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Preparation of 5-Aryl-2-Alkyltetrazoles with Aromatic Aldehydes, Alkylhydrazine, Di-*tert*-butyl Azodicarboxylate, and [Bis(trifluoroacetoxy)iodo]benzene

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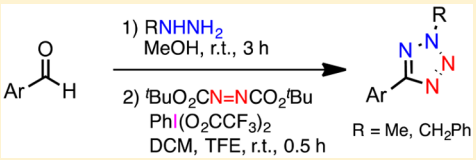
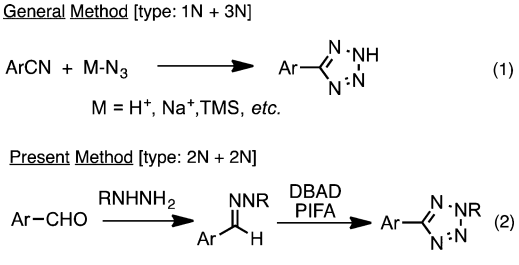
Supporting Information

ABSTRACT: A variety of 5-aryl-2-methyltetrazoles and 5-aryl-2-benzyltetrazoles were directly prepared in good to moderate yields by the reaction of aromatic aldehydes with methylhydrazine and benzylhydrazine, followed by treatment with di-*tert*-butyl azodicarboxylate and [bis(trifluoroacetoxy)iodo]-benzene in a mixture of dichloromethane and 2,2,2-trifluoroethanol at room temperature. The present method is a novel one-pot preparation of 5-aryl-2-methyltetrazoles and 5-aryl-2-benzyltetrazoles through a [2N + 2N] combination under transition metal-free and mild conditions.



Tetrazoles are one of the most important heterocyclic units because they can be considered as bioisosteres of amides and carboxylic acids having high lipophilicity.[1] For example, Losartan which is used as a hypertensive drug is a 5-aryl-1*H*-tetrazole,[1h] and Candesartan Cilexetil which is used as an angiotensin II receptor blocker (ARB) is also a 5-aryl-1*H*-tetrazole.[2] Other 5-aryl-1*H*-tetrazoles possessing antiallergic, antiasthmatic, antiviral, and anti-inflammatory activities have also been reported.[3] The most common method for the preparation of 5-substituted 1*H*-tetrazoles is the reaction of nitriles with sodium azide [type: 1N + 3N] in the presence of acid catalysts, such as NH_4Cl, transition-metal catalysts, such as Cu_2O, ZnO, $ZnBr_2$, and Bu_2SnO, or microwave-irradiation, *etc.*, as shown in Scheme 1 (eq 1).[1] Recent reports for the preparation of tetrazoles with [type: 1N + 3N] are as follows: 5-aryl-1*H*-tetrazoles from aromatic nitriles with sodium azide in the presence of 4-(*N*,*N*-dimethylamino)pyridinium acetate without solvent at 100 °C;[4a] 5-amino-1-aryltetrazoles from selenourea and sodium azide in the presence of (diacetoxyiodo)benzene (DIB) at room temperature;[4b] 5-aryl- or 5-alkyl-1*H*-tetrazoles from aromatic or aliphatic nitriles with sodium azide in the presence of $Yb(OTf)_3$ in DMF at 100−120 °C;[4c] 5-substituted 1*H*-tetrazoles from thiocyanates or nitriles and sodium azide with $ZnCl_2$ in propanol at 95−110 °C;[4d] 5-aryl- or 5-alkyl-1*H*-tetrazoles from aromatic or aliphatic nitriles with sodium azide in the presence of Amberlyst 15 in DMSO at 85 °C;[4e] and 1,5-disubstituted tetrazoles using the Ugi reaction from isocyanides, trimethylsilyl azide, and ketimines in methanol at room temperature.[4f,g] However, most of the reactions require sodium azide or azide derivatives. In particular, hydrazoic acid, which is prepared from sodium azide with an acid catalyst, is extremely toxic and explosive. On the other hand, studies for the preparation of tetrazoles through [type: 2N + 2N] are quite limited. Typical reports for the preparation of tetrazoles with [type: 2N + 2N] are as follows: the dimerization of α-diazoacetophenone derivatives with *t*-BuOK to form 1,5-disubstituted tetrazoles;[5a] the reaction of *N*-phenylsulfonylbenzhydrazidoyl chloride and arylhydrazines with K_2CO_3 to form 2,5-diaryltetrazoles;[5b] the reaction of arenediazonium salts and 2,2,2-trifluorodiazoethane with AcOAg and Cs_2CO_3 to form 2-aryl-5-trifluoromethyl-tetrazoles,[5c] and the reaction of arenediazonium salts and amidines, followed by the reaction with I_2−KI, to form 2,5-disubstituted tetrazoles.[5d]

Scheme 1. Preparation of Tetrazoles



Here, as part of our synthetic study of heterocycles with trivalent iodines,[6] we would like to report a novel preparation of 2-alkyl-5-aryltetrazoles that involved the reaction of aromatic aldehydes with alkylhydrazine, followed by the reaction with di-*tert*-butyl azodicarboxylate (DBAD) and [bis(trifluoroacetoxy)-iodo]benzene through [type: 2N + 2N], as shown in eq 2 of Scheme 1.

