting point determination was taken on a Melt–Temp apparatus (X-4) and was uncorrected.

General Procedure. To a Schlenk tube equipped with a magnetic stir bar were added (**1** or **4**, 0.5 mmol) in 3 mL of aliphatic primary alcohol (20–50 mmol). Then TBHP (5.5 M in decane, 1 mmol, 0.2 mL) was added before the tube was sealed and the reaction mixture was stirred at 120 °C for 12 h. After required reaction time, the mixture was cooled down to room temperature, diluted in ethyl acetate, and washed with brine. The aqueous phase was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to afford the product. All the reactions were carried out in a 50 mL vessel filled with nitrogen. The volume of the solution is about 4 mL. Over 90% of head space was left in the vessel. Although the reaction was heated to a high

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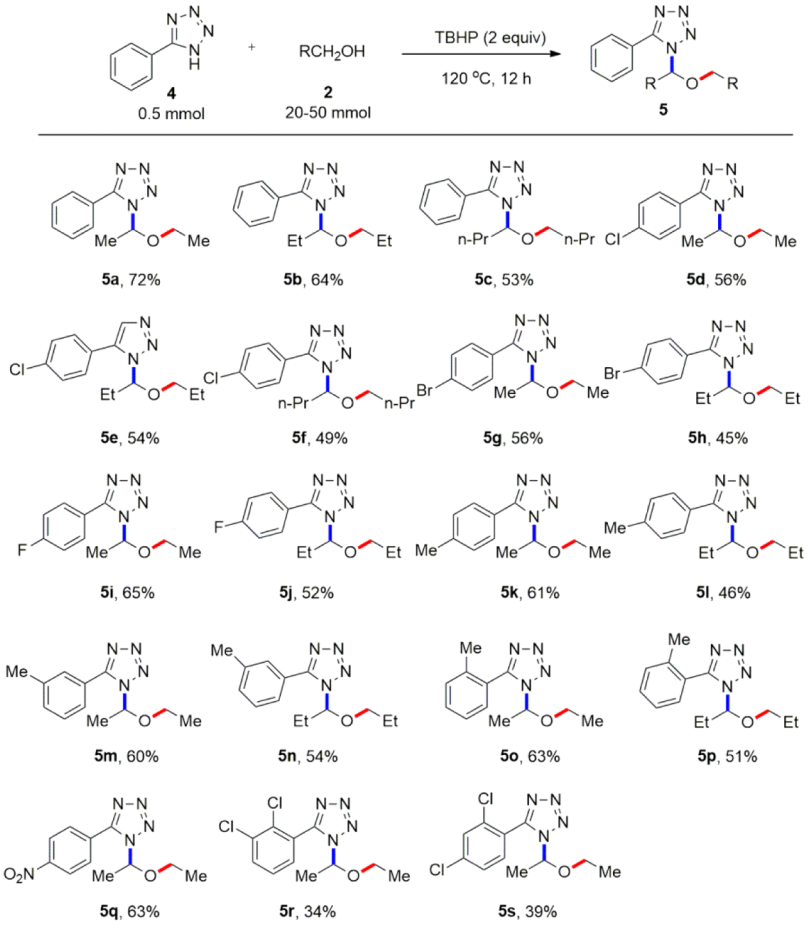
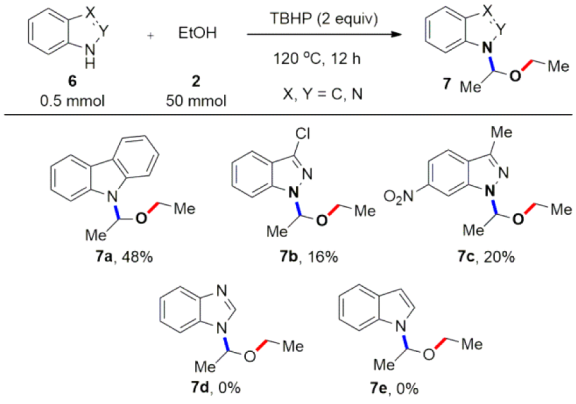
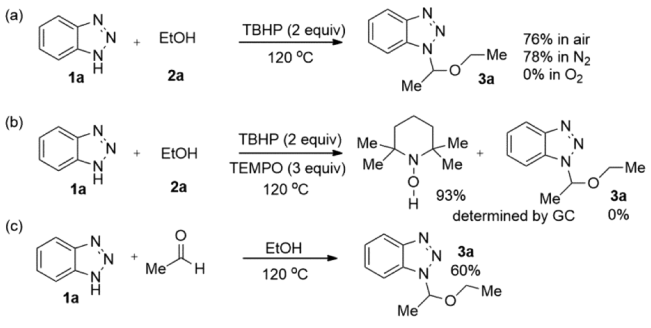
Scheme 2. Reactions of 5-Phenyl-1*H*-tetrazole Derivatives with Aliphatic Primary Alcohols



