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Bromo-Directed *N*-2 Alkylation of *NH*-1,2,3-Triazoles: Efficient Synthesis of Poly-Substituted 1,2,3-Triazoles

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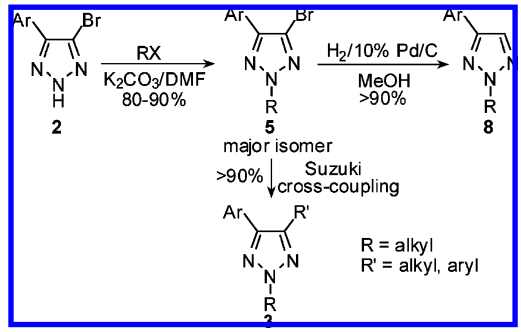
ABSTRACT



Reaction of 4-bromo-*NH*-1,2,3-triazoles 2 with alkyl halides in the presence of K_2CO_3 in DMF produced the corresponding 2-substituted 4-bromo-1,2,3-triazoles 5 in a regioselective process. Subsequent Suzuki cross-coupling reaction of these bromides provided an efficient synthesis of 2,4,5-trisubstituted triazoles 3. In addition, reduction of the bromotriazoles by hydrogenation furnished an efficient synthesis of 2,4-disubstituted triazoles 8.

The triazole moiety serves as an important structural element in many biologically active products.[1] The copper(I)-promoted 1,3-dipolar azide−alkyne cycloaddition provides a poweful method to access 1,4-disubstituted 1,2,3-triazoles,[2] while ruthenium-catalyzed cycloaddition produces 1,5-disubstituted 1,2,3-triazoles.[3] A general method for the preparation of 2-substituted triazoles, however, is lacking.[4] Recently, we have developed a route to 2-aryl-1,2,3-triazoles through a regioselective *N*-2 arylation of 4,5-dibromo-*NH*-triazole[5] in which the 4,5-dibromo substitution pattern suppresses *N*-1 arylation. With these findings in hand, we explored the scope of this bromo-directed *N*-2 alkylation of triazoles **2**, as outlined in Scheme 1.

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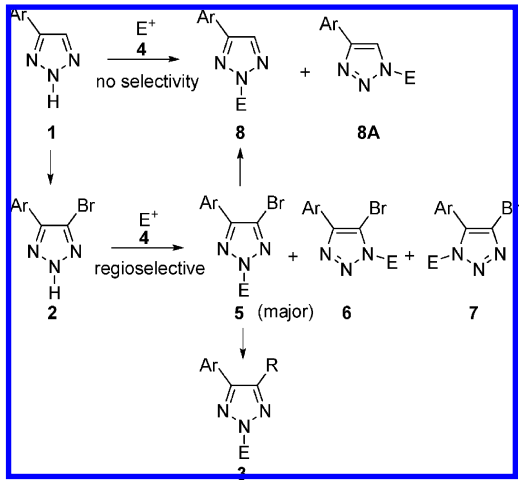
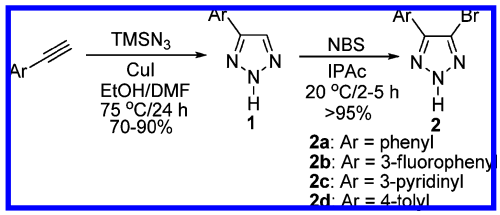
Scheme 1



2,4-Disubstituted triazoles **8** can be accessed by alkylation of monosubstituted triazoles **1**, but typically, a mixture of **8** and **8a** is produced with no regioselectivity (Scheme 1).[6] We envisioned that an additional, removable substituent, in particular, a bromine atom, would suppress the *N*-3 alkylation in a manner similar to that demonstrated by Shi and co-workers.[7] As a result, the product of *N*-2 alkylation, **5**, would be favored. Subsequent reduction of **5** would produce the 2,4-disubstituted triazole **8**, while further elaboration of the bromo substituent by cross-coupling chemistry, for example, would provide an efficient route to 2,4,5-trisubstituted triazoles **3**, as illustrated in Scheme 1.

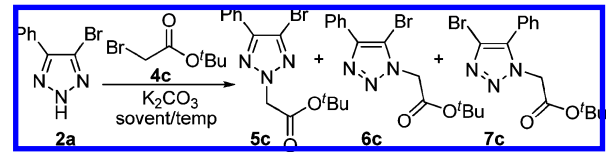
Triazoles **1a**−**d** were prepared by the copper-catalyzed 1,3-dipolar cycloaddition of the corresponding terminal alkynes and trimethylsilyl azide.[8] Bromination of **1a**−**d** with NBS in isopropyl acetate produced **2a**−**d** in excellent yields (Scheme 2).

