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The Synthesis of Tetrazoles in Nanometer Aqueous Micelles at Room Temperature

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A newly developed nonionic amphiphile (GPGS-1500), a diester composed of a Guerbet alcohol (2-octyldodecan-1-ol), poly(ethylene glycol) 1500 (PEG 1500), and succinic acid esters, has been prepared as an effective nanomicelle-forming species for the synthesis of tetrazoles in water at room temperature.

Introduction

During recent decades, tetrazoles have occupied an important position in chemistry. Tetrazole derivatives have been used as ligands in coordination chemistry,[1] as metabolically stable surrogates for carboxylic acid compounds in medicinal chemistry,[2] as specialty explosives in the field of energetic materials[3] and to form photoinducible bioorthogonal ligations for the selective covalent attachment of synthetic groups to biopolymers such as proteins.[4] The main method for the synthesis of tetrazoles is the 1,3-dipolar cycloaddition of nitriles and azides, and extensive work in this area has been reported in the literature.[5] Among these approaches, the use of copious amounts of organic solvents is necessary, and this is not consistent with the notion of green chemistry, because 80% of chemical waste is estimated to be solvents.[6] Sharpless and coworkers have reported an improved method for the synthesis of tetrazoles in water.[7] However, an elevated reaction temperature was required.

Micellar catalysis refers to the acceleration of the rate of a reaction by catalytic amounts of amphiphiles that self-aggregate spontaneously to form micelles in water.[8] Many successful reactions in micellar systems have been reported. Jursic et al. synthesized tetrazoles in dodecyl/hexadecyl trimethyl ammonium bromide aqueous solutions, although a high temperature was needed.[9] Recently, Lipshutz et al. have reported a series of metal-catalyzed cross-coupling reactions catalyzed by the surfactant polyoxyethanyl-α-tocopheryl sebacate (PTS) or TPGS-750-M in water at ambient temperature.[10]

Despite these successful applications, there is limited research on the formation of tetrazoles in nanomicelles under ambient conditions. Herein, we report the design of a new kind of nonionic surfactant (**1**, GPGS, Figure 1) by replacing the hydrophobic chain of TPGS (**2**, Figure 1) with the Guerbet alcohol 2-octyldodecan-1-ol. We have screened an effective amphiphile (**3**, GPGS-1500, Scheme 1) for the

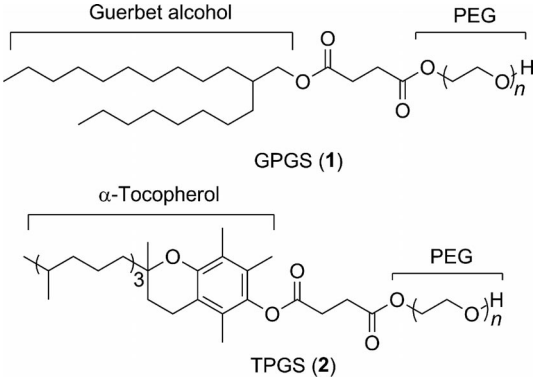
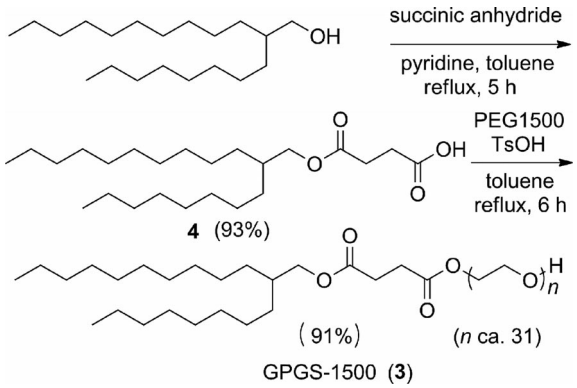


Figure 1. Structural comparison between TPGS and GPGS.



Scheme 1. Synthesis of GPGS-1500.

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http://219.230.65.173/gmis/xkjsb/yjsdsfc.aspx?id = S030817008

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preparation of tetrazoles in water at room temperature by tuning the length of the polyethylene glycol (PEG) chain.

Results and Discussion

Structure and Synthesis of GPGS Analogues: Spotlight on GPGS-1500

GPGS (**1**, Figure 1) is composed of a hydrophobic chain (Guerbet alcohol), a PEG moiety and a succinic acid ester linker and is synthesized through the straightforward two-step route outlined in Scheme 1. Under optimized conditions on a scale of <10 g, as illustrated for GPGS-1500, each of the two steps afforded the desired product in good yield. The ring-opening of succinic anhydride by the Guerbet alcohol in toluene at reflux occurred smoothly in 5 h. The resulting acid was then purified though a pad of silica gel to give colourless oil **4**. The esterification of PEG 1500 with acid **4** under the general conditions (cat. TsOH, toluene, reflux, Dean–Stark trap) afforded the desired product **3** as a white wax. This route could be smoothly scaled to >100 g with comparable yields for each step (86 and 94% yields, respectively). In a similar fashion, GPGS-1000 (**5**, Figure 2) and GPGS-2000 (**6**, Figure 2) were prepared as a slightly yellow wax and a white solid, respectively. All GPGS analogues were stable enough to air at ambient temperatures.