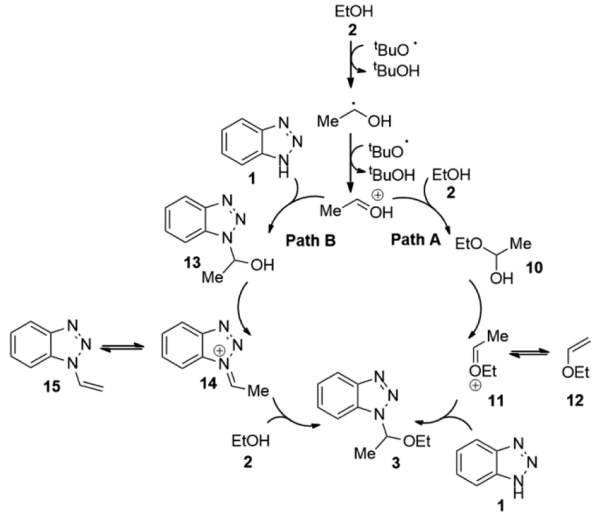
Scheme 3. Reactions of Ethanol with Other *N*-Heterocycles



Scheme 4. Control Experiments



Scheme 5. Proposed Mechanism for Oxidative Coupling of Primary Alcohols with Azoles



temperature (120 °C for the oil bath), the temperature in the vessel was only about 100 °C and the pressure was not too high to be hazardous. We have also attempted the reaction in a mild reaction, when the temperature lowered down to 80 °C, however, the yield decreased to 60%. Therefore, these conditions are reasonable and necessary.

1-(1-Ethoxyethyl)-1H-benzo[d][1,2,3]triazole (***3a***). Colorless oil. Yield: 72 mg (76%). Large scale reaction (10 mmol) has been performed. Yield: 1.1 g (56%). ^{1}H NMR δ 8.05 (d, J = 8.4 Hz, 1H),

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7.78 (d, J = 8.3 Hz, 1H), 7.51−7.39 (m, 1H), 7.41−7.32 (m, 1H), 6.24 (q, J = 6.1 Hz, 1H), 3.50 (dq, J = 9.4, 7.0 Hz, 1H), 3.23 (dq, J = 9.4, 7.1 Hz, 1H), 1.84 (d, J = 6.1 Hz, 3H), 1.11 (t, J = 7.0 Hz, 3H). ^{13}C NMR δ 146.7, 131.1, 127.3, 124.1, 120.0, 111.1, 87.0, 64.3, 21.1, 14.6. HRMS (ESI) Calcd for $C_{10}H_{13}N_3ONa$ (M + Na)$^+$ 214.0956, found 214.0957.

*1-(1-Propoxypropyl)-1H-benzo[d][1,2,3]triazole (**3b**).* Colorless oil. Yield: 75 mg (68%). ^{1}H NMR δ 8.06 (d, J = 8.3 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.45 (ddd, J = 8.2, 7.0, 0.9 Hz, 1H), 7.36 (ddd, J = 8.0, 7.0, 0.9 Hz, 1H), 5.95 (t, J = 6.8 Hz, 1H), 3.41 (dt, J = 9.3, 6.5 Hz, 1H), 3.15 (dt, J = 9.3, 6.7 Hz, 1H), 2.35−2.21 (m, 1H), 2.19−2.08(m, 1H), 1.59−1.41 (m, 2H), 0.88 (t, J = 7.5 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H). ^{13}C NMR δ 146.7, 131.2, 127.2, 124.1, 120.0, 111.3, 92.2, 70.7, 28.0, 22.4, 10.4, 9.3. HRMS (ESI) Calcd for $C_{12}H_{17}N_3ONa$ (M + Na)$^+$ 242.1269, found 242.1272.

*1-(1-Butoxybutyl)-1H-benzo[d][1,2,3]triazole (**3c**).* Colorless oil. Yield: 77 mg (63%). ^{1}H NMR δ 8.07 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.46 (m, 1H), 7.37 (m, 1H), 6.04 (t, J = 6.8 Hz, 1H), 3.45 (dt, J = 9.4, 6.4 Hz, 1H), 3.20 (dt, J = 9.4, 6.6 Hz, 1H), 2.31−2.18 (m, 1H), 2.14−2.02 (m, 1H), 1.54−1.42 (m, 3H), 1.31−1.22 (m, 3H), 0.92 (t, J = 7.4 Hz, 3H), 0.80 (t, J = 7.4 Hz, 3H). ^{13}C NMR δ 146.8, 131.2, 127.3, 124.1, 120.0, 111.3, 90.9, 68.9, 36.7, 31.2, 19.1, 18.2, 13.6, 13.4. HRMS (ESI) Calcd for $C_{14}H_{21}N_3ONa$ (M + Na)$^+$ 270.1582, found 270.1580.

*1-(1-(Pentyloxy)pentyl)-1H-benzo[d][1,2,3]triazole (**3d**).* Colorless oil. Yield: 71 mg (52%). ^{1}H NMR δ 8.04 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.47−7.40 (m, 1H), 7.37−7.30 (m, 1H), 6.00 (t, J = 6.8 Hz, 1H), 3.42 (dt, J = 9.4, 6.5 Hz, 1H), 3.16 (dt, J = 9.3, 6.6 Hz, 1H), 2.29−2.20 (m, 1H), 2.13−2.04 (m, 1H), 1.52−1.42 (m, 2H), 1.40−1.25 (m, 3H), 1.22−1.08 (m, 5H), 0.82 (t, J = 7.2 Hz, 3H), 0.77 (t, J = 7.2 Hz, 3H). ^{13}C NMR δ 146.7, 131.2, 127.2, 124.0, 119.9, 111.2, 91.0, 69.0, 34.3, 28.7, 27.9, 26.7, 22.1, 22.0, 13.8, 13.7. HRMS (ESI) Calcd for $C_{16}H_{26}N_3O$ (M + H)$^+$ 276.2076, found 276.2078.

