An Easy Access to Aryl Azides from Aryl Amines under Neutral Conditions

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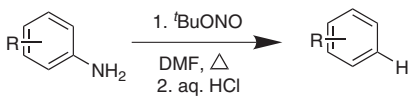
Abstract: A variety of substituted aryl amines were transformed into aryl azides using *t*-BuONO and moist NaN_3 in *t*-BuOH in good to excellent yields. Smooth transformation was observed with anilines, having electron withdrawing and donating groups. Both acid- and base-sensitive groups survived the reaction conditions.

Key words: amines, azides, anilines, diazo compounds, sodium azide

Azides are versatile intermediates in organic synthesis.[1] A major application of this class of compounds is 1,3-dipolar cycloaddition with an unsaturated reactant to give a variety of five-membered heterocycles.[2] While numerous methods are available for the preparation of aliphatic azides, there is a limited choice for aryl azides. The most straightforward route for the preparation of aryl azides involves diazotization of amines with nitrous acid followed by addition of sodium azide at low temperature.[3] Alternatively, aryl amines have been transformed into aryl azides by treating the former with *para*-toluenesulfonyl azide in the presence of a Grignard reagent or strong base.[4] Aryl azides have also been prepared from arylmagnesium halides or aryl lithium reagents, generated from aryl halides, and *para*-toluenesulfonyl azide.[5] The above conversion has also been accomplished under mild condition using a combination of triflyl azide, $CuSO_4$, and triethylamine.[6] Very recently, the coupling of aromatic and vinyl halides with sodium azide under catalysis with CuI–L-proline was reported to produce aryl/vinyl azides in good to excellent yields.[7] However, all these transformations require either acidic or basic conditions, which are not compatible with many functional groups present in a substrate. This has prompted us to report our results for the same transformation.

During the course of our ongoing investigations, we needed a process for the preparation of aryl azides from aryl amines, having acid- and base-sensitive groups. This led us to investigate neutral conditions for the preparation of aryl azides. Here we describe our successful efforts towards this endeavor.



Scheme 1

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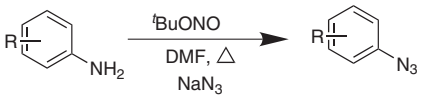
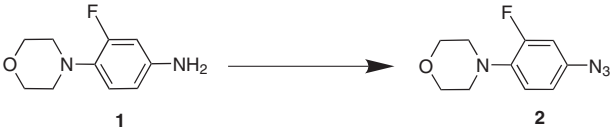


Scheme 2

Deamination of aryl amines with alkyl nitrite is being carried out in our laboratories as a routine work (Scheme 1). We reasoned that in the presence of a strong nucleophile such as azide, a deamination reaction could be diverted to azide formation (Scheme 2), since aryl amines do undergo diazotization with alkyl nitrite.[8]



Scheme 3

We chose compound **1** as a model substrate to optimize the reaction conditions for the transformation to azide **2** (Scheme 3). Initially, the reaction was carried out in DMF in the presence of excess *t*-BuONO[9] (10 equiv) and NaN_3 (5 equiv) at 80 °C leading to decomposition of the amine. Although azide formation was observed at room temperature, the reaction was not complete even after 24 hours. Subsequently, reactions were carried out in other solvents such as toluene, chloroform and *t*-BuOH. Reactions in toluene and chloroform were found to be very slow because of the poor solubility of NaN_3 in these solvents. Addition of a phase transfer catalyst, benzyltriethylammonium bromide, produced a mixture of products. On the other hand, the reaction proceeded well in *t*-BuOH and was completed within two hours with an isolated yield of 59%. Further, we observed that addition of small quantities of water[10] increased the rate of the reaction considerably and the reaction was complete within 10–15 minutes.

It is important to note that when commercial isoamyl nitrite[11] was used, the reaction was slow and 50% conversion was observed after 72 hours.

To find out the optimum quantity of reagents, we carried out several reactions with a varied quantity of *t*-BuONO and NaN_3. However, six equivalents of *t*-BuONO and three equivalents of NaN_3 were found to be the optimum quantity required for the transformation (0.25 h, 60%).

A variety of substituted amines were converted to the corresponding azides and the results are presented in Table 1.