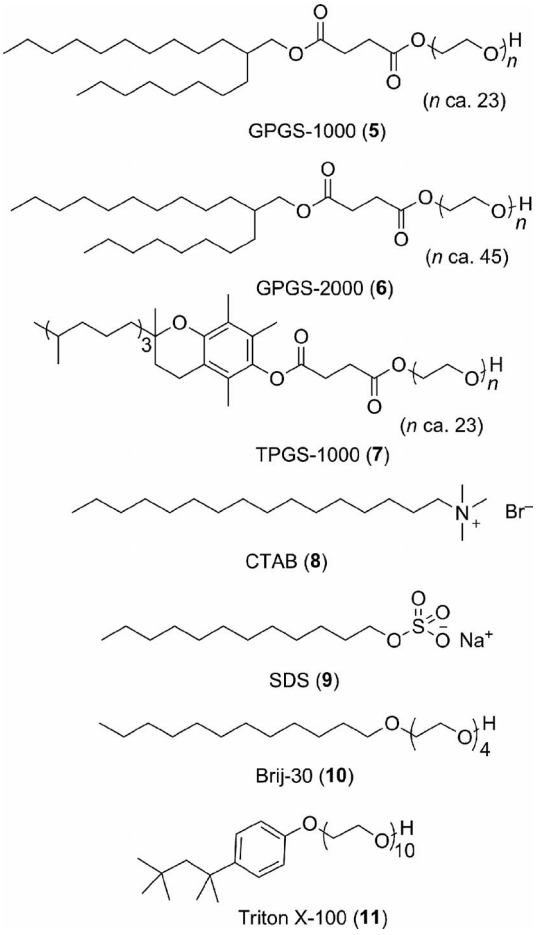
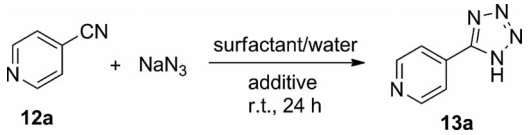


Figure 2. The structures of the used amphiphiles.

Our initial experiment was performed with 4-pyridinecarbonitrile (2 mmol, 1 equiv.), $ZnCl_2$ (1 equiv.) and sodium azide (1.2 equiv.) in aqueous TPGS-1000 (**7**, Figure 2) at room temperature (25 °C). To our delight, the reaction afforded 4-(1*H*-tetrazol-5-yl)pyridine (**13a**) in 73% yield (Table 1, Entry 1). This yield was nearly three times as much as that obtained without any amphiphile (Table 1, Entry 2). It was thus demonstrated that the formation of tetrazoles with nitrile and sodium azide can be catalyzed by micelles formed in water. We then tried the reaction with a newly designed amphiphile (GPGS-1000; Table 1, Entry 3). The high yield of 90% obtained was superior to that obtained with TPGS-1000. This result encouraged us to optimize the structure of GPGS. By tuning the length of the PEG chain, nearly stoichiometric amounts of product were obtained with the optimal amphiphile (GPGS-1500; Table 1, Entries 3–5). Other commercially available surfactants, such as cetrimonium bromide (CTAB), sodium dodecyl sulfate (SDS), Brij-30 and Triton X-100 (**8**, **9**, **10** and **11**, Figure 2), were also used (Table 1, Entries 6–9). Only Triton X-100 can compete with GPGS-1000, and the ionic surfactants CTAB and SDS were disadvantageous to the reaction. When the amount of GPGS-1500 or $ZnCl_2$ was reduced, the yield of 4-(1*H*-tetrazol-5-yl)pyridine decreased (Table 1, Entries 10–12). In addition to Zn salts, some copper sources and other Lewis acids such as $AlCl_3·6H_2O$, $CoCl_2$ and $FeCl_2$ were also used, but the reaction was unsuccessful (Table 1, Entries 13–20).

Table 1. Optimization of reaction conditions for the preparation of **13a** in aqueous micelles.[a]

