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The Disappearing Director: The Case of Directed *N*-Arylation *via* a Removable Hydroxyl Group

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Abstract: A facile and broadly applicable method for the regiospecific *N*-arylation of benzotriazoles is reported. Copper-mediated reactions of diverse 1-hydroxy-1*H*-benzotriazoles with aryl boronic acids lead to 1-aryl-1*H*-benzotriazole 3-oxides. A *N*1-OH→*N*3 prototropy in the 1-hydroxy-1*H*-benzotriazoles is plausibly the underlying basis, where the tautomer is captured by the boronic acid, leading to C–N (not C–O) bond formation. Because the N–O bond in amine *N*-oxides and 1-hydroxy-1*H*-benzotriazoles can be easily reduced by diboron reagents such as $(pinB)_2$ and $B_2(OH)_4$, exposure of the 1-aryl-1*H*-benzotriazole 3-oxides to $B_2(OH)_4$ then leads to facile reduction of the N–O bond resulting in diverse, regiospecifically-arylated benzotriazoles. Thus, the *N*-hydroxyl group in 1-hydroxy-1*H*-benzotriazoles acts as a disposable arylation director.

Keywords: arylation; benzotriazoles; directing group; copper; boronic acid

1 Introduction

Among heterocycles, benzotriazoles are an important family of compounds with wide-ranging uses. In medicinal chemistry, many have shown important biological activities.[1–4] In relation to the present work, 1-aryl-1*H*-benzotriazoles display promise against various diseases. Some examples containing *N*-aryl-linked benzotriazoles are shown in Figure 1. Among these, the tetrahydronaphthalene derivative is a ligand for retinoid X receptors, and showed significant activity against type-2 diabetes *in vivo*.[5] The pyrimidine-benzotriazole conjugates were shown to be potent inhibitors of JNK1 (mitogen-activated protein kinase 1), with selectivity over JNK2.[6] The acridine derivatives showed antibacterial activity, comparable to ampicillin, against *S. areus*, *B. subtilis*, and *E. coli*.[7] The benzotriazolyl chalcones demonstrated antifilarial activity against *Setaria cervi* causing parasitic death,[8] and against *Plasmodium falciparum*.[9]

Also, benzotriazoles are corrosion inhibitors for copper and copper alloys,[10] they are found in formulations that contact metals (such as aircraft deicing and brake fluids, and in metal-cutting fluids),[11] and are antifog agents in photographic applications.[12] Benzotriazoles are important in organic synthesis,[13] including as ligands in cross-coupling reactions.[14]

Many methods, metal-catalyzed and uncatalyzed, have been developed for the *N*-arylation of benzotriazoles, but reaction at the *N*1 and *N*2 and formation of regioisomeric products from unsymmetrical benzotriazoles have to be contended with. Among methods not involving metal-mediated processes, the most common is diazotization of *N*-aryl-*o*-phenylenediamines.[15] Also, reaction of 2-(arylamino)iminophosphoranes

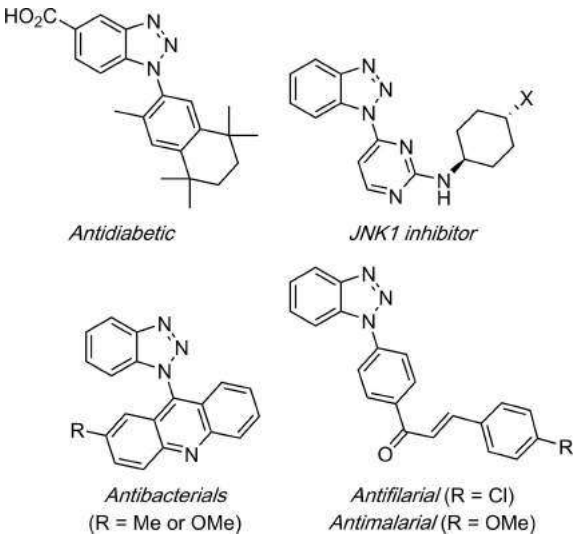
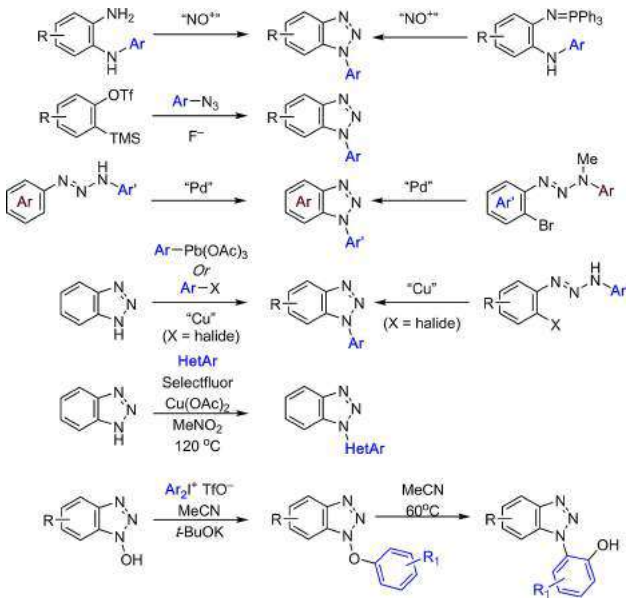