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Table 1 Conversion of Aryl Amines into the Corresponding Aryl Azides

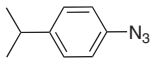
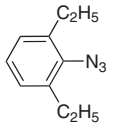
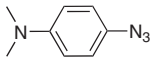
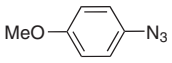
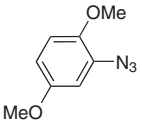
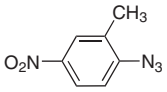
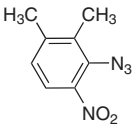
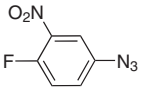
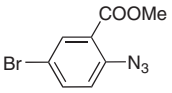
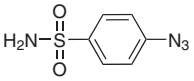
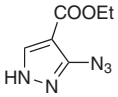
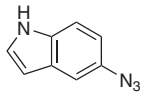
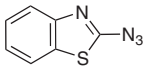
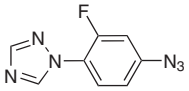
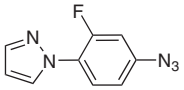
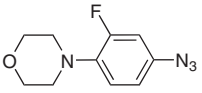
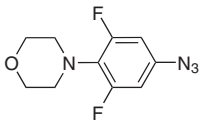
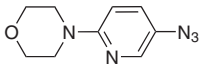
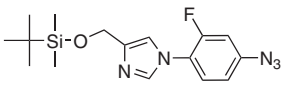
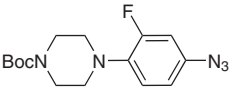
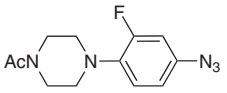
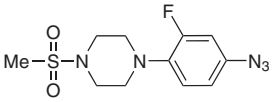
Entry	Azide	Time (h)	Yield (%)
1		1	70
2		3	74
3		0.25	60
4		1	80
5		3	71
6		2	73
7		1	85
8		1	92
9		1	91
10		4	61[a]
11		5	64[a]
12		3	50
13		6	54[a]
14		1	60[a]
15		1	61[a]
16		0.25	60[a]

Table 1 Conversion of Aryl Amines into the Corresponding Aryl Azides (continued)

Entry	Azide	Time (h)	Yield (%)
17		4	64[a]
18		3	50[b]
19		0.25	60[a]
20		4	70
21		4	68
22		7	70

[a] Reactions were carried out with the usual 6 equiv of *t*-BuONO; 12 equiv of *t*-BuONO was used in all other examples.
[b] Reaction was carried out in DMF as solvent.

In most of the cases, the azides were isolated in very good yields. 2-Amino-1,3-diethylbenzene, a hindered amine, was converted to the corresponding azido compound (entry 2) in 74% yield. Similarly anilines having methoxy substituents (entries 4 and 5) or anilines having different electron withdrawing groups as substituents (entries 6–10) were converted into the corresponding azides in yields ranging from 61–92%. It is worthy of mention that pyrazole having a carboxylic ester as a substituent and also an unprotected NH group (entry 11) produced azide from the corresponding amine in 64% yield. 5-Aminoindole (entry 12) and 2-aminobenzothiazole[12] (entry 13) were transformed into the corresponding azides in 50% and 54% yield, respectively. Anilines having different heterocycles attached to it underwent smooth transformation to azides (entries 14–17) in good yields. Pyridyl azide, which is otherwise impossible to prepare by the nitrous acid method, was obtained from the corresponding amine in moderate yield (50%, entry 18). In this case, DMF was found to be a suitable solvent, although the reaction proceeded well in *t*-BuOH, albeit in low yield. A compound having a *tert*-butyldimethylsilyl protecting group (entry 19) underwent amine to azide conversion within 10–15 min in 60% yield, whereas the same conversion under nitrous acid conditions led to deprotection of the silyl ether. The acid labile *tert*-butyloxycarbonyl group in entry 20 survived the reaction conditions and the product was obtained in 70% yield. Some of these reactions were carried out on a large scale (10–20 mmol).

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In conclusion, we have demonstrated a facile conversion of various aryl amines having a variety of substituents, ranging from electron donating groups to electron withdrawing groups, to the corresponding azides under mild and neutral conditions. Even sterically hindered amines were converted to the corresponding azides in good yields. Protecting groups that are susceptible to cleavage under nitrous acid conditions survived the present reaction conditions. Most of the reactions were carried out at r.t. and common laboratory reagents were used. A large-scale preparation of azides is feasible using this methodology.