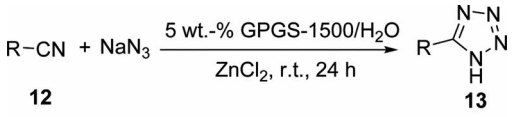


12a **13a**

Entry	Conditions	Additive (equiv.)	Yield [%][b]
1	5 wt.-% TPGS-1000/H_2O	$ZnCl_2$ (1.0)	73
2	H_2O	$ZnCl_2$ (1.0)	25
3	5 wt.-% GPGS-1000/H_2O	$ZnCl_2$ (1.0)	90
4	5 wt.-% GPGS-1500/H_2O	$ZnCl_2$ (1.0)	99[a]
5	5 wt.-% GPGS-2000/H_2O	$ZnCl_2$ (1.0)	79
6	5 wt.-% CTAB/H_2O	$ZnCl_2$ (1.0)	0
7	5 wt.-% SDS/H_2O	$ZnCl_2$ (1.0)	32
8	5 wt.-% Brij-30/H_2O	$ZnCl_2$ (1.0)	54
9	5 wt.-% Triton X-100/H_2O	$ZnCl_2$ (1.0)	91
10	2 wt.-% GPGS-1500/H_2O	$ZnCl_2$ (1.0)	95
11	1 wt.-% GPGS-1500/H_2O	$ZnCl_2$ (1.0)	91
12	5 wt.-% GPGS-1500/H_2O	$ZnCl_2$ (0.5)	53[c]
13	5 wt.-% GPGS-1500/H_2O	$ZnBr_2$(1.0)	96
14	5 wt.-% GPGS-1500/H_2O	$ZnSO_4$(1.0)	78
15	5 wt.-% GPGS-1500/H_2O	CuI (0.2)	0
16	5 wt.-% GPGS-1500/H_2O	$AlCl_3·6H_2O$ (0.1)	0
17	5 wt.-% GPGS-1500/H_2O	$CoCl_2$ (0.5)	0
18	5 wt.-% GPGS-1500/H_2O	CuCl (0.2)	0
19	5 wt.-% GPGS-1500/H_2O	$Cu(OAc)_2$ (2.0)	0
20	5 wt.-% GPGS-1500/H_2O	$FeCl_2$	0

[a] Reaction conditions: 4-pyridinecarbonitrile (2 mmol), sodium azide (2.4 mmol), $ZnCl_2$ (2 mmol), 5 wt.-% amphiphile/H_2O (5 mL), room temp., 24 h. [b] Isolated yield. [c] 48 h.

Table 2. Synthesis of tetrazoles in aqueous GPGS-1500.[a]



12 13

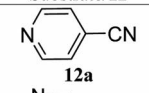
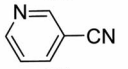
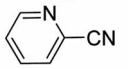
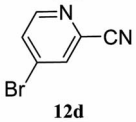
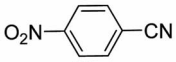
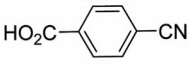
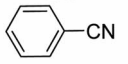
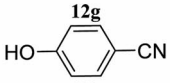
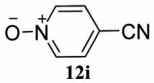
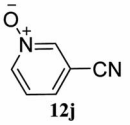
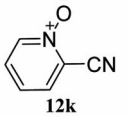
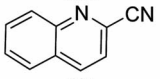
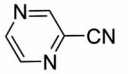
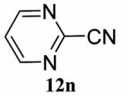
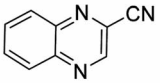
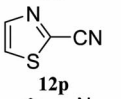
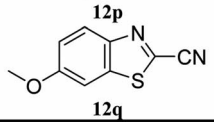
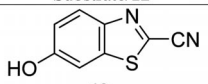
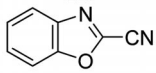
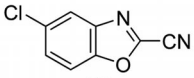
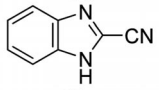
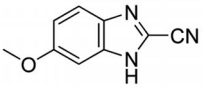
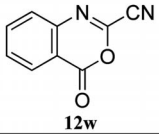
Entry	Substrate/**12**	Product	Yield [%]
1	 **12a**	**13a**	99
2	 **12b**	**13b**	95
3	 **12c**	**13c**	99
4	 **12d**	**13d**	95
5	 **12e**	**13e**	75
6	 **12f**	**13f**	79
7	 **12g**	**13g**	<5
8	 **12h**	**13h**	0
9	 **12i**	**13i**	82
10	 **12j**	**13j**	88
11	 **12k**	**13k**	95
12	 **12l**	**13l**	74
13	 **12m**	**13m**	98
14	 **12n**	**13n**	88
15	 **12o**	**13o**	86
16	 **12p**	**13p**	92
17	 **12q**	**13q**	89

Table 2. (*Continued*)

Entry	Substrate/**12**	Product	Yield [%]
18	 **12r**	**13r**	87
19	 **12s**	**13s**	90
20	 **12t**	**13t**	95[b]
21	 **12u**	**13u**	89
22	 **12v**	**13v**	95[b]
23	 **12w**	**13w**	83

[a] Reaction conditions: nitrile (2 mmol), sodium azide (2.4 mmol), $ZnCl_2$ (2 mmol), 5 wt.-% GPGS-1500/H_2O (5 mL), room temp., 24 h, isolated yield. [b] 5 wt.-% GPGS-1500/H_2O (10 mL).