Scheme 2



An initial evaluation of the regioselectivity began with triazole **2a** and *tert*-butyl α-bromoacetate (**4c**) as electrophile. Screening of reaction conditions revealed that choices of solvents had a significant impact on regioselectivity (Table 1). With K_2CO_3 as base, the alkylation reaction was completed in 5 h in THF at room temperature to produce a 70:30 mixture of **5c** to (**6c** + **7c**). Whereas both acetonitrile and acetone gave a better ratio of 80:20, dipolar solvent DMF improved the ratio to 86:14. When the same alkylation was performed at a lower temperature of −10 °C in DMF that changed the reaction kinetics by slowing down the alkylation, the ratio of **5c** to (**6c** + **7c**) was further improved to 91:9. No alkylation products were observed with CH_2Cl_2 and MTBE as solvents.

Table 1. *N*-2 Alkylation of **2a** with α-Bromoacetate **4c**

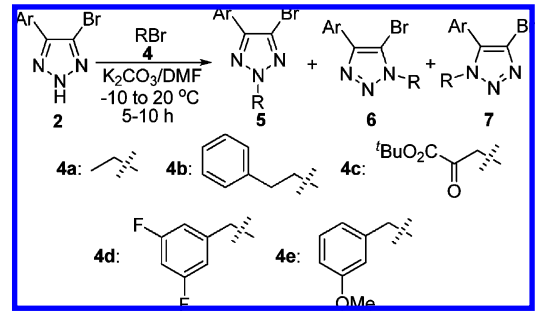


entry	solvent	temp (°C)	time (h)	ratio[a] of **5c**: (**6c** + **7c**)
1	THF	20	5	71:29
2	CH_3CN	20	2	80:20
3	CH_3COCH_3	20	2	80:20
4	CH_2Cl_2	20	5	nr[b]
5	MTBE	20	5	nr[b]
6	DMF	20	1	86:14
7	DMF	−10	6	91:9

[a] Ratio determined by both HPLC and proton NMR. [b] No product observed.

The scope of the alkylation reaction was tested with four bromo-*NH*-1,2,3-triazoles **2a**−**d** and five typical alkyl bromides **4a**−**f**, as summarized in Table 2. The reaction was performed

Table 2. *N*-2 Alkylation of **2** with Alkyl Bromides **4**



entry	**2**	**4**	**5**:**6**:**7**[a]	yield of **5** (%)[b,c]
1	**2a**	**4a**	88:8:4	83 (**5a**)
2	**2a**	**4b**	91:6:3	87 (**5b**)
3	**2a**	**4c**	91:5:4	85 (**5c**)
4	**2a**	**4d**	92:6:2	88 (**5d**)
5	**2a**	**4e**	85:8:7	80 (**5e**)
6	**2b**	**4a**	93:5:2	89 (**5f**)
7	**2b**	**4b**	94:6:<1	87 (**5g**)
8	**2b**	**4c**	93:5:2	90 (**5h**)
9	**2c**	**4a**	94:6:<1	90 (**5i**)
10	**2c**	**4b**	95:3:2[d]	88 (**5j**)
11	**2c**	**4d**	93:4:3[d]	88 (**5k**)
12	**2c**	**4e**	89:7:4[d]	83 (**5l**)
13	**2d**	**4a**	87:8:5	83 (**5m**)
14	**2d**	**4b**	89:7:4	84 (**5n**)
15	**2d**	**4c**	90:6:4	82 (**5o**)

[a] Ratio determined by both HPLC and proton NMR, which was consistent with isolated yields of **5**, **6**, and **7**. [b] Reactions usually took 5−7 h to complete with **4a** and **4b** at rt and 5−10 h to complete with **4c**, **4d**, and **4e** at −10 °C. [c] 90−96% isolated yields for **5** + **6** + **7** by flash chromatography on silica gel. [d] Inseparable mixture of **6** + **7**.

using K_2CO_3 as base in DMF at room temperature for less reactive bromides **4a** and **4b** and at −10 to 0 °C for more reactive **4c**−**e** based on the initial evaluation of reaction conditions.[9] We were pleased to find that in all cases the *N*-2-substituted products **5** could be isolated in good to excellent yields. With the phenyl-substituted *NH*-triazole **2a**, alkylation generally gave a 10:1 mixture of **5** to (**6** + **7**). In the alkylation of **2b** and **2c**, in which the triazole rings were more electron-deficient than the parent analogue **2a**, the *N*-2 regioselectivity was improved to >13:1 of **5** to (**6** + **7**). In some cases, regioisomer **7** was not observed (entries 7 and 9, Table 2). With electron-rich **2d**, the *N*-2 selectivity was slightly lower than that of the parent compound **2a**. In all cases, excellent isolated yields of combined **5**, **6**, and **7** were obtained.