Figure 1. *N*1-aryl benzotriazoles possessing biological activities.

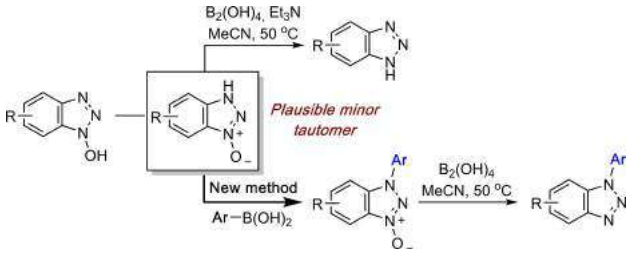


Scheme 1. Previous approaches to *N*1-aryl benzotriazoles.

with $NaNO_2$/AcOH results in *N*1-arylbenzotriazoles.[16] Perhaps the most convenient access is *via* cycloaddition of arynes with aryl azides but this can yield regioisomers with unsymmetrical arynes.[17] Among methods involving metals, Pd-mediated C–H bond activation/C–N bond formation in 1,3-diphenyltriaz-1-enes[18] and 1,7-Pd migration-cyclization-demethylation of 3-methyl-1,3-diphenyltriaz-1-enes have been reported.[19] 1*H*-Benzotriazole itself has been used as a substrate for Cu-mediated arylation. Examples are: the $Cu(OAc)_2$-catalyzed reaction of an aryllead derivative at 140 °C (1 example, *N*1/*N*2 ratio = 3.8:1),[20] arylation with a CuI-diamine system at 110 °C (2 examples, *N*1/*N*2 ratio > 25:1),[21] and $CuBr_2$/*n*-$Bu_4N^+F^-$ mediated arylation at 145 °C (in 2 examples, *N*1/*N*2 ratios = 1.3–2.7:1).[22] Cyclization of *o*-halo-1,3-diphenyltriaz-1-enes to *N*1-aryl benzotriazoles has been accomplished *via* catalysis by CuI.[23–25] In a $Cu(OAc)_2$-catalyzed method, 1*H*-benzotriazole underwent reaction with substituted thiophenes, furans, and pyrroles, in the presence of Selectfluor.[26] *N*-(2-Hydroxyaryl)benzotriazoles have been prepared by *O*-arylation with diaryliodonium triflates, followed by a [3,3] sigmatropic rearrangement.[27] A summary of these methods is shown in Scheme 1.