*1-(1-(Hexyloxy)hexyl)-1H-benzo[d][1,2,3]triazole (**3e**).* Colorless oil. Yield: 75 mg (50%). ^{1}H NMR δ 8.07 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.51−7.43 (m, 1H), 7.41−7.33 (m, 1H), 6.02 (t, J = 6.8 Hz, 1H), 3.44 (dt, J = 9.4, 6.5 Hz, 1H), 3.19 (dt, J = 9.4, 6.6 Hz, 1H), 2.26 (m, 1H), 2.10 (m, 1H), 1.54−1.44 (m, 2H), 1.30−1.13 (m, 12H), 0.84 (t, J = 4.9 Hz, 3H), 0.81 (t, J = 4.9 Hz, 3H). ^{13}C NMR δ 146.8, 131.2, 127.2, 124.1, 120.0, 111.3, 91.1, 69.1, 34.7, 31.3, 31.1, 29.1, 25.5, 24.5, 22.5, 22.3, 13.9, 13.8. HRMS (ESI) Calcd for $C_{18}H_{29}N_3ONa$ (M + Na)$^+$ 326.2208, found 326.2207.

*1-(1-Isobutoxy-2-methylpropyl)-1H-benzo[d][1,2,3]triazole (**3f**).* Colorless oil. Yield: 69 mg (56%). ^{1}H NMR δ 8.07 (d, J = 8.3 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.48−7.42 (m, 1H), 7.41−7.34 (m, 1H), 5.61 (d, J = 8.9 Hz, 1H), 3.20 (dd, J = 9.1, 6.5 Hz, 1H), 2.98 (dd, J = 9.1, 6.5 Hz, 1H), 2.56 (ddd, J = 13.5, 6.7, 2.1 Hz, 1H), 1.83 (dt, J = 13.3, 6.6 Hz, 1H), 1.21 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H), 0.63 (d, J = 6.8 Hz, 3H). ^{13}C NMR δ 146.8, 131.4, 127.2, 124.1, 120.0, 111.5, 96.5, 76.2, 33.3, 28.2, 19.2, 19.1, 18.9, 17.8. HRMS (ESI) Calcd for $C_{14}H_{21}N_3ONa$ (M + Na)$^+$ 270.1582, found 270.1576.

*1-((Trimethylsilyl)((trimethylsilyl)methoxy)methyl)-1H-benzo[d][1,2,3]triazole (**3g**).* Pale white solid. Melting point: 91−92 °C. Yield: 96 mg (63%). ^{1}H NMR δ 8.06 (d, J = 8.3 Hz, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.44 (dd, J = 11.3, 4.0 Hz, 1H), 7.36 (dd, J = 11.3, 4.0 Hz, 1H), 5.64 (s, 1H), 3.07 (d, J = 12.5 Hz, 1H), 2.98 (d, J = 12.5 Hz, 1H), 0.12 (s, 9H), −0.01 (s, 9H). ^{13}C NMR δ 146.3, 133.1, 126.9, 123.8, 119.9, 111.1, 91.0, 65.7, −3.2, −3.3. HRMS (ESI) Calcd for $C_{14}H_{26}N_3OSi_2$ (M + H)$^+$ 308.1614, found 308.1613.

*1-(1-Ethoxyethyl)-5,6-dimethyl-1H-benzo[d][1,2,3]triazole (**3h**).* Colorless oil. Yield: 81 mg (74%). ^{1}H NMR δ 7.71 (s, 1H), 7.48 (s, 1H), 6.12 (q, J = 6.1 Hz, 1H), 3.42 (dq, J = 9.3, 7.0 Hz, 1H), 3.16 (dq, J = 9.4, 7.1 Hz, 1H), 2.34 (s, 3H), 2.31 (s, 3H), 1.77 (d, J = 6.2 Hz, 3H), 1.05 (t, J = 7.0 Hz, 3H). ^{13}C NMR δ 145.8, 137.4, 133.6, 130.0, 118.8, 110.3, 86.4, 63.9, 20.8, 20.6, 20.1, 14.5. HRMS (ESI) Calcd for $C_{12}H_{17}N_3ONa$ (M + Na)$^+$ 242.1269, found 242.1268.

*5,6-Dimethyl-1-(1-propoxypropyl)-1H-benzo[d][1,2,3]triazole (**3i**).* Colorless oil. Yield: 86 mg (70%). ^{1}H NMR δ 7.75 (s, 1H), 7.49 (s, 1H), 5.86 (t, J = 6.8 Hz, 1H), 3.36 (dt, J = 9.2, 6.6 Hz, 1H), 3.13 (dt, J = 9.2, 6.7 Hz, 1H), 2.37 (s, 3H), 2.35 (s, 3H), 2.23 (td, J = 14.2, 7.2 Hz, 1H), 2.11 (td, J = 14.4, 7.3 Hz, 1H), 1.54−1.44 (m, 2H), 0.85 (t, J = 7.5 Hz, 3H), 0.79 (t, J = 7.4 Hz, 3H). ^{13}C NMR δ 146.0, 137.4, 133.7, 130.2, 118.9, 110.5, 91.8, 70.5, 27.8, 22.3, 20.7, 20.2, 10.3, 9.2. HRMS (ESI) Calcd for $C_{14}H_{21}N_3ONa$ (M + Na)$^+$ 270.1582, found 270.1570.