Caution! Although no untoward incident has taken place during our experiments, azides should be handled carefully as some of them may be explosive.

All the reactions were carried out at r.t. unless otherwise mentioned. Column chromatography was performed using 60–120 mesh silica gel and solvents used for chromatography were a mixture of petroleum ether (bp 60–80 °C) and EtOAc. The majority of the compounds were eluted with petroleum ether–EtOAc (4:1). Compounds were washed with a small quantity of petroleum ether after isolation from column chromatography in order to check the melting points. Melting points were recorded on capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded at 200 and 50 MHz, respectively. Chemical shifts are reported in d units with respect to TMS as internal standard. IR peaks have been marked as w, m or s to represent weak, medium and strong intensities. Mass spectra were recorded on a HP-5989A spectrometer (CI mode; isobutane was used as chemical ionization gas). Combustion analysis was obtained using a Perkin–Elmer 2400 analyzer. All analytical works were carried out at the Analytical Research Department of Discovery Research.

Aryl amines (entries 1–13) were obtained from commercial sources and used without further purification. Aryl amines (entries 14–22) were prepared using well-established methods[13] in the pure form.

t-BuONO

To an ice-cold solution of concd H_2SO_4 (155 g, 84 mL, 1.58 mol) and H_2O (84 mL) was added *t*-BuOH (117.9 g, 150 mL) dropwise followed by the addition of a solution of sodium nitrite (120 g in 475 mL of H_2O). The reaction was kept at 0 °C during the addition, which was complete after 1 h. The reaction mixture was warmed to r.t. and stirred overnight. The aq layer was separated and the organic portion was washed with aq $NaHCO_3$ (10 g) and NaCl (54 g) in H_2O (200 mL). The organic portion was then dried (Na_2SO_4) and distilled at normal pressure. A light yellow fraction (ca. 100–120 mL) collected at 80–90 °C was used for all the reactions. It was stored at 4 °C and protected from light.

GC Conditions for the Analysis of *t*-BuONO

Column, DB 1701 (30m × 0.25mm × 1μm), carrier gas N_2, inj. temp. 250 °C, det. temp. 270 °C, oven prog. 40 °C (5 min), 10 °C/min→250 °C (5 min). t_R = 3.52 min (*t*-BuOH) and 4.0 min (*t*-BuONO).

1-Azido-4-isopropylbenzene (Table 1, Entry 1); General Procedure

t-BuOH (1 mL) was added to sodium azide (144 mg, 2.22 mmol) moistened with H_2O (222 μL) in a round bottom flask. 4-Isopropylphenylamine (100 mg, 0.74 mmol) was added to the stirring solution followed by the addition of *t*-BuONO (1.0 mL, 8.88 mmol). Stirring was continued at r.t. (at elevated temperature wherever mentioned) for 1 h. H_2O (3 mL) was added to the reaction mixture after the completion of the reaction (monitored by TLC) and the mixture was extracted with EtOAc (5 mL × 3). Combined EtOAc layers were dried (Na_2SO_4). Removal of volatiles and purification of the resulting residue by column chromatography gave the title compound.

Yield: 84 mg (70%); brown liquid.

IR (neat): 2122 (s), 1507 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.21 (d, *J* = 8.4 Hz, 2 H), 6.95 (d, *J* = 8.4 Hz, 2 H), 2.89–2.86 (m, 1 H), 1.23 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR ($CDCl_3$): δ = 145.7, 137.3, 127.7, 118.9, 33.59, 23.9.

MS: *m*/*z* = 162 (M^+ + 1), 134, 91.

Anal. Calcd for $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.07. Found: C. 66.89; H, 6.76; N, 26.19.

2-Azido-1,3-diethylbenzene (Entry 2)

Using the general procedure at 50 °C, with 2,6-diethylphenylamine (100 mg, 0.67 mmol), sodium azide (131 mg, 2.01 mmol), H_2O (200 μL), *t*-BuONO (1.6 mL, 8.04 mmol) and *t*-BuOH (1 mL) as solvent, the title compound was obtained.

Yield: 87 mg (74%); light brown liquid.

IR (neat): 2970 (w), 2099 (s), 1449 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.09–7.02 (m, 3 H), 2.75 (q, *J* = 7.6 Hz, 4 H), 1.26 (t, *J* = 7.6 Hz, 6 H).