The Synthesis of Tetrazoles in Aqueous GPGS-1500

Under the optimized conditions, a series of nitriles (**12**) were used to explore the substrate diversity. As demonstrated in Table 2, reactions of *o*-, *m*- and *p*-cyanopyridine with sodium azide afforded nearly stoichiometric amount of the products (Table 2, Entries 1–4). For substrates with *p*-electron-withdrawing groups on the aryl nitriles, the corresponding tetrazoles were obtained in moderate yields (Table 2, Entries 5–6). However, in contrast to the original procedure at elevated temperature,[7b] no product was isolated when a nitrile bearing no substituent or an electron-donating group was used as the reactant (Table 2, Entries 7–8). Similar to the cyanopyridines, tetrazolylpyridine *N*-oxides **13i**–**13k** can be facilely prepared from the corresponding nitriles (Table 2, Entries 9–11). A similar situation was observed for quinoline-2-carbonitrile (**12l**; Table 2, Entry 12).

In addition, other aryl nitriles that contained two-heteroatom cycles were investigated. Substrates with two nitrogen atoms in the six-membered rings afforded the desired products (**13m** and **13n**) in good yields (Table 2, Entries 13–14). When quinoxaline-2-carbonitrile was employed as the reactant, the reaction proceeded smoothly to furnish a good yield of the tetrazole **13o** (Table 2, Entry 15). Both thiazole and benzothiazole derivatives can tolerate the aqueous micelle conditions to afford the relevant tetrazoles (Table 2, Entries 16–18). Similarly, the 2-tetrazolylbenzoxazoles **13s** and **13t** were effectively synthesized from the corresponding nitriles (Table 2, Entries 19–20). For the benzimidazole substrates **12u** and **12v**, the target products were obtained in high yields (Table 2, Entries 21–22). Moreover, this method

can be applied to the synthesis of 2-(1*H*-tetrazol-5-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (Table 2, Entry 23).

The Diameter of GPGS Analogues in Water

The size of the micelles formed upon dissolution of GPGS in water was investigated by dynamic light scattering (DLS). As depicted in Figure 3, the critical micelle concentration (CMC) is limited to no more than 0.3 mM. This result ensured the formation of micelles under our reaction conditions (5 wt.-% GPGS-1500/H_2O >> 0.3 mM). The micellar size of GPGS-1500 is distributed from ca. 18–22 nm with an average of 20 nm. In accordance with the results of Lipshutz, the particle size decreases (Table 3) as the PEG chain length increases.[10e] Owing to the similarities of their structures, the size of the micelles may account for the superior performance of GPGS-1500 to both GPGS-1000 (25 nm) and GPGS-2000 (14 nm) in the reaction. Consequently, 20 nm is the optimal diameter of micelles formed in water for the preparation of tetrazoles.

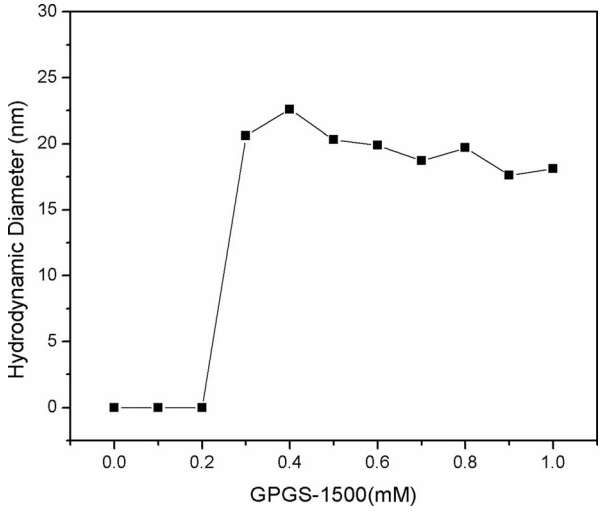


Figure 3. Diameter of GPGS-1500 measured by DLS at different concentrations.

Table 3. Average diameter of GPGS micelles in water.

Amphiphile	Average diameter [nm][a]
GPGS-1000	25
GPGS-1500	20
GPGS-2000	14

[a] Determined by dynamic light scattering (DLS).

Conclusions

We have designed a new kind of nonionic amphiphile with a Guerbet alcohol as the hydrophobic chain, a PEG moiety as the hydrophilic group and a succinic acid ester as the linker. The diameter of the micelles formed in water was measured by DLS. The optimal amphiphile (GPGS-1500) was screened for the preparation of tetrazoles in water at ambient temperature. Investigations of further applications of GPGS-1500 and thiazole, benzoxazole and benzimidazole tetrazole derivatives in organic chemistry are in progress.

Experimental Section

General Experiments: Melting points were recorded with an XD-4 digital micro melting point apparatus. IR spectra were obtained with a Bruker Tensor 27 FTIR instrument. NMR spectra were obtained with a Bruker Avance 500 spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C NMR spectroscopy. MS spectra were recorded with an Agilent liquid chromatography–mass spectrometry (LC–MS) 1100 series instrument; the ESI method was used. High-resolution mass spectra (HRMS) were recorded with a micro TOF-Q II mass spectrometer (ESI). Flash column chromatography was performed by employing 200–300 mesh silica gel. Thin-layer chromatography (TLC) was performed with silica gel HSGF254.