*1-(1-Butoxybutyl)-5,6-dimethyl-1H-benzo[d][1,2,3]triazole (**3j**).* Colorless oil. Yield: 80 mg (58%). ^{1}H NMR δ 7.76 (s, 1H), 7.50 (s, 1H), 5.96 (t, J = 6.8 Hz, 1H), 3.40 (dt, J = 9.3, 6.5 Hz, 1H), 3.17 (dt, J = 9.3, 6.6 Hz, 1H), 2.39 (s, 3H), 2.37 (s, 3H), 2.25−2.15 (m, 1H), 2.10−2.01 (m, 1H), 1.49−1.35 (m, 3H), 1.31−1.14 (m, 3H), 0.89 (t, J = 7.4 Hz, 3H), 0.79 (t, J = 7.4 Hz, 3H). ^{13}C NMR δ 145.9, 137.5, 133.8, 130.1, 118.9, 110.5, 90.4, 68.6, 36.5, 31.1, 20.8, 20.3, 19.0, 18.1, 13.5, 13.3. HRMS (ESI) Calcd for $C_{16}H_{25}N_3ONa$ (M + Na)$^+$ 298.1895, found 298.1896.

*5,6-Dimethyl-1-(1-(pentyloxy)pentyl)-1H-benzo[d][1,2,3]triazole (**3k**).* Colorless oil. Yield: 77 mg (51%). ^{1}H NMR δ 7.76 (s, 1H), 7.50 (s, 1H), 5.93 (t, J = 6.8 Hz, 1H), 3.39 (dt, J = 9.3, 6.5 Hz, 1H), 3.25−3.06 (m, 1H), 2.38 (s, 3H), 2.36 (s, 3H), 2.25−2.17 (m, 1H), 2.12−2.03 (m, 1H), 1.49−1.45 (m, 2H), 1.40−1.25 (m, 3H), 1.22−1.11 (m, 5H), 0.81 (t, J = 7.3 Hz, 3H), 0.78 (t, J = 6.9 Hz, 3H). ^{13}C NMR δ 145.9, 137.4, 133.7, 130.1, 118.9, 110.5, 90.6, 68.8, 34.2, 28.7, 28.0, 26.8, 22.1, 21.9, 20.7, 20.2, 13.8, 13.7. HRMS (ESI) Calcd for $C_{18}H_{29}N_3ONa$ (M + Na)$^+$ 326.2208, found 326.2211.

*5,6-Dimethyl-1-((trimethylsilyl)((trimethylsilyl)methoxy)methyl)-1H-benzo[d][1,2,3]triazole (**3l**).* White solid. Melting point: 114−115 °C. Yield: 110 mg (66%). ^{1}H NMR δ 7.77 (s, 1H), 7.40 (s, 1H), 5.56 (s, 1H), (3.40 and 2.56 (ABq, 2H, J = 12 Hz), 2.39 (s, 3H), 2.38 (s,3H), 0.10 (s, 9H), −0.02 (s, 9H). ^{13}C NMR δ 145.4, 137.1, 133.5, 132.2, 118.8, 110.5, 90.5, 65.3, 20.9, 20.3, −3.2, −3.3. HRMS (ESI) Calcd for $C_{16}H_{30}N_3OSi_2$ (M + H)$^+$ 336.1927, found 336.1931.

*1-(1-Ethoxyethyl)-5-methyl-1H-benzo[d][1,2,3]triazole (**3m**).* Colorless oil. Yield: 64 mg (62%). (1:1 isomers). ^{1}H NMR δ 7.90 and 7.65 (d, J = 8.5 Hz, 1H), 7.80 and 7.53 (s, 1H), 7.28 and 7.18 (d, J = 8.5 Hz, 1H), 6.19 (q, J = 6.0 Hz, 2H), 3.52−3.45 (m, 2H), 3.27−3.17 (m, 2H), 2.51 and 2.49 (s, 3H), 1.84−1.82 (m, 6H), 1.14−1.11 and 1.11−1.07 (m, 3H). ^{13}C NMR δ 147.4, 145.5, 138.0, 134.2, 131.6, 129.6, 129.5, 126.4, 119.5, 118.9, 110.6, 110.3, 86.9, 86.8, 64.3, 22.0, 21.4, 21.2, 21.1, 14.7. HRMS (ESI) Calcd for $C_{11}H_{15}N_3ONa$ (M + Na)$^+$ 228.1113, found 228.1112.

*5-Chloro-1-(1-ethoxyethyl)-1H-benzo[d][1,2,3]triazole (**3n**).* Colorless oil. Yield: 73 mg (66%). (1:1 isomers). ^{1}H NMR δ 8.06−8.02 and 7.82−7.77 (m, 1H), 7.97 and 7.73 (dd, J = 8.8, 0.4 Hz, 1H), 7.43 and 7.33 (dd, J = 8.8, 1.8 Hz, 1H), 6.25−6.19 (m, 2H), 3.56−3.46 (m, 2H), 3.30−3.20 (m, 2H), 1.84 and 1.82 (s, 3H), 1.15 and 1.12 (t, J = 4.3 Hz, 3H). ^{13}C NMR δ 147.4, 145.4, 133.8, 131.7, 130.1, 129.8, 128.4, 125.4, 121.0, 119.4, 112.1, 111.0, 64.6, 64.5, 21.3, 21.2, 14.7. HRMS (ESI) Calcd for $C_{10}H_{13}ClN_3O$ (M + H)$^+$ 226.0747, found 226.0745.