^{13}C NMR ($CDCl_3$): δ = 138.4, 127.1, 126.2, 124.2, 24.9, 14.7.

MS: *m*/*z* = 176 (M^+ + 1), 148, 102.

Anal. Calcd for $C_{10}H_{13}N_3$: C, 68.54; H, 7.46; N, 23.98. Found: C. 68.69; H, 7.37, N, 23.86.

(4-Azidophenyl)dimethylamine (Entry 3)

Using the general procedure, with *N,N*-dimethylbenzene-1,4-diamine (100 mg, 0.73 mmol), sodium azide (143 mg, 2.2 mmol), H_2O (219 μL), *t*-BuONO (1.7 mL, 8.76 mmol) and *t*-BuOH (1 mL) as solvent, the title compound was obtained.

Yield: 71 mg (60%); brown solid; mp 42–43 °C (lit.[14] 42.5–43.5 °C).

IR (KBr): 2120 (s) cm^{-1}.

1-Azido-4-methoxybenzene[15] (Entry 4)

Using the general procedure, with 4-methoxyaniline (500 mg, 4.06 mmol), sodium azide (793 mg, 12.2 mmol), H_2O (610 μL), *t*-BuONO (9.6 mL, 48.7 mmol) and *t*-BuOH (4 mL) as solvent, the title compound was obtained.

Yield: 520 mg (86%); brown liquid.

IR (neat): 2119 (s) cm^{-1}.

2-Azido-1,4-dimethoxybenzene[16] (Entry 5)

Using the general procedure, with 2,5-dimethoxyaniline (500 mg, 3.27 mmol), sodium azide (637 mg, 9.8 mmol), H_2O (980 μL), *t*-BuONO (3.9 mL, 19.62 mmol) and *t*-BuOH (3 mL) as solvent, the title compound was obtained.

Yield: 415 mg (71%); liquid.

IR (neat): 2120 (s), 1506 (m), 1220 (s) cm^{-1}.

1-Azido-2-methyl-4-nitrobenzene (Entry 6)

Using the general procedure, with 2-methyl-4-nitrophenylamine (100 mg, 0.66 mmol), sodium azide (128 mg, 1.97 mmol), H_2O (198 μL), *t*-BuONO (1.56 mL, 7.92 mmol) and *t*-BuOH (1 mL) as solvent, the title compound was obtained.

Yield: 85 mg (73%); brown solid; mp 64–65 °C (lit.[17] 64–65 °C).

IR (KBr): 2122 (s) cm^{-1}.

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2-Azido-3,4-dimethyl-1-nitrobenzene (Entry 7)
Using the general procedure, with 2,3-dimethyl-6-nitrophenylamine (100 mg, 0.60 mmol), sodium azide (117 mg, 1.8 mmol), H_2O (180 μL), *t*-BuONO (1.4 mL,7.2 mmol) and *t*-BuOH (1 mL) as solvent, the title compound was obtained.

Yield: 98 mg (85%); light yellow solid; mp 67–69 °C (lit.[18] 67–68 °C; reported yield, 91%).

IR (KBr): 2151 (m), 1517 (s) cm^{-1}.

4-Azido-1-fluoro-2-nitrobenzene (Entry 8)
Using the general procedure, with 4-fluoro-3-nitrophenylamine (100 mg, 0.64 mmol), sodium azide (125 mg, 1.92 mmol), H_2O (192 μL), *t*-BuONO (1.52 mL, 7.68 mmol) and *t*-BuOH (1 mL) as solvent, the title compound was obtained.

Yield: 107 mg (92%); brown solid; mp 54 °C (lit.[19] 53–55 °C; reported yield, 43%).

IR (KBr): 2129 (m), 1538 (s) cm^{-1}.

Methyl 2-Azido-5-bromobenzoate (Entry 9)
Using the general procedure, with methyl 2-amino-5-bromobenzoate (100 mg, 0.43 mmol), sodium azide (84 mg, 1.29 mmol), H_2O (129 μL), *t*-BuONO (1.0 mL, 5.16 mmol) and *t*-BuOH (0.5 mL) as solvent, the title compound was obtained.

Yield: 100 mg (90%); white solid; mp 68–70 °C.