4-(2-Octyldodecyloxy)-4-oxobutanoic Acid (4), <10 g Scale: A solution of succinic anhydride (0.91 g, 18 mmol) and pyridine (0.06 mL) in toluene (15 mL) was heated to reflux. 2-Octyldodecan-1-ol (2.25 g, 7.5 mmol) in toluene (5 mL) was added dropwise, and the mixture was heated to reflux for 5 h. The reaction mixture was cooled to room temp., washed with 1 N HCl (3× 10 mL) and water (3× 10 mL), dried with anhydrous Na_2SO_4 and condensed in vacuo. The residue was purified by column chromatography on silica gel (eluted with petroleum ether/EtOAc 10:1–1:1) to afford the product **3** (2.8 g, 93%) as a colourless oil. FTIR (KBr): $\tilde{\nu}$ = 2923, 2854, 1739, 1714, 1463, 1168, 931, 721 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.00 (d, J = 5.8 Hz, 2 H), 2.69 (t, J = 7.0 Hz, 2 H), 2.63 (t, J = 6.3 Hz, 2 H), 1.28 (d, J = 19.7 Hz, 33 H), 0.88 (t, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.56, 172.26, 67.65, 37.23, 31.90, 31.15, 29.92, 29.64, 29.33, 29.00, 28.88, 26.67, 22.68, 14.09 ppm. HRMS (ESI): calcd. for $C_{24}H_{47}O_4$ $[M + H]^+$ 399.3469; found 399.3458.

GPGS-1500 (3), <10 g Scale: A mixture of 4-(2-octyldodecyloxy)-4-oxobutanoic acid (1.99 g, 5 mmol), PEG 1500 (9 g, ca. 6 mmol), 4-methylbenzenesulfonic acid (0.17 g, 1 mmol) and toluene (30 mL) was heated to reflux for 6 h with a Dean–Stark trap. The mixture was cooled to room temp., poured into saturated $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3× 30 mL). The combined organic layers were washed with saturated $NaHCO_3$ (3× 30 mL) and brine (2× 30 mL), dried with anhydrous Na_2SO_4 and concentrated in vacuo to afford the title compound (8.53 g, 91%) as a waxy solid. FTIR (KBr): $\tilde{\nu}$ = 3421, 2887, 1967, 1737, 1348, 1112, 960, 1168, 567 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.29–4.20 (m, 2 H), 3.99 (d, J = 5.8 Hz, 2 H), 3.66 (m, 122 H), 2.74–2.56 (m, 4 H), 1.26 (m, 33 H), 0.88 (t, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.22, 172.14, 72.48, 70.47, 70.23, 68.95, 67.41, 63.70, 61.51, 37.15, 31.78, 31.07, 29.81, 29.51, 29.20, 29.03, 28.97, 26.56, 22.56, 14.03 ppm. MS (ESI): m/z = 751.4 $[M + 2H]^{2+}$.

4-(2-Octyldodecyloxy)-4-oxobutanoic Acid (4), >100 g Scale: A mixture of succinic anhydride (45 g, 0.9 mol), pyridine (10 mL) and toluene (400 mL) was added to a 1 L three-necked round-bottom flask and heated to reflux. Then, a solution of 2-octyldodecan-1-ol (112 g, 0.375 mol) in toluene (200 mL) was slowly added over 2 h by using dropping funnel. The mixture was then heated to reflux until the reaction was complete as indicated by TLC (hexane/EtOAc 10:1, R_f = 0.46). The mixture was cooled to room temp., and the white solid was removed by filtration. The filtrate was

washed with 1 N HCl (3 × 200 mL) and water (2 × 300 mL), dried with anhydrous Na_2SO_4 and condensed in vacuo. The residue was filtered through a pad of silica gel (eluted with petroleum ether/EtOAc 1:1) to afford the product **3** (128 g, 86%) as a slightly yellow oil. The NMR ($CDCl_3$) data was consistent with that of the desired product prepared on a scale of <10 g.

GPGS-1500 (3), >100 g Scale: A mixture of 4-(2-octyldodecyloxy)-4-oxobutanoic acid (40 g, 0.1 mol), PEG 1500 (180 g, ca. 0.12 mol), 4-methylbenzenesulfonic acid (3.4 g, 20 mmol) and toluene (500 mL) was added to a 1 L single-necked round-bottom flask equipped with a Dean–Stark trap. The mixture was heated to reflux until the toluene layer in the Dean–Stark trap became clear. The mixture was cooled to room temp., poured into saturated $NaHCO_3$ (1 L) and extracted with CH_2Cl_2 (3 × 500 mL). The combined organic layers were washed with saturated $NaHCO_3$ (3 × 500 mL) and brine (2 × 500 mL), dried with anhydrous Na_2SO_4 and concentrated in vacuo to afford the title compound (176 g, 94%) as a slightly yellow waxy solid. The data for the product were identical in all aspects (^{1}H NMR, ^{13}C NMR, MS) to those of the sample prepared on a smaller scale.