*1-(1-Ethoxyethyl)-5-phenyl-1H-tetrazole (**5a**).* Light yellow solid. Melting point: 197−198 °C. Yield: 77 mg (72%). ^{1}H NMR δ 8.37−7.81 (m, 2H), 7.56−7.29 (m, 3H), 6.01 (q, J = 6.0 Hz, 1H), 3.55 (dq, J = 9.4, 7.0 Hz, 1H), 3.38 (dq, J = 9.4, 7.0 Hz, 1H), 1.84 (d, J = 6.0 Hz, 3H), 1.11 (t, J = 7.0 Hz, 3H). ^{13}C NMR δ 165.2, 130.4, 128.8, 127.3, 126.9, 88.9, 65.3, 20.8, 14.6. HRMS (ESI) Calcd for $C_{11}H_{14}N_4ONa$ (M + Na)$^+$ 241.1065, found 241.1064.

*5-Phenyl-1-(1-propoxypropyl)-1H-tetrazole (**5b**).* Colorless oil. Yield: 79 mg (64%). ^{1}H NMR δ 8.25- 8.11 (m, 2H), 7.54−7.43 (m, 3H), 5.81 (t, J = 6.7 Hz, 1H), 3.50 (dt, J = 9.3, 6.7 Hz, 1H), 3.35 (dt, J = 9.3, 6.6 Hz, 1H), 2.37−2.19 (m, 2H), 1.64−1.50 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H). ^{13}C NMR δ 165.2, 130.3, 128.8, 127.4, 126.9, 94.0, 71.6, 27.8, 22.3, 10.3, 8.9. HRMS (ESI) Calcd for $C_{13}H_{18}N_4ONa$ (M + Na)$^+$ 269.1378, found 269.1373.

*1-(1-Butoxybutyl)-5-phenyl-1H-tetrazole (**5c**).* Colorless oil. Yield: 71 mg (53%). ^{1}H NMR δ 8.20 (dd, J = 7.6, 1.9 Hz, 2H), 7.48 (dd, J = 6.0, 5.1 Hz, 3H), 5.89 (t, J = 6.7 Hz, 1H), 3.53 (dt, J = 9.3, 6.6 Hz, 1H), 3.37 (dt, J = 9.4, 6.5 Hz, 1H), 2.33−2.24 (m, 1H), 2.22−2.11 (m, 1H), 1.57−1.43 (m, 3H), 1.39−1.23 (m, 3H), 0.96 (t, J = 7.4 Hz, 3H), 0.86 (t, J = 7.4 Hz, 3H). ^{13}C NMR δ 165.2, 130.3, 128.8, 127.4, 126.9,

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92.6, 69.6, 36.4, 31.1, 19.0, 17.9, 13.6, 13.4. HRMS (ESI) Calcd for $C_{15}H_{22}N_4ONa$ $(M + Na)^+$ 297.1691, found 297.1689.

*5-(4-Chlorophenyl)-1-(1-ethoxyethyl)-1H-tetrazole (**5d**).* Colorless oil. Yield: 70 mg (56%). ^1H NMR δ 8.16−8.07 (m, 2H), 7.49−7.41 (m, 2H), 6.07 (q, J = 6.0 Hz, 1H), 3.61 (dq, J = 9.4, 7.0 Hz, 1H), 3.44 (dq, J = 9.4, 7.0 Hz, 1H), 1.89 (d, J = 6.0 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H). ^{13}C NMR δ 164.3, 136.4, 129.1, 128.2, 125.8, 89.0, 65.3, 20.8, 14.6. HRMS (ESI) Calcd for $C_{11}H_{13}ClN_4ONa$ $(M + Na)^+$ 275.0676, found 275.0673.

*5-(4-Chlorophenyl)-1-(1-propoxypropyl)-1H-tetrazole (**5e**).* Colorless oil. Yield: 75 mg (54%). ^1H NMR δ 8.22−8.00 (m, 2H), 7.60−7.32 (m, 2H), 5.80 (t, J = 6.6 Hz, 1H), 3.50 (dt, J = 9.3, 6.7 Hz, 1H), 3.35 (dt, J = 9.3, 6.6 Hz, 1H), 2.38- 2.15 (m, 2H), 1.61−1.54 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR δ 164.4, 136.4, 129.2, 128.3, 125.9, 94.2, 71.7, 27.9, 22.4, 10.3, 8.9. LRMS (ESI) Calcd For $C_{13}H_{18}ClN_4O$ $[M + H]^+$ 281.12, found: 281.20.