First, treatment of 4-chlorobenzaldehyde **1a** with methylhydrazine (1.2 equiv) in methanol at 60 °C generated the

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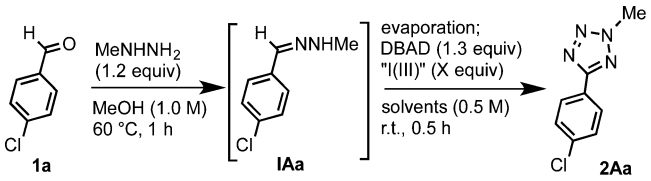
corresponding *N*-methylhydrazone **IAa** quantitatively. After removal of methanol by evaporation, dichloromethane (DCM), 1,2-dichloroethane (DCE), acetonitrile, toluene, DMSO, and 2,2,2-trifluoroethanol (TFE), which cannot be easily oxidized by [bis(trifluoroacetoxy)iodo]benzene (PIFA), were added to the residue, respectively. Then, di-*tert*-butyl azodicarboxylate (DBAD, 1.3 equiv) and PIFA (2.2 equiv) were added to the solution, and the mixture was stirred at room temperature for 0.5 h to give 5-(4′-chlorophenyl)-2-methyltetrazole **2Aa**. The yield was dependent on the solvent used, as shown in Table 1

Table 1. One-Pot Preparation of 5-(4′-Chlorophenyl)-2-methyltetrazole from 4-Chlorobenzaldehyde



entry	"I(III)" (X)	solvent	yield (%)
1	PIFA (2.2)	DCM	11
2	PIFA (2.2)	DCE	11
3	PIFA (2.2)	MeCN	17
4	PIFA (2.2)	PhMe	8
5	PIFA (2.2)	DMSO	18
6	PIFA (2.2)	TFE	59
7	PIFA (2.2)	DCM/TFE = 1:1	68
8	PIFA (2.2)	DCE/TFE = 1:1	60
9	PIFA (2.2)	MeCN/TFE = 1:1	64
10	PIFA (2.2)	PhMe/TFE = 1:1	62
11	PIFA (2.2)	DMSO/TFE = 1:1	50
12[a]	PIFA (2.2)	DCM/TFE = 1:1	25
13[b]	PIFA (2.2)	DCM/TFE = 1:1	44
14[c]	PIFA (2.2)	DCM/TFE = 1:1	16
15	DIB (2.2)	DCM/TFE = 1:1	1
16	HTIB (2.2)	DCM/TFE = 1:1	1
17	PIFA (2.5)	DCM/TFE = 1:1	71
18[d]	PIFA (2.5)	DCM/TFE = 1:1	74
19[d]	PIFA (2.5)	DCM/TFE = 3:1	68
20[d]	PIFA (2.5)	DCM/TFE = 3:2	70
21[d]	PIFA (2.5)	DCM/TFE = 2:3	72
22[d]	PIFA (2.5)	DCM/TFE = 1:3	70
23[d,e]	PIFA (2.5)	DCM/TFE = 1:1	57

[a]TFE (1.0 M) was used instead of MeOH at the first reaction step, and the solvent was not evaporated at the second reaction step. [b]TFA (1.0 equiv) was added at the second reaction step. [c]$BF_3{\cdot}OEt_2$ (1.0 equiv) was added at the second reaction step. [d]The first reaction step was carried out at rt for 3 h. [e]DBAD (2.0 equiv) was used.

(Table 1, entries 1−6), and TFE was the most effective solvent, giving compound **2Aa** in 59% yield (Table 1, entry 6). To improve the yield of compound **2Aa**, mixed solvents were examined at the second reaction step, and it was found that the mixture of DCM and TFE (1:1) is the best solvent, providing compound **2Aa** in 68% yield (Table 1, entry 7 in entries 7−11). Use of TFE instead of MeOH at the first reaction step and the addition of dichloromethane at the second reaction step without evaporation resulted in a low yield of compound **2Aa** (Table 1, entry 12). Acid additives, such as trifluoroacetic acid (TFA) and $BF_3{\cdot}OEt_2$, had a detrimental effect on the reaction (Table 1, entries 13 and 14). Use of other trivalent iodines, such as (diacetoxyiodo)benzene (DIB) and [(hydroxy)-(tosyloxy)iodo]benzene (HTIB), instead of PIFA at the second reaction step was not effective at all (Table 1, entries 15 and 16). Finally, it was found that treatment of *p*-chlorobenzaldehyde **1a** and methylhydrazine in methanol at room temperature for 3 h at the first reaction step, followed by the reaction with DBAD (1.3 equiv) and PIFA (2.5 equiv) in a mixture of DCM and TFE (1:1) at room temperature at the second reaction step, was the best choice, giving compound **2Aa** in 74% yield (Table 1, entry 18). Reducing the amount of TFE decreased the yield of compound **2Aa** slightly (Table 1, entries 19 and 20), and increasing the amount of TFE had almost no effect on the yield of compound **2Aa** (Table 1, entries 21 and 22). Increasing the amount of DBAD (2.0 equiv) using the same procedure and conditions was also not effective (Table 1, entry 23).

Based on those results, several aromatic aldehydes **1b−1q** were treated with methylhydrazine in MeOH at room temperature for 3 h, and then the solvent was removed. Dichloromethane (DCM) and TFE (1:1) were added to the residue, and the addition of DBAD (1.3 equiv) and PIFA (2.5 equiv) to the residue at room temperature provided 5-aryl-2-methyltetrazoles **2Ab−2Aq** in good to moderate yields, as shown in Table 2. The reactivity of 2-naphthoaldehyde **1r** was low because the formation of *N*-methylhydrazone did not proceed smoothly. Treatment of electron-deficient heteroaromatic aldehydes, such as 3-pyridinecarboxaldehyde and 4-quinolinecarboxaldehyde, with methylhydrazine and then TBAD and PIFA under the same procedure and conditions furnished 2-methyl-5-(3′-pyridyl)tetrazole **2As** and 2-methyl-5-(4′-quinolyl)tetrazole **2At** in moderate yields. However, when less electron-deficient heteroaromatic aldehydes, such as benzofuran-3-carboxaldehyde and benzothiopene-3-carboxaldehyde, than 3-pyridinecarboxyaldehyde were treated with methylhydrazine and then DBAD and PIFA under the same procedure and conditions, the corresponding tetrazoles were obtained in low yield, i.e., 12% and 11% yields, respectively.