General Procedure for the Preparation of Tetrazoles: A vial was charged with nitrile (2 mmol), NaN_3 (2.4 mmol, 1.2 equiv.), $ZnCl_2$ (2 mmol, 1.0 equiv.) and 5 wt.-% GPGS-1500/H_2O solution (5 mL). The mixture was stirred for 24 h at 25 °C and adjusted to pH 2–5 with 1 N aqueous HCl solution. The precipitate was collected by filtration and washed with water (5 mL). The filter cake was dissolved in 0.25 N NaOH, and the solution was filtered through a pad of Celite. The filtrate was acidified with 1 N HCl to pH 2–5 and stirred for 10 min. The resulting precipitate was collected by filtration and dried in vacuo to afford the pure tetrazole (**13**).

4-(1*H*-Tetrazol-5-yl)pyridine (13a): White solid; m.p. 251–253 °C (ref.[11] 254–255 °C). FTIR (KBr): $\tilde{\nu}$ = 3442, 3098, 2440, 2105, 1630, 1528, 1353, 1094, 870, 749 cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.82 (d, J = 5.1 Hz, 2 H), 8.01 (d, J = 5.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 156.11, 150.69, 133.92, 121.37 ppm. MS (ESI): m/z = 148.0 [M + H]$^+$.

3-(1*H*-Tetrazol-5-yl)pyridine (13b): White solid; m.p. 224–225 °C (ref.[12] 226–228 °C). FTIR (KBr): $\tilde{\nu}$ = 3423, 3083, 2477, 2130, 1641, 1573, 1478, 1459, 1335, 1110, 832, 612 cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.21 (s, 1 H), 8.77 (d, J = 4.0 Hz, 1 H), 8.44–8.35 (m, 1 H), 7.65 (dd, J = 7.8, 4.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 154.49, 152.21, 148.04, 135.00, 124.80, 121.46 ppm. MS (ESI): m/z = 148.1 [M + H]$^+$.

2-(1*H*-Tetrazol-5-yl)pyridine (13c): White solid; m.p. 211–213 °C (ref.[7b] 211 °C). FTIR (KBr): $\tilde{\nu}$ = 3421, 1612, 1468, 1444, 1170, 1138, 1029, 802, 757, 732 cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.29 (s, 1 H), 8.41 (d, J = 6.3 Hz, 1 H), 8.20 (d, J = 7.8 Hz, 1 H), 7.61 (t, J = 6.8 Hz, 1 H), 7.56 (t, J = 7.7 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 159.27, 148.00, 145.96, 140.85, 125.81, 121.24 ppm. MS (ESI): m/z = 148.0 [M + H]$^+$.

5-Bromo-2-(1*H*-tetrazol-5-yl)pyridine (13d):[13] White solid; m.p. 219–221 °C. FTIR (KBr): $\tilde{\nu}$ = 3226, 2171, 1600, 1425, 1097, 848, 653 cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.90 (br, 1 H), 8.34 (d, J = 8.0 Hz, 1 H), 8.15 (d, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 156.83, 151.32, 144.09, 141.44, 124.24, 122.28 ppm. MS (ESI): m/z = 225.9 [M + H]$^+$, 227.9 [(M + 2) + H]$^+$.

5-(4-Nitrophenyl)-1*H*-tetrazole (13e): White solid; m.p. 215–217 °C (ref.[14] 218–220 °C). FTIR (KBr): $\tilde{\nu}$ = 3444, 3328, 2563, 1945, 1701, 1607, 1562, 1531, 1339, 852 cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.44 (d, J = 8.6 Hz, 2 H), 8.30 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 155.89, 149.14, 131.06, 128.60, 124.99 ppm. MS (ESI): m/z = 191.9 [M + H]$^+$.

4-(1*H*-Tetrazol-5-yl)benzoic Acid (13f): Off-white solid; m.p. 247–248 °C (ref.[14] 248–250 °C). FTIR (KBr): $\tilde{\nu}$ = 3482, 2505, 1684, 1583, 1438, 1321, 1285, 1241, 995, 734 cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 13.54 (s, 1 H), 8.09 (d, J = 8.1 Hz, 2 H), 7.99 (d, J = 8.1 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 167.03, 155.93, 133.38, 130.71, 128.69, 127.59 ppm.

4-(1*H*-Tetrazol-5-yl)pyridine 1-Oxide (13i):[15] White solid; m.p. 252–254 °C. FTIR (KBr): $\tilde{\nu}$ = 3419, 3110, 2443, 1947, 1699, 1440, 1232, 991, 649 cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.41 (d, J = 7.3 Hz, 1 H), 7.98 (d, J = 7.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 154.93, 140.22, 124.57, 121.58 ppm. MS (ESI): m/z = 164.1 [M + H]$^+$.