IR (KBr): 2951 (w), 2125 (m), 2084 (m), 1730 (s), 1483 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.98 (d, *J* = 2.2 Hz, 1 H), 7.61 (dd, *J* = 2.3, 8.4 Hz, 1 H), 7.10 (d, *J* = 8.4 Hz, 1 H), 3.90 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 166.6, 147.6, 135.9, 134.6, 121.5, 117.2, 52.6.

MS: *m*/*z* = 257 (M^+ + 1), 229, 198, 150, 107.

Anal. Calcd for $C_8H_6BrN_3O_2$: C, 37.53; H, 2.36; N, 16.41. Found: C. 37.61; H, 2.39; N, 16.48.

4-Azidobenzensulfonamide (Entry 10)
Using the general procedure, with 4-aminobenzensulfonamide (500 mg, 2.91 mmol), sodium azide (567.5 mg, 8.73 mmol), H_2O (435 μL), *t*-BuONO (3.46 mL, 17.5 mmol) and *t*-BuOH (3 mL) as solvent, the title compound was obtained.

Yield: 351 mg (61%); white solid; mp 157–160 °C.

IR (KBr): 3349 (m), 2924 (w), 2132 (m), 2099 (m), 1589 (w) cm^{-1}.

^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ = 7.91 (d, *J* = 8.3 Hz, 2 H), 7.13 (d, *J* = 8.8 Hz, 2 H), 3.95 (br s, 2 H).

^{13}C NMR (DMSO-d_6): δ = 142.8, 140.4, 127.5, 119.4.

MS: *m*/*z* = 199 (M^+ + 1), 182, 173, 158.

Anal. Calcd for $C_6H_6N_4O_2S$: C, 36.36; H, 3.05; N, 28.27. Found: C. 36.88; H, 3.14; N, 28.40.

Ethyl 3-Azido-1*H*-pyrazole-4-carboxylate (Entry 11)
Using the general procedure, with ethyl 3-amino-1*H*-pyrazole-4-carboxylate (500 mg, 3.23 mmol), sodium azide (630 mg, 9.7 mmol), H_2O (485 μL), *t*-BuONO (3.84 mL, 19.4 mmol) and *t*-BuOH (3.5 mL) as solvent, the title compound was obtained.

Yield: 374 mg (64%); white solid; mp 110–112 °C.

IR (KBr): 2128 (m), 1668 (s), 1550 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.10 (s, 1 H), 4.32 (q, *J* = 6.8 Hz, 2 H), 1.36 (t, *J* = 6.8, 3 H).

^{13}C NMR (DMSO-d_6): δ = 161.3, 147.0, 135.0, 103.4, 59.6, 14.2.

MS: *m*/*z* = 182 (M^+ + 1), 154, 126.

Anal. Calcd for $C_6H_7N_5O_2$: C, 39.77; H, 3.89; N, 38.66. Found: C, 39.56; H, 3.86; N, 38.79.

5-Azido-1*H*-indole (Entry 12)
Using the general procedure at 45 °C, with 5-amino-1*H*-indole (250 mg, 1.89 mmol), sodium azide (364 mg, 5.6 mmol), H_2O (567 μL), *t*-BuONO (4.5 mL, 22.7 mmol) and *t*-BuOH (2 mL) as solvent, the title compound was obtained.

Yield: (149 mg, 50%); light brown solid; mp 75–78 °C.

IR (KBr): 2112 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.17 (br s, 1 H), 7.41–7.18 (m, 3 H), 6.90 (d, *J* = 8.1 Hz, 1 H), 6.52 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 133.5, 132.2, 128.7, 125.6, 114.1, 112.1, 110.2, 102.5.

MS: *m*/*z* = 159 (M^+ + 1), 143, 131.

Anal. Calcd for $C_8H_6N_4$: C, 60.75; H, 3.82; N, 35.42. Found: C, 60.55; H, 3.81; N, 35.54.

2-Azidobenzothiazole (Entry 13)
Using the general procedure, with 2-aminobenzothiazole (500 mg, 3.33 mmol), sodium azide (650 mg, 10.0 mmol), H_2O (500 μL), *t*-BuONO (3.96 mL, 20 mmol) and *t*-BuOH (3.5 mL) as solvent, the title compound was obtained.

Yield: 316 mg (54%); brown, low-melting solid.