The same treatment of several aromatic aldehydes **1a**, **1b**, **1d**, **1g−1i**, and **1l** with benzylhydrazine instead of methylhydrazine in DCM at room temperature, followed by evaporation and the subsequent reaction with DBAD (1.3 equiv) and PIFA (2.5 equiv) together with addition of DCM and TFE (1:1) at room temperature, also gave the corresponding 5-aryl-2-benzyltetrazoles **2Ba**, **2Bb**, **2Bd**, **2Bg−2Bi**, and **2Bl** in good to moderate yields, as shown in Table 2. However, when *p*-chlorobenzaldehyde was treated with hydrazine, phenylhydrazine, and tosylhydrazine instead of methylhydrazine using the same procedure and conditions, 5-(4′-chlorophenyl)-tetrazole, 5-(4′-chlorophenyl)-2-phenyltetrazole, and 5-(4′-chlorophenyl)-2-tosyltetrazole were not obtained at all, respectively.

The structure of 2-methyl-5-(4′-nitrophenyl)tetrazole **2Ag** was supported by X-ray crystallographic analysis (see Supporting Information).

On the other hand, when aliphatic aldehydes, such as cyclohexanecarboxaldehyde and 1-adamantanecarboxaldehyde, were treated with methylhydrazine and then DBAD and PIFA with the same procedure and conditions, the corresponding tetrazoles were not obtained at all. The reactions gave complex mixtures containing cyclohexanecarboxylic acid and 1-adamantanecarboxylic acid, respectively.

The plausible reaction mechanism for the formation of tetrazoles is shown in Scheme 2. Aromatic aldehyde **1** reacts with methylhydrazine or benzylhydrazine to form methylhy-

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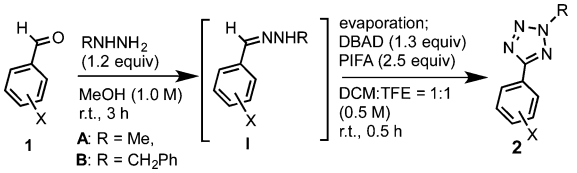
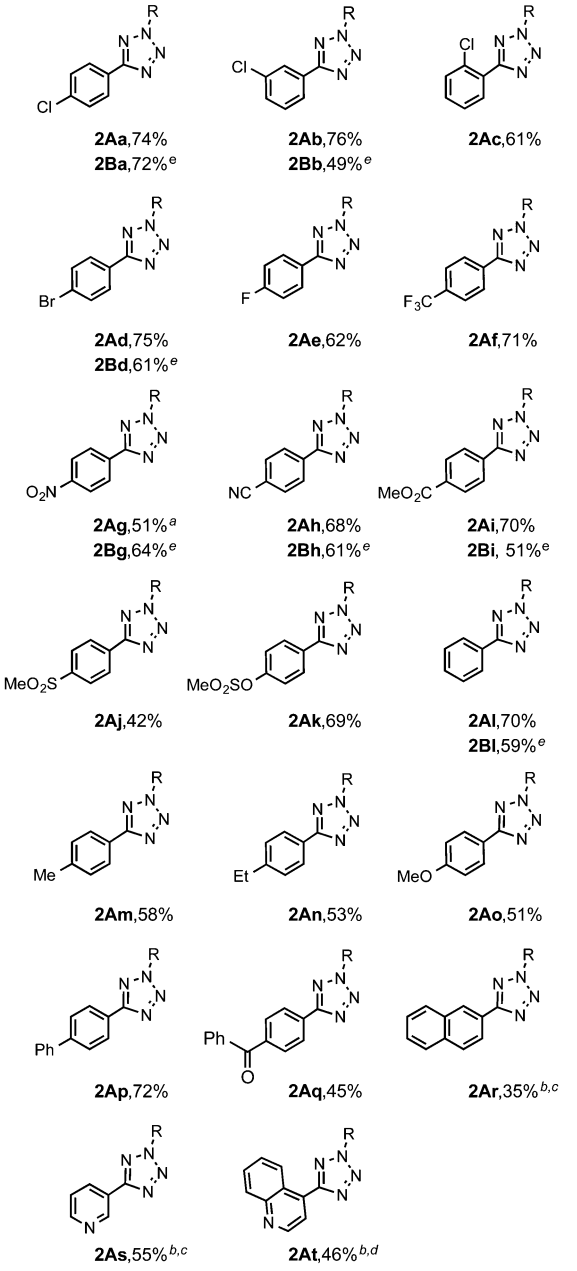
Table 2. One-Pot Preparation of 2-Alkyl-5-aryltetrazoles from Aromatic Aldehydes



