Regioselective Synthesis of Polysubstituted *N*2-Alkyl/Aryl-1,2,3-Triazoles via 4-Bromo-5-iodo-1,2,3-triazole

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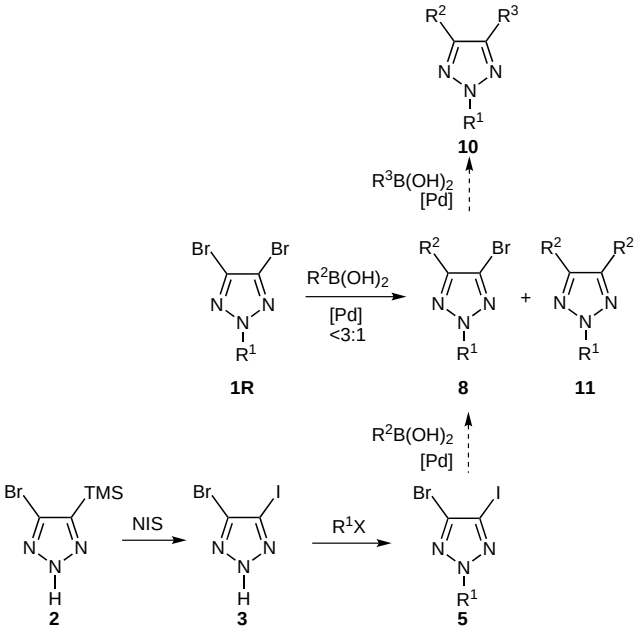
Abstract: The regioselective N2-substitution of 4-bromo-5-iodo-1,2,3-triazole with alkyl/aryl halides in the presence of K_2CO_3 in DMF produced the desired 2-substituted 4-bromo-5-iodo-1,2,3-triazoles as a major products in good to excellent regioselectivity. Subsequent chemoselective Suzuki–Miyaura cross-coupling reaction of N2-substituted 4-bromo-5-iodo-1,2,3-triazoles provided polysubstituted 1,2,3-triazoles efficiently.

Key words: 4-bromo-5-iodo-1,2,3-triazole, regioselectivity, N2-substitution, chemoselectivity, cross-coupling

1,2,3-Triazoles have been studied and utilized for over a century[1] in the chemical industry, medicinal chemistry, and biological sciences.[2] Although a number of methods have been developed for the synthesis of N1/N3-substituted triazoles,[3] an effective general synthetic method for N2-substituted triazoles is still lacking.[4] Recently, we reported a N2-regioselective direct alkylation/arylation with 4,5-dibromo-1,2,3-triazole **1**.[5,6] Attempts to utilize these 4,5-dibromo-1,2,3-triazoles **1R** for the synthesis of unsymmetrical triazoles by conducting sequential Suzuki–Miyaura cross-coupling reactions[8] failed to significantly differentiate between the two bromo substituents (Scheme 1). A significant amount of double cross-coupling product **11** was produced when monocoupling product **8** reached a conversion of about 70%. Typically, >25% of **11** was observed with a complete consumption of the starting dibromotriazoles. We envisioned that Suzuki–Miyaura cross-coupling of 4-bromo-5-iodo-1,2,3-triazole **5** could chemoselectively lead to monocoupling product **8** due to the lower dissociation energy of the C–I bond relative to the C–Br bond.[9] Subsequent Suzuki coupling of **8** would furnish unsymmetrical 2,4,5-trisubstituted 1,2,3-triazoles **10**.