3-(1*H*-Tetrazol-5-yl)pyridine 1-Oxide (13j): White solid; m.p. 248–250 °C. (ref.[16] 248 °C dec.). FTIR (KBr): $\tilde{\nu}$ = 3419, 3081, 2169, 1465, 1386, 1126, 891, 665 cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.72 (s, 1 H), 8.34 (d, J = 6.6 Hz, 1 H), 7.90 (d, J = 7.9 Hz, 1 H), 7.59 (dd, J = 7.9, 6.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]-DMSO): δ = 154.19, 140.73, 136.94, 127.85, 125.77, 123.47 ppm. MS (ESI): m/z = 164.1 [M + H]$^+$.

2-(1*H*-Tetrazol-5-yl)pyridine 1-Oxide (13k): White solid; m.p. 241–243 °C. (ref.[17] 245 °C). FTIR (KBr): $\tilde{\nu}$ = 3423, 3106, 3087, 1637, 1452, 1266, 1244, 1110, 1014, 840, 753 cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.56 (d, J = 6.2 Hz, 1 H), 8.41 (dd, J = 8.0, 2.0 Hz, 1 H), 7.73–7.64 (m, 1 H), 7.60 (dt, J = 7.8, 1.1 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 153.36, 140.63, 138.47, 133.55, 131.06, 126.92 ppm. MS (ESI): m/z = 164.0 [M + H]$^+$.

2-(1*H*-Tetrazol-5-yl)quinoline (13l): White solid; m.p. 190–191 °C (ref.[18] 192–193 °C). FTIR (KBr): $\tilde{\nu}$ = 3442, 2632, 1735, 1409, 1124, 916, 752 cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.65 (d, J = 8.4 Hz, 1 H), 8.31 (d, J = 8.5 Hz, 1 H), 8.17 (d, J = 8.5 Hz, 1 H), 8.12 (d, J = 8.1 Hz, 1 H), 7.90 (m, 1 H), 7.74 (m, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 147.37, 145.65, 139.46, 139.19, 131.30, 128.74, 128.00, 124.53, 119.21 ppm. MS (ESI): m/z = 198.1 [M + H]$^+$.

2-(1*H*-Tetrazol-5-yl)pyrazine (13m): White solid; m.p. 191–193 °C (ref.[7b] 193–195 °C). FTIR (KBr): $\tilde{\nu}$ = 3442, 2497, 1700, 1650, 1478, 1444, 1362, 1168, 1105, 870 cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]-DMSO): δ = 9.37 (br, 1 H), 8.74 (br, 1 H), 8.11 (br, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 153.95, 147.24, 145.31, 143.81, 140.43 ppm. MS (ESI): m/z = 149.1 [M + H]$^+$.

2-(1*H*-Tetrazol-5-yl)pyrimidine (13n): White solid; m.p. 228–230. (ref.[17] 229–230 °C dec). FTIR (KBr): $\tilde{\nu}$ = 3419, 3103, 2169, 1876, 1579, 1392, 1170, 738, 638 cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.05 (s, 2 H), 7.72 (t, J = 4.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 158.83, 155.28, 154.32, 123.06 ppm. MS (ESI): m/z = 149.0 [M + H]$^+$.

2-(1*H*-Tetrazol-5-yl)quinoxaline (13o): White solid; m.p. 265–267 °C (ref.[19] 269–270 °C). FTIR (KBr): $\tilde{\nu}$ = 2891, 2169, 1648, 1498, 1122, 777 cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.56 (s, 1 H), 8.15 (d, J = 8.0 Hz, 1 H), 7.93 (m, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 156.06, 144.06, 142.65, 140.93, 131.83, 129.62, 129.03 ppm. MS (ESI): m/z = 199.0 [M + H]$^+$.

2-(1*H*-Tetrazol-5-yl)thiazole (13p): White solid; m.p. 222–223 °C. FTIR (KBr): $\tilde{\nu}$ = 3423, 3132, 2757, 1776, 1581, 1346, 985, 759 cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.16 (d, J = 3.1 Hz, 1 H), 8.12 (d, J = 3.1 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]-DMSO): δ = 152.59, 152.05, 144.96, 124.59 ppm. HRMS (ESI): calcd. for $C_4H_4N_5S$ [M + H]$^+$ 154.0182; found 154.0183.