IR (neat): 2132 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.54 (d, *J* = 7.8 Hz, 2 H), 7.10 (d, *J* = 7.8 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 142, 132.2, 129.9, 129.7, 120.6, 119.4, 110.2.

MS: *m*/*z* = 177 (M^+ + 1), 151.

Anal. Calcd for $C_7H_4N_4S$: C, 47.72; H, 2.29; N, 31.80. Found: C, 47.49; H, 2.16; N, 31.71.

1-(4-Azido-2-fluorophenyl)-1*H*-1,2,4-triazole (Entry 14)
Using the general procedure, with 1-(4-amino-2-fluorophenyl)-1*H*-1,2,4-triazole (500 mg, 2.80 mmol), sodium azide (547 mg, 8.42 mmol), H_2O (425 μL), *t*-BuONO (3.3 mL, 16.8 mmol) and *t*-BuOH (3 mL) as solvent, the title compound was obtained.

Yield: 345 mg (60%); solid; mp 53–55 °C.

IR (KBr): 2119 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.62 (s, 1 H), 8.12 (s, 1 H), 7.88 (t, *J* = 8.5 Hz, 1 H), 7.01–6.85 (m, 2 H).

^{13}C NMR (DMSO-d_6): δ = 154.3 (d, *J* = 250 Hz), 152.2, 145.0 (d, *J* = 7 Hz), 141.3 (d, *J* = 10 Hz), 126.5, 121.0 (d, *J* = 9 Hz), 116.0 (d, *J* = 3 Hz), 108.2 (d, *J* = 24 Hz).

MS: *m*/*z* = 205 (M^+ + 1), 179.

Anal. Calcd for $C_8H_5FN_6$: C, 47.05; H, 2.47; N, 41.16. Found: C, 46.98; H, 2.31; N, 41.27.

1-(4-Azido-2-fluorophenyl)-1*H*-pyrazole (Entry 15)
Using the general procedure, with 1-(4-amino-2-fluorophenyl)-1*H*-pyrazole (500 mg, 2.82 mmol), sodium azide (550 mg, 8.46 mmol), H_2O (423 μL), *t*-BuONO (3.3 mL, 16.9 mmol) and *t*-BuOH (3 mL) as solvent, the title compound was obtained.

Yield: 350 mg (61%); white solid; mp 90–91 °C.

IR (KBr): 2112 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.96–7.85 (m, 2 H), 7.73 (s, 1 H), 6.92 (t, *J* = 8.3 Hz, 2 H), 6.48 (s, 1 H).

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^{13}C NMR (DMSO-d_6): δ = 153.7 (d, J = 248 Hz), 140.9, 139.4 (d, J = 10 Hz), 131.2 (d, J = 7.5 Hz), 125.8 (d, J = 1.5 Hz), 124.8 (d, J = 10 Hz), 115.9 (d, J = 3.5 Hz), 108.1 (d, J = 2.5 Hz), 107.6.

MS: m/z = 204 (M^+ + 1), 178.

Anal. Calcd for $C_9H_6FN_5$: C, 53.19; H, 2.98; N, 34.47. Found: C, 53.10; H, 3.02, 34.66.

4-(4-Azido-2-fluorophenyl)morpholine (Entry 16)
Using the general procedure, with 4-(4-amino-2-fluorophenyl)morpholine (500 mg, 2.55 mmol), sodium azide (497 mg, 7.65 mmol), H_2O (382 μL), *t*-BuONO (3.03 mL, 15.3 mmol) and *t*-BuOH (2.5 mL) as solvent, the title compound was obtained,

Yield: 340 mg (60%); brown semi-solid.

IR (neat): 2113 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.95–6.65 (m, 2 H), 6.48–6.32 (m, 1 H), 3.95–3.75 (br s, 4 H), 3.10–3.01 (m, 2 H), 3.00–2.88 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 158.5 (d, J = 250 Hz), 137.2 (d, J = 8.7), 134.5 (d, J = 10 Hz), 119.6 (d, J = 4.2 Hz), 114.8 (d, J = 3.0 Hz), 107.7 (d, J = 24.3 Hz), 66.9, 51.0 (d, J = 3.5 Hz).

MS: m/z = 223 (M^+ + 1), 208, 194, 163, 136, 103.