*1-(1-Butoxybutyl)-5-(4-chlorophenyl)-1H-tetrazole (**5f**).* Colorless oil. Yield: 76 mg (49%). ^1H NMR δ 8.13 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 5.88 (t, J = 6.7 Hz, 1H), 3.53 (dt, J = 9.4, 6.6 Hz, 1H), 3.37 (dt, J = 9.4, 6.5 Hz, 1H), 2.33−2.23 (m, 1H), 2.19−2.10 (m, 1H), 1.56−1.41 (m,3H), 1.36−1.23 (m, 3H), 0.96 (t, J = 7.4 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H). ^{13}C NMR δ 164.4, 136.4, 129.1, 128.2, 125.9, 92.7, 69.7, 36.4, 31.1, 19.0, 17.9, 13.6, 13.4. HRMS (ESI) Calcd for $C_{15}H_{21}ClN_4ONa$ $(M + Na)^+$ 331.1302, found 331.1301.

*5-(4-Bromophenyl)-1-(1-ethoxyethyl)-1H-tetrazole (**5g**).* Colorless oil. Yield: 82 mg (56%). ^1H NMR δ 8.05 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 6.06 (q, J = 6.0 Hz, 1H), 3.60 (dq, J = 9.3, 7.0 Hz, 1H), 3.44 (dq, J = 9.4, 7.0 Hz, 1H), 1.88 (d, J = 6.0 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H). ^{13}C NMR δ 164.4, 132.0, 128.4, 126.3, 124.7, 65.3, 20.8, 14.6. HRMS (ESI) Calcd for $C_{11}H_{14}BrN_4O$ $(M + H)^+$ 297.0351, found 297.0348.

*5-(4-Bromophenyl)-1-(1-propoxypropyl)-1H-tetrazole (**5h**).* Colorless oil. Yield: 72 mg (45%). ^1H NMR δ 8.07 (d, J = 8.6 Hz, 2H), 7.63 (d, J = 8.6 Hz, 2H), 5.80 (t, J = 6.6 Hz, 1H), 3.49 (dt, J = 9.3, 6.7 Hz, 1H), 3.35 (dt, J = 9.3, 6.6 Hz, 1H), 2.35−2.19 (m, 2H), 1.60−1.54 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H). ^{13}C NMR δ 164.5, 132.1, 128.5, 126.4, 124.7, 94.1, 71.7, 27.9, 22.3, 10.3, 8.9. HRMS (ESI) Calcd for $C_{13}H_{18}BrN_4O$ $(M + H)^+$ 325.0664, found 325.0669.

*1-(1-Ethoxyethyl)-5-(4-fluorophenyl)-1H-tetrazole (**5i**).* Yellow solid. Melting point: 199−200 °C. Yield: 76 mg (65%). ^1H NMR δ 8.31−8.13 (m, 2H), 7.22−7.09 (m,2H), 6.07 (q, J = 6.0 Hz, 1H), 3.62 (dq, J = 9.4, 7.0 Hz, 1H), 3.45 (dq, J = 9.4, 7.0 Hz, 1H), 1.90 (d, J = 6.0 Hz, 3H), 1.19 (t, J = 7.0 Hz, 3H). ^{13}C NMR δ 165.3 and 162.8 (d, J = 250 Hz, CF), 164.5, 129.0 (d, J = 8 Hz), 123.6 (d, J = 4 Hz), 116.0 (d, J = 22 Hz), 88.9, 65.3, 20.8, 14.6. HRMS (ESI) Calcd for $C_{11}H_{14}FN_4O$ $(M + H)^+$ 237.1152, found 237.1134.

*5-(4-Fluorophenyl)-1-(1-propoxypropyl)-1H-tetrazole (**5j**).* Yellow solid. Melting point: 183−184 °C. Yield: 67 mg (52%). ^1H NMR δ 8.19 (dd, J = 8.8, 5.4 Hz, 2H), 7.24−7.12 (m, 2H), 5.80 (t, J = 6.6 Hz, 1H), 3.49 (dt, J = 9.3, 6.7 Hz, 1H), 3.35 (dt, J = 9.3, 6.6 Hz, 1H), 2.35−2.19 (m, 2H), 1.62−1.52 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H). ^{13}C NMR δ 165.3 and 162.8 (d, J = 250 Hz, CF), 164.5, 129.0 (d, J = 9 Hz), 123.7 (d, J = 4 Hz), 116.0 (d, J = 22 Hz), 94.1, 71.6, 27.9, 22.3, 10.3, 8.9. HRMS (ESI) Calcd for $C_{13}H_{17}FN_4ONa$ $(M + Na)^+$ 287.1284, found 287.1288.

*1-(1-Ethoxyethyl)-5-p-tolyl-1H-tetrazole (**5k**).* Colorless oil. Yield: 70 mg (61%). ^1H NMR δ 8.07 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 6.06 (q, J = 6.0 Hz, 1H), 3.61 (dq, J = 9.4, 7.0 Hz, 1H), 3.44 (dq, J = 9.4, 7.0 Hz, 1H), 2.41 (s, 3H), 1.89 (d, J = 6.0 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H). ^{13}C NMR δ 165.3, 140.5, 129.5, 126.8, 124.5, 88.7, 65.2, 21.4, 20.8, 14.6. HRMS (ESI) Calcd for $C_{12}H_{17}N_4O$ $(M + H)^+$ 233.1402, found 233.1390.