4-Bromo-5-iodo-1,2,3-triazole **3** was obtained in 76% yield by treating 4-bromo-5-trimethylsilyl-1,2,3-triazole **2**[6] with *N*-iodosuccinimide in ethyl acetate.[7] Next, we conducted the regioselective N2-alkylation of **3** following the protocol we established previously.[6,10] The results of the N2-substitution reaction of **3** with halides **4a**–**j** are summarized in Table 1. The reactions were performed using K_2CO_3 as base in DMF at temperatures ranging from –10 °C to 80 °C, depending on the reactivity of various substrates. Among the substrates, reaction with 2-fluoro-



Scheme 1 Designed approach to unsymmetrical triazoles

nitrobenzene at 80 °C afforded the desired N2-arylated product as a single isomer in 93% isolated yield (Table 1, entry 10). While alkylation with α-bromoacetate **4h** at –10 °C to 20 °C afforded **5h**/**(6h** + **7h)** in 10:1 ratio (Table 1, entry 8), the alkylation with α-branched bromoacetate **4i** yielded **5i**/**(6i** + **7i)** in a 15:1 ratio (Table 1, entry 9). The alkylation of **3** with 2-bromoethylbenzene (**4e**) at room temperature gave over 10:1 selectivity of **5e**/(**6e** + **7e**, Table 1, entry 5). The regioselectivity deteriorated to about 4–6:1 with other alkyl halides (Table 1, entries 1–4, 6, and 7). Nevertheless, compound **5** was isolated easily via flash column chromatography from other isomers due to their substantial difference in polarity. For all these experiments the substitution reaction gave good to excellent isolated yields of the desired product **5**. In general, the N2-regioselectivity of 4-bromo-5-iodo-1,2,3-triazole (**3**) is slightly less than that of the analogous 4,5-dibromo-1,2,3-triazole (**1**), which is consistent with the conclusion we obtained in an earlier account.[6]

We selected 4-bromo-5-iodo-1,2,3-triazole (**5a**) and 4-methoxyphenyl boronic acid for the initial study on chemoselective Suzuki–Miyaura cross-coupling, and the results are summarized in Table 2. Screening of reaction conditions revealed that choices of solvent, catalyst, and stoichiometry of the boronic acid were critical to the che-

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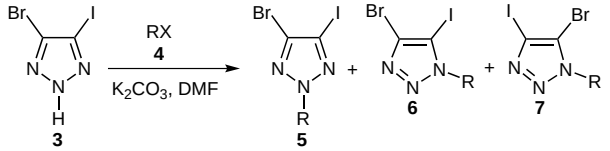
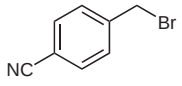
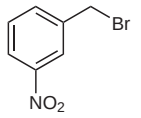
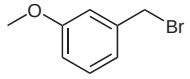
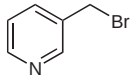
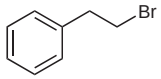
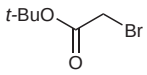
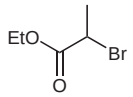
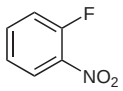
Table 1 N2-Substitution of **3** with Halides **4**



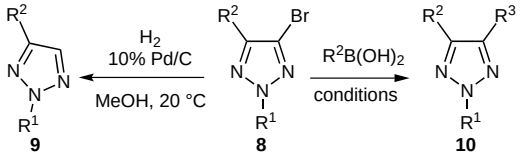
Entry	RX **4**	**5**/(**6** + **7**)	Yield of **5** (%)
1[a]	 **4a**	5:1	**5a** 80
2[a]	 **4b**	5:1	**5b** 77
3[a]	 **4c**	4:1	**5c** 74
4[a]	 **4d**	4:1	**5d** 76
5[b]	 **4e**	10:1	**5e** 87
6[b]	 **4f**	6:1	**5f** 84
7[b]	 **4g**	5:1	**5g** 81
8[a]	 **4h**	10:1	**5h** 85
9[a]	 **4i**	15:1	**5i** 91
10[c]	 **4j**	single isomer	**5j** 93

[a] Reactions completed at –10 °C to 20 °C for 2–5 h.
[b] Reactions completed at 20 °C for 10 h.
[c] Reaction completed at 80 °C for 16 h.