Anal. Calcd for $C_{10}H_{11}FN_4O$: C, 54.05; H, 4.99; N, 25.21. Found: C, 53.87; H, 4.76; N, 25.11.

4-(4-Azido-2,6-difluorophenyl)morpholine (Entry 17)
Using the general procedure, with 4-(4-amino-2,6-difluorophenyl)morpholine (500 mg, 2.34 mmol), sodium azide (456 mg, 7.02 mmol), H_2O (350 μL), *t*-BuONO (2.78 mL, 14 mmol) and *t*-BuOH (2.5 mL) as solvent, the title compound was obtained.

Yield: 359 mg (64%); brown solid; mp 69–70 °C.

IR (KBr): 2121 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.55 (d, J = 9.4 Hz, 2 H), 3.80 (t, J = 4.3 Hz, 4 H), 3.15 (t, J = 4.3 Hz, 4H).

^{13}C NMR (DMSO-d_6): δ = 158.0 (dd, J = 9, 247 Hz), 136.1 (t, J = 13 Hz), 124.1 (t, J = 13.5 Hz), 104.0 (m), 66.7, 51.1 (t, J = 3 Hz).

MS: m/z = 241 (M^+ + 1), 215, 200, 169, 113, 97.

Anal. Calcd for $C_{10}H_{10}F_2N_4O$: C, 49.98; H, 4.20; N, 23.32. Found: C, 50.10; H, 4.28; N, 23.39.

4-(5-Azidopyridin-2-yl)morpholine (Entry 18)
Using the general procedure, with 4-(5-aminopyridin-2-yl)morpholine (500 mg, 2.79 mmol), sodium azide (544 mg, 8.37 mmol), H_2O (418 μL), *t*-BuONO (6.6 mL, 33.5 mmol) and DMF (3 mL) as solvent, the title compound was obtained.

Yield: 287 mg (50%); brown solid; mp 60–62 °C.

IR (KBr): 2097 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.96 (d, J = 2.4 Hz, 1 H), 7.22 (dd, J = 2.9, 9.2 Hz, 1 H), 6.64 (d, J = 8.8 Hz, 1 H), 3.82 (t, J = 4.9 Hz, 4 H), 3.46 (t, J = 4.9 Hz, 4 H).

^{13}C NMR ($CDCl_3$): δ = 157.2, 138.8, 128.3, 127.1, 107.1, 66.6, 45.8.

MS: m/z = 206 (M^+ + 1), 178, 150.

Anal. Calcd for $C_9H_{11}N_5O$: C, 52.66; H, 5.41; N, 34.13. Found: C, 52.83; H, 5.41; N, 34.01.

1-(4-Azido-2-fluorophenyl)-4-(*tert*-butyldimethylsilanyloxymethyl)-1*H*-imidazole (Entry 19)
Using the general procedure at 70 °C, with 1-(4-amino-2-fluorophenyl)-4-(*tert*-butyldimethylsilanyloxymethyl)-1*H*-imidazole (100 mg, 0.31 mmol), sodium azide (60 mg, 0.93 mmol), H_2O (93 μL), *t*-BuONO (0.74 mL, 3.72 mmol) and *t*-BuOH (0.3 mL) as solvent, the title compound was obtained.

Yield: 65 mg (60%); liquid.

IR (KBr): 2115 (s), 1521 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.70 (s, 1 H), 7.36 (t, J = 8.3 Hz, 1 H), 7.11 (s, 1H), 6.91–6.96 (m, H), 4.76 (s, 2 H), 0.94 (s, 9 H), 0.13 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 155.4 (d, J = 251.1 Hz), 143.7, 140.8 (d, J = 10 Hz), 136.5 (d, J = 4.1 Hz), 126 (d, J = 1.9 Hz), 116.4 (d, J = 2.2 Hz), 115.4 (d, J = 3.4 Hz), 108.4, 107.9, 60.1, 25.9, 18.4, –5.3.

MS: m/z = 348 (M^+ + 1), 307, 238.

Anal. Calcd for $C_{16}H_{22}FN_5OSi$: C, 55.31; H, 6.38; N, 20.16. Found: C, 55.49; H, 6.36; N, 20.02.