*1-(1-Propoxypropyl)-5-p-tolyl-1H-tetrazole (**5l**).* Colorless oil. Yield: 58 mg (46%). ^1H NMR δ 8.08 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 5.79 (t, J = 6.7 Hz, 1H), 3.49 (dt, J = 9.3, 6.7 Hz, 1H), 3.35 (dt, J = 9.3, 6.6 Hz, 1H), 2.41 (s, 3H), 2.35−2.20 (m, 2H), 1.62−1.52 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H). ^{13}C NMR δ 165.3, 140.5, 129.5, 126.8, 124.6, 93.9, 71.5, 27.8, 22.3, 21.4, 10.3, 8.9. HRMS (ESI) Calcd for $C_{14}H_{21}N_4O$ $(M + H)^+$ 261.1715, found 261.1714.

*1-(1-Ethoxyethyl)-5-m-tolyl-1H-tetrazole (**5m**).* Yellow solid. Melting point: 121−122 °C. Yield: 68 mg (60%). ^1H NMR δ 8.04−7.96 (m, 2H), 7.38 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 6.08 (q, J = 6.0 Hz, 1H), 3.61 (dq, J = 9.4, 7.0 Hz, 1H), 3.45 (dq, J = 9.4, 7.0 Hz, 1H), 2.43 (s, 3H), 1.91 (d, J = 6.0 Hz, 3H), 1.18 (t, J = 7.0 Hz, 3H). ^{13}C NMR δ 165.4, 138.6, 131.1, 128.8, 127.5, 127.2, 124.1, 88.8, 65.3, 21.3, 20.8, 14.6. HRMS (ESI) Calcd for $C_{12}H_{17}N_4O$ $(M + H)^+$ 233.1402, found 233.1390.

*1-(1-Propoxypropyl)-5-m-tolyl-1H-tetrazole (**5n**).* Yellow solid. Melting point: 110−112 °C. Yield: 70 mg (54%). ^1H NMR δ 8.05−7.97 (m, 2H), 7.38 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 5.80 (t, J = 6.7 Hz, 1H), 3.49 (dt, J = 9.3, 6.7 Hz, 1H), 3.35 (dt, J = 9.3, 6.6 Hz, 1H), 2.43 (s, 3H), 2.34−2.22 (m, 2H), 1.62−1.54 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR δ 165.4, 138.6, 131.1, 128.8, 127.5, 127.2, 124.1, 94.0, 71.6, 27.9, 22.4, 21.3, 10.3, 9.0. HRMS (ESI) Calcd for $C_{14}H_{21}N_4O$ $(M + H)^+$ 261.1715, found 261.1717.

*1-(1-Ethoxyethyl)-5-o-tolyl-1H-tetrazole (**5o**).* Colorless oil. Yield: 73 mg (63%). ^1H NMR δ 8.05 (d, J = 7.6 Hz, 1H), 7.37−7.29 (m, 3H), 6.09 (q, J = 6.0 Hz, 1H), 3.63 (dq, J = 9.4, 7.0 Hz, 1H), 3.47 (dq, J = 9.4, 7.0 Hz, 1H), 2.64 (s, 3H), 1.91 (d, J = 6.0 Hz, 3H), 1.18 (t, J = 7.0 Hz, 3H). ^{13}C NMR δ 165.5, 137.4, 131.3, 129.9, 129.5, 126.4, 125.9, 88.7, 65.2, 21.6, 20.7, 14.6. HRMS (ESI) Calcd for $C_{12}H_{17}N_4O$ $(M + H)^+$ 233.1402, found 233.1398.

*1-(1-Propoxypropyl)-5-o-tolyl-1H-tetrazole (**5p**).* Colorless oil. Yield: 64 mg (51%). ^1H NMR δ 8.08−8.03 (m, 1H), 7.38−7.27 (m, 3H), 5.82 (t, J = 6.6 Hz, 1H), 3.52 (dt, J = 9.3, 6.6 Hz, 1H), 3.36 (dt, J = 9.3, 6.6 Hz, 1H), 2.64 (s, 3H), 2.37−2.19 (m, 2H), 1.60−1.50 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H). ^{13}C NMR δ 165.5, 137.4, 131.3, 129.8, 129.4, 126.4, 125.9, 93.8, 71.4, 27.7, 22.3, 21.6, 10.2, 8.9. HRMS (ESI) Calcd for $C_{14}H_{21}N_4O$ $(M + H)^+$ 261.1715, found 261.1719.

*1-(1-ethoxyethyl)-5-(4-nitrophenyl)-1H-tetrazole (**5q**).* Yellow solid. Melting point: 84−85 °C. Yield: 83 mg (63%). ^1H NMR δ 8.36 (q, J = 8.9 Hz, 4H), 6.12 (q, J = 6.0 Hz, 1H), 3.64 (dq, J = 14.1, 7.1 Hz, 1H), 3.47 (dq, J = 14.1, 7.0 Hz, 1H), 1.92 (d, J = 6.0 Hz, 3H), 1.19 (t, J = 7.0 Hz, 3H). ^{13}C NMR δ 163.4, 148.9, 133.2, 127.8, 124.1, 89.4, 65.5, 20.8, 14.6. LRMS (ESI) Calcd For $C_{11}H_{14}N_5O_3$ $[M + H]^+$ 264.11, found: 264.20.