moselectivity. As shown in Table 2, entry 1, the cross-coupling reaction proceeded slowly in toluene–water (3:1) at 100 °C, with complete consumption of **5a** after 16 hours with 5 mol% of $PdCl_2(PPh_3)_2$ and 1.3 equivalents of boronic acid in the presence of K_3PO_4. The desired selective cross-coupling product **8a** was obtained in 85% isolated yield, along with 5% of double-coupling product **11a**. While the use of dioxane–water (3:1) as solvent under the same conditions showed no improvement of the chemoselectivity, the reaction was completed in two hours (Table 2, entry 2). With a mixture of MeCN–water as solvent, more double-coupling product **11a** was observed under the same conditions (Table 2, entries 3 and 4). The large excess of boronic acid contributes to the formation of **11a**, as shown in entry 5 (Table 2) where the cross-coupling with 5 mol% of $PdCl_2(PPh_3)_2$ and reduced amount of boronic acid (1.1 equiv) in a 1:1 mixture of MeCN–water produced **8a** in 95% yield with only 3% of **11a**.[11] The results with other solvents such as aqueous EtOH or DMF were not comparable to that with aqueous MeCN (Table 2, entries 6 and 7). The use of other catalysts such as $Pd(PPh_3)_4$, $Pd_2(dba)_3$, and $Pd(OAc)_2$ showed either lower conversion and higher boronic acid consumption, or more formation of **11a** (Table 2, entries 8–10).

With the optimized conditions in hand, the scope of chemoselective Suzuki–Miyaura cross-coupling of several N2-substituted 4-bromo-5-iodo-1,2,3-triazoles **5** with a variety of boronic acid derivatives was studied (Table 3). Generally, the cross-coupling of **5** with boronic acids was very chemoselective, producing the desired monocoupling products **8** in good to excellent isolated yields with less than 5% of double-coupling products **11**. The coupling of **5h** bearing a carboxylate ester in aqueous MeCN gave rise to the hydrolysis product, which was circumvented by using toluene as solvent instead (Table 3, entry 10).[10] Under Molander's conditions of Xphos as ligand[12a] or aqueous THF solvent,[12b] the coupling of **5b** with alkyl trifluoroborate led to poor chemoselectivity (Table 3, entry 5). A satisfactory chemoselectivity of >95:5 of **8e**/**11e** was achieved under milder conditions.[12c]

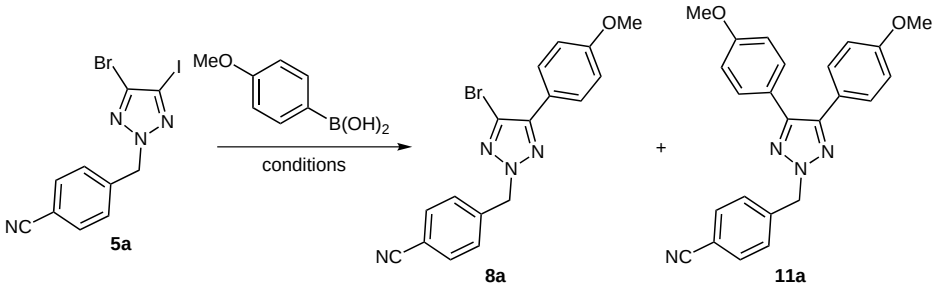
Further functionalization of the bromides **8** provides an efficient and versatile way to synthesize 2,4-disubstituted and 2,4,5-trisubstituted 1,2,3-triazoles (Scheme 2). Hydrogenation of **8f** and **8j** produced 2,4-disubstituted triazoles **9a** and **9b**,[10] while Suzuki–Miyaura cross-coupling of **8a**, **8f**, and **8i** yielded 2,4,5-trisubstituted triazoles **10a**, **10b**,[10] and **10c**. With the many available methodologies