product, yield

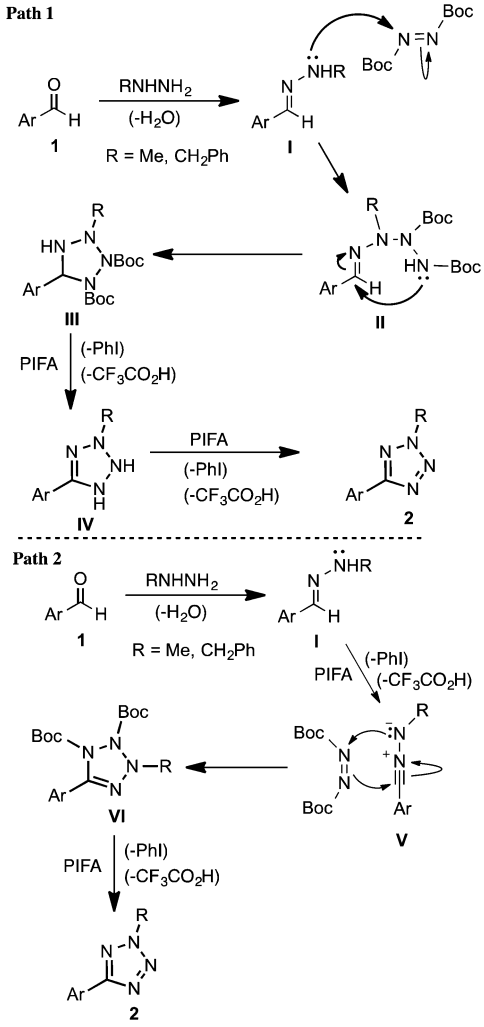


2Aa,74%
2Ba,72%[e]
2Ab,76%
2Bb,49%[e]
2Ac,61%
2Ad,75%
2Bd,61%[e]
2Ae,62%
2Af,71%
2Ag,51%[a]
2Bg,64%[e]
2Ah,68%
2Bh,61%[e]
2Ai,70%
2Bi, 51%[e]
2Aj,42%
2Ak,69%
2Al,70%
2Bl,59%[e]
2Am,58%
2An,53%
2Ao,51%
2Ap,72%
2Aq,45%
2Ar,35%[b,c]
2As,55%[b,c]
2At,46%[b,d]

[a]The second reaction step was carried out in 0.25 M solution. [b]MeCN (0.25 M) was used instead of MeOH at the first reaction step and the reaction was carried out at 70 °C. [c]PIFA (2.1 equiv) was used. [d]MeCN/TFE = 1:3 (0.5 M) was used as the solvent at the second reaction step. [e]CH_2Cl_2 (0.25 M) was used instead of MeOH at the first reaction step.

dorazone or benzylhydrazone **I**. The amino group of hydrazone **I** adds to an azo group of DBAD to form adduct **II**, which further cyclizes to compound **III** via the nucleophilic 5-*endo-trig* cyclization mode. Practically, when methylhydrazone prepared from the reaction of *p*-chlorobenzaldehyde and methylhydrazine was treated with DBAD, compound **III** was isolated [HRMS (ESI) Calcd for $C_{18}H_{28}O_4N_4Cl$ $(M + H)^+$ 399.1794, Found 399.1789]. PIFA oxidizes adduct **III** and induces the deprotection of BOC groups to give 5-aryl-2-methyltetrazole or 5-aryl-2-benzyltetrazole **2**, as shown in **Path 1**. On the other hand, another mechanism **Path 2** may be possible. Thus, methylhydrazone or benzylhydrazone **I** is oxidized to diazomethine ylide **V** by PIFA. Once diazomethine ylide **V** is formed, it reacts with DBAD via 1,3-dipolar cycloaddition to form 5-aryl-2-methyltetrazole or 5-aryl-2-benzylterazole **2** through the oxidative deprotection of BOC groups in compound **VI** by PIFA. However, when the present second reaction step was carried out in the presence of diphenylacetylene (3.0 equiv) or dimethyl acetylenedicarboxylate (3.0 equiv) under the same procedure and conditions, the corresponding cycloaddition product, 1-methyl-3-(4′-chlorophenyl)-4,5-diphenylpyrazole or 1-methyl-3-(4′-chlorophenyl)-4,5-di(methoxycarbonyl)pyrazole, was not obtained at all. Instead, tetrazole compound **2Aa** was obtained in 57% and 63% yields, respectively. Therefore, we are of the opinion that the present reaction mainly proceeds through the mechanism **Path 1** shown in Scheme 2.

Scheme 2. Plausible Reaction Mechanism for Formation of Tetrazoles



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In conclusion, treatment of various aromatic aldehydes with alkylhydrazines, such as methylhydrazine and benzylhydrazine, followed by the reaction with di-*tert*-butyl azodicarboxylate and [bis(trifluoroacetoxy)iodo]benzene at room temperature directly gave the corresponding 2-alkyl-5-aryltetrazoles, such as 5-aryl-2-methyltetrazoles and 5-aryl-2-benzyltetrazoles, respectively, in good to moderate yields via the [type: 2N + 2N] process in one pot. We believe the present method would be useful for the preparation of tetrazole derivatives from aromatic aldehydes with alkylhydrazine under transition-metal-free and mild conditions.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR spectra were measured on 400 MHz spectrometers. Chemical shifts were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on 100 MHz spectrometers. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.0 ppm). High-resolution mass spectra (HRMS) were measured on orbitrap mass spectrometers. Characteristic peaks in the infrared (IR) spectra were recorded in wave numbers, cm^{-1}. Melting points were uncorrected. Thin-layer chromatography (TLC) was performed using 0.25 mm silica gel plates (60F-254). The products were purified by short column chromatography on silica gel 60 (63−200 mesh).

