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Highly Regioselective *N*-2 Arylation of 4,5-Dibromo-1,2,3-triazole: Efficient Synthesis of 2-Aryltriazoles

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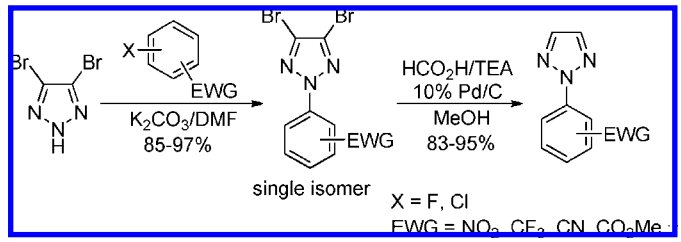
ABSTRACT



Reaction of 4,5-dibromo-1,2,3-triazole with electron-deficient aromatic halides in the presence of potassium carbonate in DMF produces the corresponding 2-aryl-4,5-dibromotriazoles with high regioselectivity. Subsequent debromination of these triazoles by hydrogenation furnishes 2-aryltriazoles in excellent yields. Overall, this two-step process provides an efficient access to 2-aryl-1,2,3-triazoles.

1,2,3-Triazoles have broad applications in chemical industries, medicinal chemistry, and biological sciences.[1] A number of synthetic methods have been developed to prepare these heterocycles. Whereas both thermal and Cu(I)-catalyzed condensations of alkynes and azides provide an excellent method for the synthesis of *N*-1 substituted triazoles,[2] the synthesis of *N*-2 substituted triazoles remains a challenge,[3] especially for 4,5-unsubstituted substrates. The current main approach to 2-aryltriazoles by condensation of arylhydrazines and α-hydroxyketones requires quite specific arylhydrazines, which limits its broader utility.[4]

We recently required access to *N*-2 aryl-substituted triazole derivatives such as **1A** (Scheme 1) and were interested in developing a regioselective *N*-2 arylation process. However, *N*-1 arylation/alkylation to **1B** was well documented to be the main course for direct nucleophilic substitution with triazole **1** (Scheme 1). From a simple statistical perspective, *N*-2 arylation/alkylation should comprise about one-third of the product mixture, since there are one *N*-2 nitrogen and two terminal nitrogens available for reaction. Recently, Shi[3c,d] reported a highly regioselective *N*-2 arylation of 4,5-disubstituted 1,2,3-triazoles where steric hindrance of a 4,5-disubstitution pattern prevented terminal *N*-arylation.[5] In this

(1) (a) Wamhoff, H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergman: Oxford, UK, 1984; Vol. 5, p 669. (b) Dehne, H. In *Methoden der Organischen Chemie (Houben-Weyl)*; Schumann, E., Ed.; Thieme: Stuttgart, Germany, 1994; Vol. E8d, p 305. (c) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128.

(2) (a) Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984. (b) Kolb, H. C.; Fin, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (c) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (d) Wu, P.; Fokin, V. V. *Aldrichim. Acta* **2007**, *40*, 7.

(3) For recent development on selective synthesis of *N*-2 substututed triazoles, see: (a) Kalisiak, J.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2008**, *10*, 3171. (b) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7786. (c) Liu, Y.; Yan, W.; Chen, Y.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 5389. (d) Chen, Y.; Liu, Y.; Petersen, J. L.; Shi, X. *Chem. Commun.* **2008**, 3254.

(4) Tang, W.; Hu, Y. *Synth. Commun.* **2006**, *36*, 2461.

(5) (a) Lacerda, P. S. S.; Silva, A. M. G.; Tome, A. C.; Neves, M.; Silva, A. M. S.; Cavaleiro, J. A. S.; Llamas-Saiz, A. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 5487. (b) Revesz, L.; Di Padova, F. E.; Buhl, T.; Feifel, R.; Gram, H.; Hiestand, P.; Manning, U.; Wolf, R.; Zimmerlin, A. G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2109. (c) Kim, D. K.; Kim, J.; Park, H. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2405.

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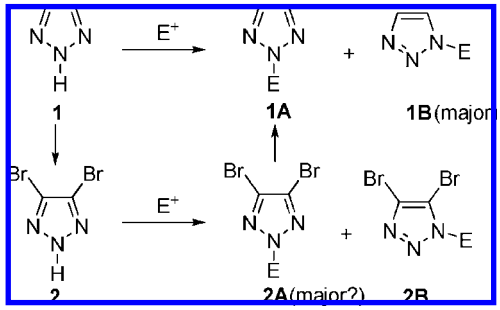
Scheme 1



instance specific substituents were incorporated into the reacting triazoles, which potentially limited the utility to particular product types.