9a (96%): R^1 = 3-methoxybenzyl, R^2 = phenyl
9b (92%): R^1 = CH_2CO_2t-Bu, R^2 = 4-tolyl
10a (88%): R^1 = 4-cyanobenzyl, R^2 = 4-methoxylphenyl, R^3 = 2-pyridyl
10b (77%): R^1 = 3-methoxybenzyl, R^2 = phenyl, R^3 = cyclopropyl
10c (92%): R^1 = Et, R^2 = 3-thiophenyl, R^3 = 3-fluorophenyl

Scheme 2 Further functionalization of **8**

Table 2 Selective Suzuki–Miyaura Cross-Coupling of **5a**



Entry	Solvent system	Catalyst	Temp (°C)	Time (h)	Yield of **8a** (%)[c]	Yield of **11a** (%)[c]
1[a]	toluene–H_2O (3:1)	$PdCl_2(PPh_3)_2$	100	16	85	5
2[a]	dioxane–H_2O (3:1)	$PdCl_2(PPh_3)_2$	100	2	88	4
3[a]	MeCN–H_2O (3:1)	$PdCl_2(PPh_3)_2$	85	2	88	12
4[a]	MeCN–H_2O (1:1)	$PdCl_2(PPh_3)_2$	85	1	82	18
5[b]	MeCN–H_2O (1:1)	$PdCl_2(PPh_3)_2$	85	1	95	3
6[b]	EtOH–H_2O (1:1)	$PdCl_2(PPh_3)_2$	85	1	42	6
7[b]	DMF–H_2O (1:1)	$PdCl_2(PPh_3)_2$	85	2	49	1
8[a]	MeCN–H_2O (1:1)	$Pd(PPh_3)_4$	85	1	90	2
9[b]	MeCN–H_2O (1:1)	$Pd_2(dba)_3$	85	1	81	7
10[b]	MeCN–H_2O (1:1)	$Pd(OAc)_2$	85	1	46	3

[a] With 1.3 equiv of boronic acid, 5 mol% of catalyst and 2.5 equiv of K_3PO_4.
[b] With 1.1 equiv of boronic acid, 5 mol% of catalyst and 2.5 equiv of K_3PO_4.
[c] Isolated yield.

for the transformation of aromatic bromides,[13,14] this strategy can be expanded to synthesize many different polysubstituted 1,2,3-triazoles.

In summary, we have developed an efficient synthesis of polysubstituted 1,2,3-triazoles via N2-alkylation/arylation of 4-bromo-5-iodo-1,2,3-triazole in a regioselective fashion. The subsequent chemoselective Suzuki–Miyaura cross-coupling followed by further elaboration of the bromotriazole intermediates unveil a convenient and versatile synthetic strategy for the synthesis of N2-polysubstituted 1,2,3-triazoles.

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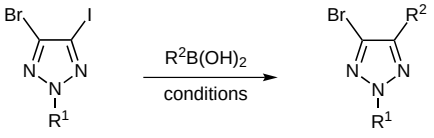
Table 3 Selective Suzuki–Miyaura Cross-Coupling of **5**