General Procedure for the Preparation of 5-Aryl-2-Methyltetrazoles (Table 1, entry 18 and Table 2). To a solution of 4-chlorobenzaldehyde **1a** (70.3 mg, 0.5 mmol) in methanol (0.5 mL) was added methylhydrazine (31.7 μL, 0.6 mmol) at room temperature. The mixture was stirred at rt for 3 h. Then, the solvent was removed, and di-*tert*-butyl azodicarboxylate (149.7 mg, 0.65 mmol), [bis(trifluoroacetoxy)iodo]benzene (537.6 mg, 1.25 mmol), dichloromethane (0.5 mL), and trifluoroethanol (0.5 mL) were added, and the obtained mixture was stirred at room temperature for 0.5 h. The reaction mixture was quenched with sat. aq. Na_2SO_3 and was extracted with $CHCl_3$ (3 × 10 mL). The organic layer was washed with brine and dried over Na_2SO_4. Purification by short column chromatography on silica gel (hexane/AcOEt = 4:1) yielded 5-(4′-chlorophenyl)-2-methyltetrazole **2Aa** (72.0 mg, 74%).

5-(4′-Chlorophenyl)-2-methyltetrazole (2Aa).[7a] Colorless solid (71.7 mg, 74% yield): mp 107−108 °C (mp 108−109 °C); IR (neat) 2952, 1605, 1448, 1134, 1016 cm^{-1}; ^{1}H NMR ($CDCl_3$: 400 MHz) δ = 4.40 (s, 3H), 7.46 (d, J = 8.6 Hz, 2H), 8.07 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.5, 125.8, 128.0, 129.2, 136.3, 164.4; HRMS (APCI) Calcd for $C_8H_8N_4Cl$ (M + H)$^+$ 195.0432, Found 195.0429.

5-(3′-Chlorophenyl)-2-methyltetrazole (2Ab). Colorless solid (74.3 mg, 76% yield): mp 85−86 °C; IR (neat) 3043, 1577, 1453, 1192, 1051 cm^{-1}; ^{1}H NMR ($CDCl_3$: 400 MHz) δ = 4.41 (s, 3H), 7.40−7.46 (m, 2H), 8.00−8.05 (m, 1H), 8.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.6, 124.8, 126.9, 129.0, 130.2, 130.3, 134.9, 164.1; HRMS (APCI) Calcd for $C_8H_8N_4Cl$ (M + H)$^+$ 195.0432, Found 195.0427.

5-(2′-Chlorophenyl)-2-methyltetrazole (2Ac).[7a] Colorless oil (59.7 mg, 61% yield); IR (neat) 2987, 1602, 1441, 1193, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$: 400 MHz) δ = 4.44 (s, 3H), 7.35−7.44 (m, 2H), 7.51−7.57 (m, 1H), 7.91−7.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.6, 126.4, 126.9, 130.8, 131.1, 131.3, 132.9, 163.4.

5-(4′-Bromophenyl)-2-methyltetrazole (2Ad).[7b] Colorless solid (89.1 mg, 75% yield): mp 126−127 °C (mp 124−126 °C); IR (neat) 2972, 1603, 1449, 1132, 1013 cm^{-1}; ^{1}H NMR ($CDCl_3$: 400 MHz) δ = 4.40 (s, 3H), 7.63 (d, J = 8.5 Hz, 2H), 8.01 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.5, 124.6, 126.2, 128.2, 132.1, 164.4.

5-(4′-Fluorophenyl)-2-methyltetrazole (2Ae).[7c] Colorless solid (55.3 mg, 62% yield): mp 88−89 °C; IR (neat) 2987, 1602, 1458, 1156, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$: 400 MHz) δ = 4.40 (s, 3H), 7.18 (t, J = 8.9 Hz, 2H), 8.13 (dd, J = 8.9, 5.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.6, 116.0 (d, J_{C-F} = 22.5 Hz), 123.6 (d, J_{C-F} = 2.8 Hz), 128.8 (d, J_{C-F} = 8.5 Hz), 164.0 (d, J_{C-F} = 249.8 Hz), 164.4.

5-(4′-Trifluoromethylphenyl)-2-methyltetrazole (2Af). Colorless solid (83.2 mg, 71% yield): mp 113−114 °C; IR (neat) 2969, 1546, 1427, 1160, 1017 cm^{-1}; ^{1}H NMR ($CDCl_3$: 400 MHz) δ = 4.43 (s, 3H), 7.75 (d, J = 8.1 Hz, 2H), 8.26 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.7, 123.9 (q, J_{C-F} = 272.5 Hz), 126.0 (q, J_{C-F} = 3.8 Hz), 127.1, 130.8, 132.1 (q, J_{C-F} = 32.9 Hz), 164.1; HRMS (APCI) Calcd for $C_9H_8N_4F_3$ (M + H)$^+$ 229.0696, Found 229.0698

2-Methyl-5-(4′-nitrophenyl)tetrazole (2Ag).[7d] Colorless solid (52.4 mg, 51% yield): mp 169−170 °C (mp 171−172 °C); IR (neat) 2973, 1604, 1454, 1310, 1195, 1008 cm^{-1}; ^{1}H NMR ($CDCl_3$: 400 MHz) δ = 4.46 (s, 3H), 8.31−8.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.7, 124.2, 127.5, 133.2, 148.8, 163.3.

5-(4′-Cyanophenyl)-2-methyltetrazole (2Ah).[7b] Colorless solid (62.7 mg, 68% yield): mp 127−128 °C (mp 126−128 °C); IR (neat) 2987, 2223, 1536, 1419, 1133, 1006 cm^{-1}; ^{1}H NMR ($CDCl_3$: 400 MHz) δ = 4.44 (s, 3H), 7.79 (d, J = 7.8 Hz, 2H), 8.26 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.7, 113.7, 118.3, 127.2, 131.4, 132.7, 163.6.