6-Methoxy-2-(1*H*-tetrazol-5-yl)benzo[*d*]thiazole (13q): Off-white solid; m.p. 241–243 °C. FTIR (KBr): $\tilde{\nu}$ = 3415, 3136, 2169, 1616, 1569, 1386, 1135, 979, 578 cm^{-1}. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 8.04 (d, J = 8.9 Hz, 1 H), 7.84 (d, J = 2.5 Hz, 1 H), 7.24 (dd, J = 9.0, 2.6 Hz, 1 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]-DMSO): δ = 158.95, 152.77, 150.84, 147.59, 137.03, 124.50, 117.51, 105.34, 56.30 ppm. HRMS (ESI): calcd. for $C_9H_8N_5OS$ $[M + H]^+$ 234.0444; found 234.0445.

2-(1*H*-Tetrazol-5-yl)benzo[*d*]thiazol-6-ol (13r): Yellowish solid; m.p. >290 °C. FTIR (KBr): $\tilde{\nu}$ = 3447, 3162, 2169, 1731, 1573, 1384, 1135, 979 cm^{-1}. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 9.75 (s, 1 H), 7.78 (d, J = 8.7 Hz, 1 H), 7.34 (d, J = 2.4 Hz, 1 H), 6.93 (dd, J = 8.7, 2.4 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 157.70, 156.73, 155.99, 147.56, 136.27, 123.70, 116.11, 107.08 ppm. HRMS (ESI): calcd. for $C_8H_6N_5OS$ $[M + H]^+$ 220.0288; found 220.0291.

2-(1*H*-Tetrazol-5-yl)benzo[*d*]oxazole (13s): White solid; m.p. 221–224 °C. FTIR (KBr): $\tilde{\nu}$ = 3207, 2659, 1911, 1675, 1450, 1037, 748 cm^{-1}. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 7.83 (dd, J = 7.5, 3.8 Hz, 2 H), 7.46 (td, J = 15.3, 7.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 154.64, 151.34, 150.37, 140.87, 126.86, 125.76, 120.64, 111.74 ppm. HRMS (ESI): calcd. for $C_8H_6N_5O$ $[M + H]^+$ 188.0567; found 188.0562.

5-Chloro-2-(1*H*-tetrazol-5-yl)benzo[*d*]oxazole (13t): White solid; m.p. 217–219 °C. FTIR (KBr): $\tilde{\nu}$ = 3454, 3161, 2383, 2169, 1913, 1637, 1386, 1155, 1043, 578 cm^{-1}. ^1H NMR (500 MHz, [D$_6$]-DMSO): δ = 8.09 (d, J = 2.0 Hz, 1 H), 7.99 (d, J = 8.8 Hz, 1 H), 7.62 (dd, J = 8.7, 2.1 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]-DMSO): δ = 153.68, 149.35, 149.26, 142.09, 130.27, 127.60, 120.73, 113.38 ppm. HRMS (ESI): calcd. for $C_8H_5ClN_5O$ $[M + H]^+$ 222.0177; found 222.0176.

2-(1*H*-Tetrazol-5-yl)-1*H*-benzo[*d*]imidazole (13u): Off-white solid; m.p. >290 °C. FTIR (KBr): $\tilde{\nu}$ = 3442, 2632, 1735, 1409, 1124, 916, 752 cm^{-1}. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 7.72 (dd, J = 6.1, 3.2 Hz, 2 H), 7.43 (dd, J = 6.1, 3.1 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 157.09, 143.32, 138.85, 125.94, 118.18 ppm. HRMS (ESI): calcd. for $C_8H_7N_6$ $[M + H]^+$ 187.0727; found 187.0727.

6-Methoxy-2-(1*H*-tetrazol-5-yl)-1*H*-benzo[*d*]imidazole (13v): Off-white solid; m.p. >290 °C. FTIR (KBr): $\tilde{\nu}$ = 3444, 3126, 2169, 1633, 1386, 1128, 949, 578 cm^{-1}. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 7.62 (d, J = 8.9 Hz, 1 H), 7.13 (d, J = 2.2 Hz, 1 H), 7.05 (dd, J = 8.9, 2.4 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 159.80, 152.33, 142.77, 140.46, 138.06, 119.58, 117.68, 99.96, 58.74 ppm. HRMS (ESI): calcd. for $C_9H_6N_5O_2$ $[M + H]^+$ 217.0832; found 217.0836.

2-(1*H*-Tetrazol-5-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (13w): Off-white solid; m.p. >290 °C. FTIR (KBr): $\tilde{\nu}$ = 3417, 3118, 1677, 1606, 1386, 1272, 754, 551 cm^{-1}. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 12.56 (s, 1 H), 8.76 (dd, J = 8.4, 0.8 Hz, 1 H), 8.16–8.06 (m, 1 H), 7.76–7.63 (m, 1 H), 7.3–7.18 (m, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 157.28, 156.66, 140.38, 139.22, 135.99, 134.41, 131.19, 124.60, 114.75 ppm. HRMS (ESI): calcd. for $C_4H_4N_5S$ $[M + H]^+$ 216.0516; found 216.0516.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and characterization data for some of the starting materials, ^1H and ^{13}C NMR and HRMS spectra for the products.

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