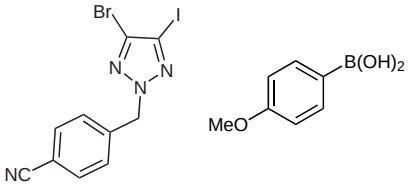
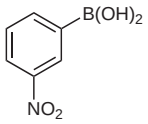
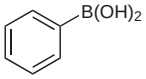
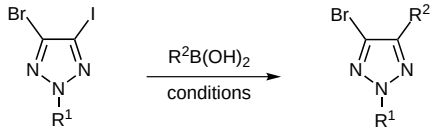
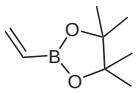
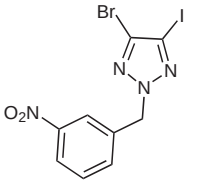
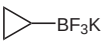
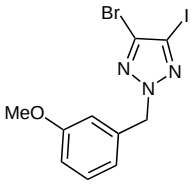
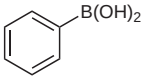
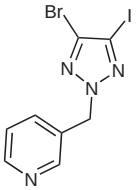
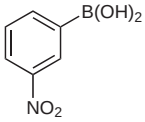
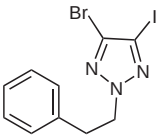
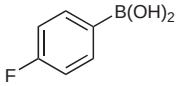
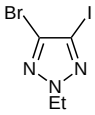
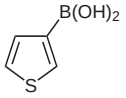
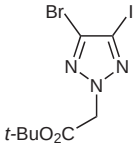
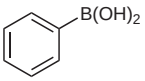
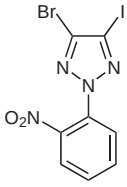
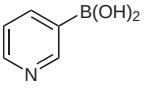
Entry	Triazole **5**	$R^2B(OH)_2$	Yield of **8** (%)
1[a]	**5a**		**8a** 95
2[a]	**5a**		**8b** 89
3[a]	**5a**		**8c** 92

Table 3 Selective Suzuki–Miyaura Cross-Coupling of **5** (continued)



5 **8**

Entry	Triazole **5**	$R^2B(OH)_2$	Yield of **8** (%)
4[a]	**5a**		**8d** 84
5[b]	**5b**	 	**8e** 74
6[a]	**5c**	 	**8f** 93
7[a]	**5d**	 	**8g** 92
8[a]	**5e**	 	**8h** 91
9[a]	**5f**	 	**8i** 81
10[c]	**5h**	 	**8j** 85
11[a]	**5i**	 	**8k** 87

[a] With 1.1 equiv of boronic acid, 5 mol% of $PdCl_2(PPh_3)_2$ and 2.5 equiv of K_3PO_4 in MeCN–H_2O (1:1) at 85 °C for 0.5–2 h.
[b] With 1.0 equiv of trifluoroborate, 9 mol% of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ and 3 equiv of Cs_2CO_3 in toluene–H_2O (3:1) at 80 °C for 24 h.[12c]
[c] With 1.1 equiv of boronic acid, 5 mol% of $PdCl_2(PPh_3)_2$ and 2.5 equiv of K_3PO_4 in toluene–H_2O (10:1) at 90 °C for 2 h.[10]

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(7) **Preparation of 4-Bromo-5-iodo-2*H*-1,2,3-triazole 3:** To a slurry of 4-bromo-5-trimethylsilyl-1,2,3-triazole **2** (5.29 g, 24 mmol) and K_2CO_3 (0.01 g, 0.094 mmol) in EtOAc (50 mL) was added NIS (5.58 g, 24.8 mmol) at r.t. The mixture was allowed to react for 2 h at r.t. and quenched with 1% Na_2SO_3 (30 mL) and EtOAc (30 mL). The organic layer was washed with H_2O (30 mL) and dried over anhyd $MgSO_4$. The solvent in organic layer was evaporated under vacuum. The crude product was purified either by crystallization or by silica gel column chromatography. Compound **3** was isolated as a white solid (5.0 g, 76% yield). ^1H NMR (400 MHz, DMSO-d_6): not detectable. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 96.6, 129.7. ESI-HRMS: *m/z* calcd for $[C_2HBrIN_3 + H]^+$: 273.8477; found: 273.8470.
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(11) **Preparation of Triazoles 8 and 11:** To a mixture of **5** (1 mmol), boronic acid derivative (1.1 mmol) and potassium phosphate monohydrate (576 mg, 2.5 mmol) in MeCN–H_2O (1:1, 10 mL) was added $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol). The mixture was heated to 85 °C for 0.5–2 h to allow complete reaction. The organic layer was dried over anhyd $MgSO_4$. The solvent in organic layer was evaporated under vacuum. The crude product was purified by silica gel column chromatography.
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