*5-(2,3-Dichlorophenyl)-1-(1-ethoxyethyl)-1H-tetrazole (**5r**).* Yellow solid. Melting point: 159−160 °C. Yield: 47 mg (34%). ^1H NMR δ 7.84 (dd, J = 7.8, 1.6 Hz, 1H), 7.60 (dd, J = 8.0, 1.6 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H), 6.12 (q, J = 6.0 Hz, 1H), 3.65 (dq, J = 9.4, 7.0 Hz, 1H), 3.49 (dq, J = 9.4, 7.0 Hz, 1H), 1.93 (d, J = 6.0 Hz, 3H), 1.19 (t, J = 7.0 Hz, 3H). ^{13}C NMR δ 163.0, 134.5, 132.0, 131.8, 129.7, 128.7, 127.3, 89.3, 65.5, 20.8, 14.6. HRMS (ESI) Calcd for $C_{11}H_{13}Cl_2N_4O$ $(M + H)^+$ 287.0466, found 287.0463.

*5-(2,4-Dichlorophenyl)-1-(1-ethoxyethyl)-1H-tetrazole (**5s**).* Colorless oil. Yield: 54 mg (39%). ^1H NMR δ 7.95 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 2.0 Hz, 1H), 7.38 (dd, J = 8.4, 2.1 Hz, 1H), 6.11 (q, J = 6.0 Hz, 1H), 3.64 (dq, J = 9.4, 7.0 Hz, 1H), 3.48 (dq, J = 9.4, 7.0 Hz, 1H), 1.92 (d, J = 6.0 Hz, 3H), 1.19 (t, J = 7.0 Hz, 3H). ^{13}C NMR δ 161.6, 135.6, 132.9, 131.1, 129.7, 126.3, 124.1, 88.3, 76.3, 76.0, 75.7, 64.5, 19.8, 13.6. HRMS (ESI) Calcd for $C_{11}H_{13}Cl_2N_4O$ $(M + H)^+$ 287.0466, found 287.0463.

*9-(1-Ethoxyethyl)-9H-carbazole (**7a**).* Yellow solid. Melting point: 75−76 °C. Yield: 57 mg (48%). ^1H NMR δ 8.09 (d, J = 7.8 Hz, 2H), 7.64 (d, J = 8.3 Hz, 2H), 7.43 (t, J = 7.2 Hz, 2H), 7.24 (t, J = 7.1 Hz, 2H), 5.99 (q, J = 6.1 Hz, 1H), 3.44−3.37 (m, 1H), 3.36−3.27 (m, 1H), 1.78 (d, J = 6.1 Hz, 3H), 1.15 (t, J = 7.0 Hz, 3H). ^{13}C NMR δ 139.1, 125.6, 123.5, 120.2, 119.3, 110.5, 82.2, 63.4, 20.2, 14.9. HRMS (ESI) Calcd for $C_{16}H_{17}NONa$ $(M + Na)^+$ 262.1208, found 262.1215.

*3-Chloro-1-(1-ethoxyethyl)-1H-indazole (**7b**).* Colorless oil. Yield: 18 mg (16%). ^1H NMR δ 7.68 (dd, J = 9.4, 1.4 Hz, 2H), 7.46−7.38 (m, 1H), 7.22 (dd, J = 11.2, 4.1 Hz, 1H), 5.81 (q, J = 6.1 Hz, 1H), 3.47 (dq, J = 14.0, 7.0 Hz, 1H), 3.31 (dq, J = 14.1, 7.1 Hz, 1H), 1.77 (d, J = 6.1 Hz, 3H), 1.14 (t, J = 7.0 Hz, 3H). ^{13}C NMR δ 139.7, 133.3, 127.5,

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122.0, 121.7, 119.8, 110.9, 87.2, 63.8, 20.8, 14.8. HRMS (ESI) Calcd for $C_{11}H_{13}ClN_2ONa$ $(M + Na)^+$ 247.0614, found 247.0624.

1-(1-Ethoxyethyl)-3-methyl-6-nitro-1H-indazole (7c). Yellow oil. Yield: 32 mg (20%). ^1H NMR δ 8.57 (s, 1H), 7.99 (dd, J = 8.8, 1.5 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 5.86 (q, J = 6.0 Hz, 1H), 3.48 (dq, J = 14.1, 7.0 Hz, 1H), 3.28 (dq, J = 14.3, 7.1 Hz, 1H), 2.60 (s, 3H), 1.78 (d, J = 6.0 Hz, 3H), 1.15 (t, J = 7.0 Hz, 3H). ^{13}C NMR δ 146.5, 142.3, 137.8, 127.4, 121.1, 115.1, 107.0, 87.2, 64.1, 21.1, 14.8, 11.8. HRMS (ESI) Calcd for $C_{12}H_{15}N_3O_3Na$ $(M + Na)^+$ 272.1011, found 272.1010.

Radical-Trapping Procedure. To a Schlenk tube equipped with a magnetic stir bar was added 1*H*-Benzotriazole (60 mg, 0.5 mmol) in 3 mL of ethanol. Then TBHP (5.5 M in decane, 1 mmol, 0.2 mL) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (1.5 mol) were added before the tube was sealed and the reaction mixture was stirred at the 120 °C for 12 h. After required reaction time, the mixture was cooled down to room temperature. There is no desired hemiaminal product, only a proton was captured and detected by GC−MS.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02516.

^1H and ^{13}C spectra of all new compounds. (PDF)

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Notes

The authors declare no competing financial interest.

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