Our approach to developing a practical method for direct *N*-2 arylation involved the use of 4,5-dibromotriazole (**2**) as a nucleophile.[6] We hoped that the 4,5-dibromo-substitution pattern would provide sufficient steric hindrance to block reaction at the two terminal nitrogen positions. In addition, the electron-withdrawing effect of dibromo-substitution might also lower the electron density (and hence reactivity) of these two positions (*N*-1 and *N*-3). We also expected that the two halogen atoms could be easily removed after the arylation reaction. Overall, the process would allow us to achieve a selective *N*-2 arylation to **1A** via the intermediate **2A**, as shown in Scheme 1.

In our initial experiments, we were pleased to find that treatment of a 1:1 mixture of 4,5-dibromide **2** and 2-fluoronitrobenzene (**2b**) in DMF with K_2CO_3 as base at 70 °C for 1 h afforded the *N*-2 arylated product **3b** as a single isomer in 96% isolated yield (entry 2, Table 1). By comparison, when the same reaction was performed with unsubstituted triazole **1**, a 2:1 mixture of *N*-1 and *N*-2 arylation products was produced in accord with previous results.[7] The scope of this highly regioselective *N*-2 arylation was tested with a series of electron-deficient aryl halides and 2-halopyridine derivatives. As summarized in Table 1, the S_NAr substitution afforded *N*-2 products exclusively in all cases in excellent isolated yields. Several of the reactions were also executed on kilogram scale, establishing the practicality and robustness of the methodology.

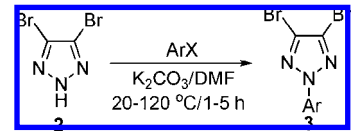
Next, debromination of these triazoles to 4,5-unsubstituted triazoles was tested. Dibromotriazole **3b** was simply

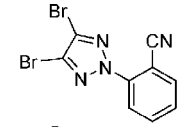
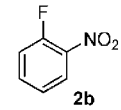
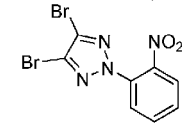
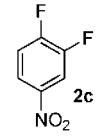
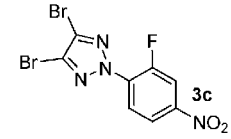
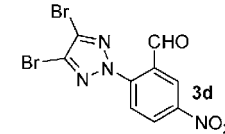
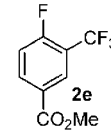
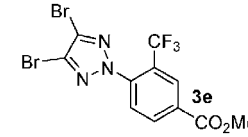
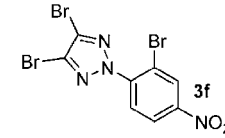
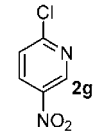
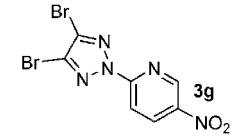
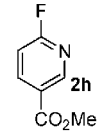
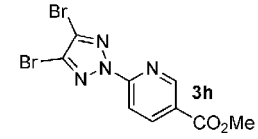
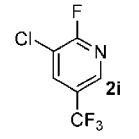
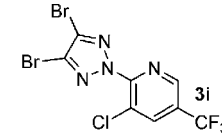
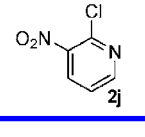
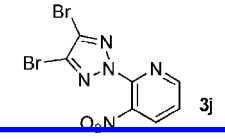
(6) Iddon, B.; Nicholas, M. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1341.

(7) Albini, A.; Bettinetti, G. F.; Minoli, G. *J. Org. Chem.* **1983**, *48*, 1080.

(8) **Typical experimental procedure for *N*-2 arylation:** A mixture of 3-bromo-4-fluoronitrobenzene (**2f**) (100 g, 0.45 mol), 4,5-dibromo-1,2,3-triazole (**2**) (102 g, 0.45 mol), and K_2CO_3 (62 g, 0.45 mol) in DMF (100 mL) was heated to 85 °C for 1 h. The mixture was then quenched with water (100 mL), and the solid was collected by filtration. The crude solid was crystallized from a 1:1 mixture of hexane and ethyl acetate to give 179 g (93%) of **3f** as a colorless solid: mp 167−168 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.68 (d, J = 2.4 Hz, 1H), 8.42 (dd, J = 2.4, 8.8 Hz, 1H), 8.04 (d, J = 8.8 Hz, 1H); ^{13}C NMR (400 MHz, DMSO) δ 148.2, 142.3, 129.3, 129.0, 128.0, 124.1, 117.9. Anal. Calcd for $C_8H_3Br_3N_4N_2$: C, 22.51; H, 0.71; N, 13.13. Found: C, 22.72; H, 0.60; N, 13.24.