***tert*-Butyl 4-(4-Azido-2-fluorophenyl)piperazine-1-carboxylate (Entry 20)**
Using the general procedure with an exception (reaction carried out at 70 °C), with *tert*-butyl 4-(4-amino-2-fluorophenyl)piperazine-1-carboxylate (3.0 g, 10.2 mmol), sodium azide (2.0 g, 30.6 mmol), H_2O (1.5 mL), *t*-BuONO (24.2 mL, 122.4 mmol) and *t*-BuOH (10 mL) as solvent, the title compound was obtained.

Yield: 2.3 g (70%); yellow solid; mp 58–60 °C.

IR (KBr): 2115 (m), 1686 (w) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.91 (t, J = 8.8 Hz, 1 H), 6.78–6.72 (m, 2 H), 3.59 (t, J = 4.8 Hz, 4 H), 2.98 (t, J = 4.8 Hz, 4 H), 1.48 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 156.6 (d, J = 200 Hz), 153.7 (d, J = 6.5 Hz), 135.9 (dd, J = 10, 120 Hz), 120.1 (d, J = 5.5 Hz), 114.8 (d, J = 3 Hz), 107.7 (d, J = 25 Hz), 79.8, 50.6, 43.7, 28.4.

MS: m/z = 322 (M^+ + 1), 293, 266, 237.

Anal. Calcd for $C_{15}H_{20}FN_5O_2$: C, 56.05; H, 6.28; N, 21.79. Found: C, 55.89; H, 6.16; N, 21.87.

1-Acetyl-4-(4-azido-2-fluorophenyl)piperazine (Entry 21)
Using the general procedure, with 1-[4-(4-amino-2-flurorophenyl)piperazin-1-yl]ethanone (100 mg, 0.42 mmol), sodium azide (82 mg, 1.26 mmol), H_2O (63 μL), *t*-BuONO (1 mL, 5.0 mmol) and *t*-BuOH (0.5 mL) as solvent, the title compound was obtained.

Yield: 75 mg (68%); orange solid; mp 108–110 °C.

IR (KBr): 2116 (m), 1647 (m), 1508 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.95–6.67 (m, 3 H), 3.83–3.70 (m, 2 H), 3.68–3.55 (m, 2 H), 3.08–2.94 (m, 4 H), 2.14 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 168.9, 156.0 (d, J = 250 Hz), 135.6 (dd, J = 10, 85 Hz), 120.2 (d, J = 4 Hz), 114.8 (d, J = 3.5 Hz), 107.7 (d, J = 25 Hz), 51.0 (d, J = 3 Hz), 50.4 (d, J = 3 Hz), 46.3, 41.4, 21.2.

MS: m/z = 264 (M^+ + 1), 235, 223.

Anal. Calcd for $C_{12}H_{14}FN_5O$: C, 54.75; H, 5.36; N, 26.60. Found: C, 54.42; H, 5.21; N, 26.71.

1-(4-Azido-2-fluorophenyl)-4-methylsulfonylpiperazine (Entry 22)
Using the general procedure, with 3-fluoro-4-(4-methylsulfonylpiperazin-1-yl)phenylamine (100 mg, 0.37 mmol), sodium azide (72 mg, 1.1 mmol), H_2O (111 μL), *t*-BuONO (0.9 mL, 4.44 mmol) and *t*-BuOH (0.4 mL) as solvent, the title compound was obtained.

Yield: 70 mg (64%); yellow solid; mp 118–120 °C.

IR (KBr): 2118 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.10–6.82 (m, 2 H), 6.78–6.68 (m, 1 H), 3.46–3.28 (m, 4 H), 3.22–3.05 (m, 4 H), 2.83 (s, 3 H).

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^{13}C NMR ($CDCl_3$): δ = 156 (d, *J* = 248 Hz), 136.0 (dd, *J* = 10, 50 Hz), 123.5 (d, *J* = 3 Hz), 120.3 (d, *J* = 3.5 Hz), 114.8 (d, *J* = 3 Hz), 108 (d, *J* = 25 Hz), 50.3 (d, *J* = 3 Hz), 50.2 (d, *J* = 2.5 Hz), 46.1 (d, *J* = 2.5 Hz).

MS: *m*/*z* = 300 (M^+ + 1), 274, 259.

Anal. Calcd for $C_{11}H_{14}FN_5O_2S$: C, 44.14; H, 4.71; N, 23.40. Found: C, 43.95; H, 4.53; N, 23.47.

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