Methyl 4-(2′-Methyl-2′*H*-tetrazol-5′-yl)benzoate (2Ai). Colorless solid (76.0 mg, 70% yield): mp 181−183 °C; IR (neat) 2960, 1709, 1424, 1274, 1197, 1108 cm^{-1}; ^{1}H NMR ($CDCl_3$: 400 MHz) δ = 3.96 (s, 3H), 4.43 (s, 3H), 8.16 (d, J = 8.8 Hz, 2H), 8.23 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.6, 52.3, 126.7, 130.2, 131.4, 131.6, 164.4, 166.5; HRMS (APCl) Calcd for $C_{10}H_{11}O_2N_4$ (M + H)$^+$ 219.0877, Found 219.0876.

2-Methyl-5-(4′-(methylsulfonyl)phenyl) Tetrazole (2Aj). Colorless solid (50.0 mg, 42% yield): mp 214−215 °C; IR (neat) 2923, 1416, 1290, 1149, 1131, 1085 cm^{-1}; ^{1}H NMR ($CDCl_3$: 400 MHz) δ = 3.11 (s, 3H), 4.45 (s, 3H), 8.08 (d, J = 8.6 Hz, 2H), 8.36 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.7, 44.5, 127.6, 128.1, 132.4, 141.8, 163.6; HRMS (APCl) Calcd for $C_9H_{11}O_2N_4S$ (M + H)$^+$ 239.0597, Found 239.0600.

4-(2′-Methyl-2′*H*-tetrazol-5′-yl)phenyl Methanesulfonate (2Ak). Colorless solid (87.3 mg, 69% yield): mp 141−142 °C ; IR (neat) 2924, 1608, 1455, 1360, 1151 cm^{-1}; ^{1}H NMR ($CDCl_3$: 400 MHz) δ = 3.20 (s, 3H), 4.42 (s, 3H), 7.42 (d, J = 9.0 Hz, 2H), 8.21 (d, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 37.6, 39.6, 122.6, 126.6, 128.5, 150.4, 164.1; HRMS (ESI) Calcd for $C_9H_{11}O_3N_4S$ (M + H)$^+$ 255.0546, Found 255.0545.

2-Methyl-5-phenyltetrazole (2Al).[7e] Colorless oil (56.5 mg, 70% yield); IR (neat) 2953, 1722, 1449, 1195, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$: 400 MHz) δ = 4.36 (s, 3H), 7.50−7.43 (m, 3H), 8.16−8.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.4, 126.7, 127.3, 128.8, 130.2, 165.2.

2-Methyl-5-(4′-methylphenyl)tetrazole (2Am).[7a] Colorless solid (50.3 mg, 58% yield): mp 104−105 °C (mp 108−109 °C); IR (neat) 2920, 1618, 1457, 1173, 1005 cm^{-1}; ^{1}H NMR ($CDCl_3$: 400 MHz) δ = 2.41 (s, 3H), 4.38 (s, 3H), 7.29 (d, J = 8.0 Hz, 2H), 8.02 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.5, 39.4, 124.5, 126.7, 129.6, 140.4, 165.3.

5-(4′-Ethylphenyl)-2-methyltetrazole (2An). Colorless oil (49.6 mg, 53% yield); IR (neat) 2966, 1737, 1618, 1463, 1369, 1182 cm^{-1}; $_1$H NMR ($CDCl_3$: 400 MHz) δ = 1.28 (t, J = 7.7 Hz, 3H), 2.72 (q, J = 7.7 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 15.3, 28.8, 39.4, 124.7, 126.7, 128.4, 146.7, 165.3; HRMS (APCl) Calcd for $C_{10}H_{13}N_4$ (M + H)$^+$ 189.1135, Found 189.1134.

5-(4′-Methoxyphenyl)-2-methyltetrazole (2Ao).[7b] Colorless solid (48.6 mg, 51% yield): mp 85−87 °C (mp 85−86 °C); IR (neat) 2963, 1616, 1466, 1170, 1001 cm^{-1}; ^{1}H NMR ($CDCl_3$: 400 MHz) δ = 3.87 (s, 3H), 4.37 (s, 3H), 7.00 (d, J = 8.9 Hz, 2H), 8.07 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.4, 55.3, 114.2, 119.9, 128.2, 161.2, 165.1.

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2-Methyl-5-(*p*-biphenyl)tetrazole (2Ap). Colorless solid (85.5 mg, 72% yield): mp 139−140 °C; IR (neat) 3036, 1614, 1543, 1446, 1415, 1048 cm^{-1}; ^1H NMR ($CDCl_3$: 400 MHz) δ = 4.40 (s, 3H), 7.38 (t, J = 7.41 Hz, 1H), 7.47 (dd J = 7.41, 7.18 Hz, 2H), 7.65 (d, J = 7.18 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H), 8.21 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.5, 126.2, 127.1, 127.2, 127.5, 127.7, 128.9, 140.2, 143.0, 165.0; HRMS (APCl) Calcd for $C_{14}H_{13}N_4$ $(M + H)^+$ 237.1135, Found 237.1135.

2-Methyl-5-(4′-benzoylphenyl)tetrazole (2Aq). Colorless solid (59.2 mg, 45% yield): mp 162−163 °C; IR (neat) 1650, 1442, 1418, 1308, 1047 cm^{-1}; ^1H NMR ($CDCl_3$: 400 MHz) δ = 4.44 (s, 3H), 7.52 (dd, J = 8.2, 7.5 Hz, 2H), 7.63 (tt, J = 7.5, 1.4 Hz, 1H), 7.84 (dd, J = 8.2, 1.4 Hz, 2H), 7.93 (d, J = 8.6 Hz, 2H), 8.27 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.6, 126.6, 128.4, 130.0, 130.5, 130.8, 132.6, 137.2, 138.9, 164.3, 196.0; HRMS (ESI) Calcd for $C_{15}H_{13}ON_4$ $(M + H)^+$ 265.1084, Found 265.1082.