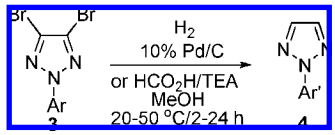
Table 1. Aromatic Substitution of 4,5-Dibromotriazole

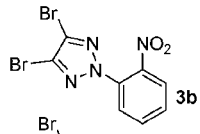
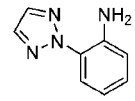
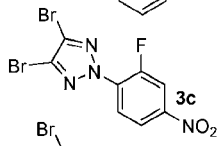
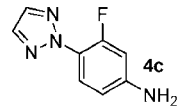
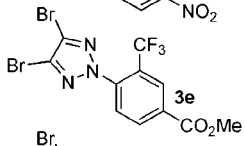
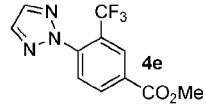
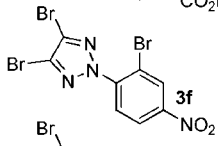
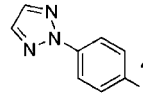
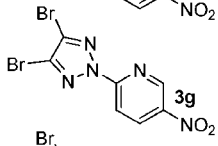
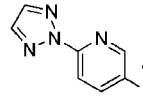
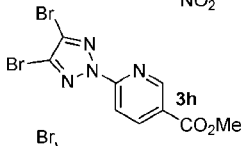
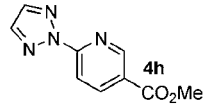
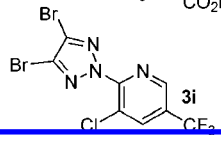
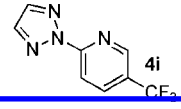


entry	ArX	temp (°C)[a]	products **3**	isolated yield[b]
1	 **2a**	120	 **3a**	85%
2	 **2b**	70	 **3b**	96%
3	 **2c**	90	 **3c**	92%
4	 **2d**	20	 **3d**	93%
5	 **2e**	90	 **3e**	93%
6	 **2f**	100	 **3f**	95%
7	 **2g**	80	 **3g**	92%
8	 **2h**	90	 **3h**	90%
9	 **2i**	90	 **3i**	89%
10	 **2j**	80	 **3j**	93%

[a] Reactions run for 1−5 h at this temperature. [b] Isolated by crystallization or by flash chromatography on silica gel.

Table 2. Reduction of Dibromotriazoles by Hydrogenation



entry	dibromides **3**	products **4**	isolated yield[a]
1	 **3b**	 **4b**	95%
2	 **3c**	 **4c**	92%
3	 **3e**	 **4e**	80%
4	 **3f**	 **4f**	96%
5	 **3g**	 **4g**	92%
6	 **3h**	 **4h**	94%
7	 **3i**	 **4i**	89%

[a] Isolated by filtration through a pad of silica gel or by falsh chromatography on silica gel.

subjected to a standard transfer hydrogenation procedure (90% formic acid and triethylamine in the presence of a catalytic amount of 10% Pd/C in methanol) and triazole **4b** was isolated in 95% yield. A similar result was obtained when debromination was performed under H_2 with 10% Pd/C in methanol. Table 2 summarizes the results obtained with the other dibromotriazoles. Again in all cases, 4,5-unsubstituted 2-aryltriazoles were produced in excellent isolated yields. For substrates containing NO_2 or halogen substituents, these labile functional groups were also reduced.

In conclusion, a new protocol for the efficient synthesis of *N*-2 aryltriazoles by a highly regioselective *N*-2 arylation of 4,5-dibromotriazole is described. Subsequent debromination of these triazoles by hydrogenation efficiently furnishes 4,5-unsubstituted-2-aryltriazoles in excellent yields.[8,9] One can imagine that a combination of steric hindrance and electronic effects induced by the 4,5-dibromo substitution may contribute to the high regioselectivity observed. We are currently studying more general *N*-2 alkylation using **2** as well as exploring opportunities to manipulate the dibromo functionality to provide a variety of *N*-2-substituted triazoles.

Acknowledgment. We thank Drs. John Proudfoot, and Carl Busacca for helpful discussion.

Supporting Information Available: Spectroscopic data and copies of ^1H and ^{13}C NMR spectra for all new compounds **3a**−**j**, **4a**−**c**, **4e**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) **A typical experimental procedure for reduction of dibromotriazoles:** A mixture of **3f** (10 g, 23.4 mmol) and 10% Pd/C in methanol (50 mL) was stirred under atomospheric H_2 for 24 h. Triethylamine (89.8 mL, 70.2 mmol) was added to the mixture. After being stirred for 10 min, the mixture was filtered. The filtrate was diluted with ethyl acetate (100 mL) and washed with water (100 mL). Concentration of the organic gave 3.59 g (96%) of **4f** as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, $J = 8.8$ Hz, 1H), 7.74 (s, 2H), 6.75 (d, $J = 8.8$ Hz, 1H), 3.95 (br s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 146.1, 134.7, 132.2, 120.5, 115.2; HRMS calcd for $C_8H_8N_4$ $[C_8H_8N_4 + H]^+$ 161.0809, found 161.0821.