The regiochemistry of **6** and **7** was determined by 2D NMR experiments, as shown in Figure 1. It was also observed that

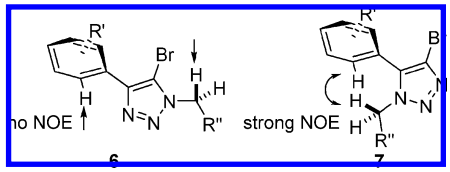
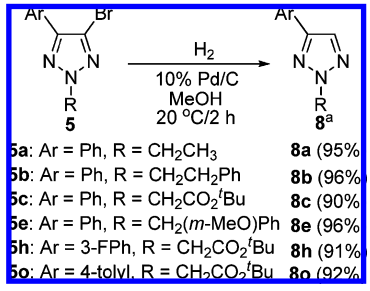


Figure 1. Two-dimensional NMR experiments on regioisomers **6** and **7**.

the chemical shift of the two methylene protons in **7** appeared at a higher field due to shielding by the aromatic ring.

This successful regioselective *N*-2 alkylation of *NH*-1,2,3-triazole **2** provides an efficient way to access a variety of substituted triazole derivatives. For example, as shown in Scheme 3, the bromotriazoles **5** can be reduced under

Scheme 3

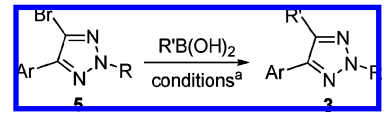


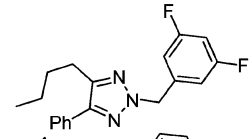
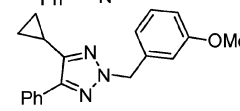
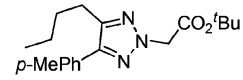
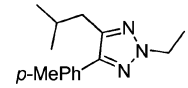
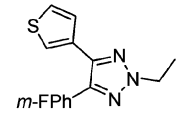
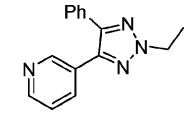
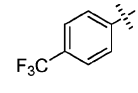
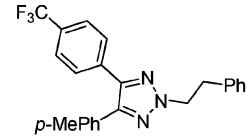
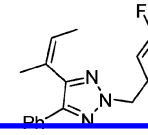
[a] Isolated yields for all cases.

standard catalytic hydrogenation conditions to produce 2,4-disubstituted triazoles **8** in excellent yields.

We next investigated the conversion of **5** to 2,4,5 fully substituted triazoles, using Suzuki cross-coupling methodology. As summarized in Table 3, with alkylboronic acids, the desired 2,4,5 fully substituted triazoles **3** were obtained in good yields using Chen's procedure.[10] A small amount of dehalogenated byproduct was also observed under these

Table 3. Synthesis of 2,4,5-Trisubstituted-1,2,3-Triazoles



5	R'	9	yield [b,c]
5d			76%(**3a**)
5e			77%(**3b**)
5o			75%(**3c**)
5m			74%(**3d**)
5f			90%(**3e**)
5i			97%(**3f**)
5n			95%(**3g**)
5d			96%(**3h**)

[a] With 1.2 equiv of boronic acid/5% of $Pd(OAc)_2$/10% of $(^tBu)_3PHBF_4$/3.5 equiv of K_3PO_4/toluene/water/90 °C/2 h for **9a**−**d** and 1.2 equiv of boronic acid/5% of $Pd(PPh_3)_2Cl_2$/2 M aq Na_2CO_3/CH_3CN/75 °C/1 h for **9e**−**h**. [b] Isolated by flash chromatography. [c] Reactions usually took 1 h to complete.

unoptimized reaction conditions. With aryl- and vinylboronic acids, the coupling reaction gave products **3** in excellent yields.

This regioselective synthesis of 2,4,5-trisubstituted triazoles is remarkably general considering the fact that 1,3-dipolar cycloaddition requires particular activated, electron-deficient internal alkynes for the preparation of fully substituted triazoles, and ruthenium-catalyzed cycloaddition gives 1,4,5-trisubstituted triazoles.[11] With all available transition-metal-catalyzed cross-coupling reactions, a fundamental method for carbon−carbon bond formation,[12] many different kinds of poly-substituted triazoles can be prepared efficiently.

In conclusion, we have developed an efficient synthesis of poly-substituted triazoles by a regioselective *N*-2 alkylation of 4-bromo-*NH*-1,2,3-triazole. The subsequent debromination of these triazoles by hydrogenation gives 2,4-disubstituted triazoles in excellent yields. Furthermore, 2,4,5 fully substituted triazoles are readily accessible by elaboration of the versatile bromotriazole intermediates using cross-coupling conditions.

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Supporting Information Available: Typical experimental procedures and spectroscopic data including spectra of ^{1}H, ^{13}C for all new compounds **1b**, **2a**−**d**, **5a**−**o**, **6a**−**o**, **7a**−**o**, **8a**−**c**, **8e**, **8h**, **8o**, **3a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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