2-Methyl-5-(naphthalen-2′-yl) Tetrazole (2Ar). Colorless solid (36.7 mg, 35% yield): mp 117−118 °C; IR (neat) 1526, 1492, 1434, 1376, 1324, 1200 cm^{-1}; ^1H NMR ($CDCl_3$: 400 MHz) δ = 4.44 (s, 3H), 7.53−7.57 (m, 2H), 7.87−7.90 (m, 1H), 7.95−7.97 (m, 2H), 8.21 (dd, J = 8.5, 1.8 Hz, 1H), 8.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.5, 123.8, 124.6, 126.6, 126.6, 127.1, 127.8, 128.6, 128.7, 133.2, 134.2, 165.4; HRMS (ESI) Calcd for $C_{12}H_{11}N_4$ $(M + H)^+$ 211.0978, Found 211.0978.

2-Methyl-5-(3′-pyridyl)tetrazole (2As).[7f] Colorless solid (44.3 mg, 55% yield): mp 125−126 °C; IR (neat) 1602, 1440, 1427, 1361, 1322, 1190 cm^{-1}; ^1H NMR ($CDCl_3$: 400 MHz) δ = 4.44 (s, 3H), 7.44 (ddd, J = 7.9, 4.9, 0.91 Hz, 1H), 8.42 (dt, J = 7.9, 2.0 Hz, 1H), 8.72 (dd, J = 4.9, 2.0 Hz, 1H), 9.37 (dd, J = 2.0, 0.91 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.6, 123.6, 123.7, 134.0, 148.1, 151.2, 163.0.

2-Methyl-5-(4′-quinolyl)tetrazole (2At). Colorless solid (48.8 mg, 46% yield): mp 106−107 °C; IR (neat) 1589, 1485, 1427, 1337, 1193, 1161 cm^{-1}; ^1H NMR ($CDCl_3$: 400 MHz) δ = 4.54 (s, 3H), 7.67−7.71 (m, 1H), 7.79−7.83 (m, 1H), 8.17 (d, J = 4.5 Hz, 1H), 8.21 (dd, J = 1.4, 8.5 Hz, 1H), 9.02 (dd, J = 0.90, 8.3 Hz, 1H), 9.07 (d, J = 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 39.8, 121.1, 124.8, 125.9, 127.8, 129.8, 130.1, 131.9, 149.0, 150.0, 163.6; HRMS (ESI) Calcd for $C_{11}H_{10}N_5$ $(M + H)^+$ 212.0931, Found 212.0927.

General Procedure for the Preparation of 5-Aryl-2-benzyltetrazoles (Table 2). To a solution of 4-chlorobenzaldehyde **1a** (70.3 mg, 0.5 mmol) in dichloromethane (2.0 mL) was added benzylhydrazine (65.0 μL, 0.55 mmol) at room temperature. The mixture was stirred at rt for 3 h. Then, the solvent was removed, and dichloromethane (0.5 mL), trifluoroethanol (0.5 mL), and di-*tert*-butyl azodicarboxylate (149.7 mg, 0.65 mmol) were added. After the obtained mixture was stirred at room temperature for 1 h, [bis(trifluoroacetoxy)iodo]benzene (537.6 mg, 1.25 mmol) was added, and the mixture was stirred at room temperature for 0.5 h. The reaction mixture was quenched with sat. aq. Na_2SO_3 and was extracted with $CHCl_3$ (3 × 10 mL). The organic layer was washed with brine and dried over Na_2SO_4. Purification by short column chromatography on silica gel (hexane/AcOEt = 10:1) yielded 5-(4′-chlorophenyl)-2-benzyltetrazole **2Ba** (97.1 mg, 72%).

2-Benzyl-5-(4′-chlorophenyl)tetrazole (2Ba). Colorless solid (97.1 mg, 72% yield): mp 109−111 °C; IR (neat) 1455, 1417, 1345, 1201, 1139, 1039 cm^{-1}; ^1H NMR ($CDCl_3$: 400 MHz) δ = 5.80 (s, 2H), 7.36−7.43 (m, 5H), 7.45 (d, J = 8.8 Hz, 2H), 8.08 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 59.6, 125.8, 128.1, 128.4, 128.8, 129.0, 129.1, 133.2, 136.3, 164.6; HRMS (APCl) Calcd for $C_{14}H_{12}N_4Cl$ $(M + H)^+$ 271.0745, Found 271.0743.

2-Benzyl-5-(3′-chlorophenyl)tetrazole (2Bb). Colorless solid (65.7 mg, 49% yield): mp 74−76 °C; IR (neat) 1454, 1435, 1198, 1077, 1048 cm^{-1}; ^1H NMR ($CDCl_3$: 400 MHz) δ = 5.81 (s, 2H), 7.40−7.44 (m, 7H), 8.03 (ddd, J = 6.8, 2.2, 1.6 Hz, 1H), 8.13−8.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 57.0, 125.0, 127.0, 128.5 (2C), 129.2 (2C), 130.3, 130.4, 133.2, 135.0, 164.4; HRMS (APCl) Calcd for $C_{14}H_{12}N_4Cl$ $(M + H)^+$ 271.0745, Found 271.0742.

2-Benzyl-5-(4′-bromophenyl)tetrazole (2Bd). Colorless solid (95.4 mg, 61% yield): mp 105−107 °C; IR (neat) 1596, 1453, 1348, 1197, 1001 cm^{-1}; ^1H NMR ($CDCl_3$: 400 MHz) δ = 5.80 (s, 2H), 7.36−7.44 (m, 5H), 7.60 (d, J = 8.61 Hz, 2H), 8.01 (d, J = 8.61 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 57.0, 124.8, 126.4, 128.5, 128.5, 128.9, 129.1, 132.2, 133.3, 164.7; HRMS (APCl) Calcd for $C_{14}H_{12}N_4Br$ $(M + H)^+$ 315.0240, Found 315.0237.

2-Benzyl-5-(4′-nitrophenyl)tetrazole (2Bg). Colorless solid (89.9 mg, 64% yield): mp 140−141 °C; IR (neat) 1516, 1337, 1041, 867 cm^{-1}; ^1H NMR ($CDCl_3$: 400 MHz) δ = 5.84 (s, 2H), 7.38−7.46 (m, 5H), 8.33 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 57.2, 124.3, 127.8, 128.6, 129.2, 129.3, 133.0, 133.3, 148.9, 163.7; HRMS (APCl) Calcd for $C_{14}H_{12}O_2N_5$ $(M + H)^+$ 282.0986, Found 282.0983.

2-Benzyl-5-(4′-cyanophenyl)tetrazole (2Bh). Colorless solid (79.7 mg, 61% yield): mp 110−112 °C; IR (neat) 2229, 1464, 1201, 1043, 856 cm^{-1}; ^1H NMR ($CDCl_3$: 400 MHz) δ = 5.83 (s, 2H), 7.37−7.45 (m, 5H), 7.77 (d, J = 8.15 Hz, 2H), 8.26 (d, J = 8.15 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 57.0, 113.6, 118.3, 127.2, 128.4, 128.9, 129.0, 131.4, 132.6, 132.8, 163.7; HRMS (APCl) Calcd for $C_{15}H_{12}N_5$ $(M + H)^+$ 262.1087, Found 262.1090.

Methyl 4-(2′-Benzyl-2*H*-tetrazol-5′-yl)benzoate (2 Bi). Colorless solid (75.1 mg, 51% yield): mp 145−146 °C; IR (neat) 1715, 1441, 1277, 1197, 1113, 1046 cm^{-1}; ^1H NMR ($CDCl_3$: 400 MHz) δ = 3.95 (s, 3H), 5.82 (s, 2H), 7.37−7.45 (m, 5H), 8.14 (d, J = 8.83 Hz, 2H), 8.22 (d, J = 8.83 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 52.4, 57.1, 126.9, 128.5, 129.2 (2C), 130.2, 131.5, 131.7, 133.2, 164.7, 166.6; HRMS (APCl) Calcd for $C_{16}H_{15}O_2N_4$ $(M + H)^+$ 295.1190, Found 295.1187.

2-Benzyl-5-phenyltetrazole (2Bl). Colorless solid (70.2 mg, 59% yield): mp 66−68 °C; IR (neat) 1713, 1449, 1334, 1274, 1200, 1161 cm^{-1}; ^1H NMR ($CDCl_3$: 400 MHz) δ = 5.81 (s, 2H), 7.37−7.46 (m, 8H), 8.14 (dd, J = 8.1, 1.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 56.9, 127.0, 127,4 128.5, 128.9, 129.0, 129.1, 130.4, 133.5, 165.5; HRMS (APCl) Calcd for $C_{14}H_{13}N_4$ $(M + H)^+$ 237.1135, Found 237.1132.

Isolation of Di-*tert*-butyl 5-(4′-Chlorophenyl)-3-methyltetrazolidine-1,2-dicarboxylate (III) with *p*-Chlorobenzaldehyde, Methylhydrazine, and Di-*tert*-butyl Azodicarboxylate (Scheme 2). To a solution of 4-chlorobenzaldehyde **1a** (70.3 mg, 0.5 mmol) in methanol (0.5 mL) was added methylhydrazine (31.7 μL, 0.6 mmol) at room temperature. The mixture was stirred at rt for 3 h. Then, the solvent was removed, and di-*tert*-butyl azodicarboxylate (149.7 mg, 0.65 mmol), dichloromethane (0.5 mL), and trifluoroethanol (0.5 mL) were added, and the obtained mixture was stirred at room temperature for 0.5 h. Then, the solvent was removed, and the residue was purified by short column chromatography on silica gel (hexane/AcOEt = 6:1) to give di-*tert*-butyl 5-(4′-chlorophenyl)-3-methyltetrazolidine-1,2-dicarboxylate (176.3 mg, 88%).

Di-*tert*-butyl 5-(4′-Chlorophenyl)-3-methyltetrazolidine-1,2-dicarboxylate (III). Colorless solid (176.3 mg, 88%yield): a mixture of two rotamers (5:3); mp 130−133 °C; IR (neat) 3288, 1738, 1683, 1394, 1153, 810 cm^{-1}; ^1H NMR ($CDCl_3$: 400 MHz) δ = 1.16 (brs, 9H, minor), 1.30 (brs, 9H, major), 1.45 (brs, 9H, minor), 1.48 (brs, 9H, major), 3.91 (brs, 3H, major), 3.92 (brs, 3H, minor), 5.97 (brs, 1H, minor), 6.20 (brs, 1H, major), 7.33−7.45 (m, 4H); HRMS (ESI) Calcd for $C_{18}H_{28}O_4N_4Cl$ $(M + H)^+$ 399.1794, Found 399.1789.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00606.

NMR spectra for all 5-aryl-2-alkyltetrazoles **2** (PDF)

X-ray analytical data for **2Ag** (CIF)

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Notes

The authors declare no competing financial interest.

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