2 Results and Discussion

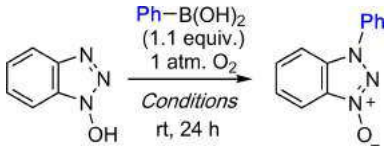
In this report, we present a new approach to regiospecific *N*1 arylation of benzotriazoles that is directed by a remote hydroxyl group. In previous work, we demonstrated facile reduction of 1-hydroxy-1*H*-benzotriazoles (BtOH) by exposure to $B_2(OH)_4$ and Et_3N in MeCN (Scheme 2).[28] In that work we proposed that a possible mechanism for the reduction could involve the *N*1-OH→*N*3 prototropy, which would expose an *N*-oxide type of intermediate. Such a species could be reduced by a diboron reagent. In this context, we and others have shown general approaches for the reduction of N–O bonds in amine *N*-oxides and O^6-(benzotriazolyl) purine nucleosides by diboron reagents.[29–31] Tautomerism in BtOH is known to be solvent dependent. The *N*-hydroxy form has been crystallized from water-free EtOH/Et_2O after drying the compound over P_2O_5 at 50 °C, whereas the *N*-oxide form was obtained from MeOH/H_2O.[32] Also, acylation of BtOH can produce *O*- or *N*-acylation, depending upon the polarity of the reaction medium,[33–35] and the *O*-acyl compound completely isomerizes to the *N*-acyl form in the solid state.[35]



Scheme 2. Reduction of BtOH derivatives and a proposed approach to hydroxyl-directed *N*-arylation of benzotriazoles.

On the basis of the tautomerism exhibited by 1-hydroxy-1*H*-benzotriazoles[32–35] and our prior results,[28] we reasoned that it should be possible to capture the *N*-oxide tautomer in a Chan-Lam-Evans type of reaction.[36–38] The ensuing product would be

Table 1. Optimization of conditions for reaction of BtOH with $PhB(OH)_2$.[a]



Entry	Solvent	Conditions	Yield [%][b]
1	$ClCH_2CH_2Cl$	$Cu(OAc)_2$ (1 equiv.), pyridine (4 equiv.)	27[c]
2	CH_2Cl_2	$Cu(OAc)_2$ (1 equiv.), pyridine (4 equiv.)	42[c]
3	DMSO	$Cu(OAc)_2$ (1 equiv.), pyridine (4 equiv.)	NR[d]
4	CH_2Cl_2	$Cu(OAc)_2$ (1 equiv.), pyridine (4 equiv.)	77[e]
5	CH_2Cl_2	$Cu(OAc)_2$ (1 equiv.), Et_3N (4 equiv.)	30[e]
6	CH_2Cl_2	$Cu(OAc)_2$ (1 equiv.), 2,2′-bipyridine (2 equiv.)	10[e]
7	CH_2Cl_2	$Cu(OAc)_2$ (0.25 equiv.), pyridine (4 equiv.)	14[e]
8	CH_2Cl_2	$Cu(OAc)_2$ (0.5 equiv.), pyridine (4 equiv.)	26[e]
9	CH_2Cl_2	CuI (1 equiv.), pyridine (4 equiv.)	11[e]
10	CH_2Cl_2	CuCl (1 equiv.), pyridine (4 equiv.)	14[e]

[a] Reactions were conducted with 100 mg of BtOH in 2 mL of solvent, under a balloon filled with O_2 gas.
[b] Yield is of isolated and chromatographically purified product.
[c] Reaction mixture was subjected to an aqueous workup.
[d] NR = no reaction.
[e] Reaction mixture was directly chromatographed without aqueous workup.

an *N*1-aryl-1*H*-benzotriazole 3-oxide, which could then be reduced to the corresponding 1*H*-benzotriazole, removing the directing hydroxyl handle. We should note that reaction of BtOH and *p*-Me-$PhB(OH)_2$, using $Cu(OAc)_2$ and either pyridine or Et_3N, has previously been reported.[39] The product obtained was identified as the *O*-arylated compound, but our results herein indicate a different outcome. While our work was being completed a similar method for Cu-catalyzed *N*-vinylation of 1-hydroxy-1*H*-benzotriazoles, leading the *N*-oxides was reported.[40] In that work, several reactions of BtOH with aryl boronic acids were also recorded, but only two substituted 1-hydroxy-1*H*-benzotriazoles were studied.[40] Comparisons of the methods are presented later.

Our present work commenced with evaluation of conditions for the reaction of 1-hydroxy-1*H*-benzotriazole (BtOH) with $PhB(OH)_2$, at room temperature (data in Table 1). Between $ClCH_2CH_2Cl$ and CH_2Cl_2, the latter proved to be superior, and no reaction occurred in DMSO (entries 1–3). We reasoned that one possible cause for the promising but modest result in CH_2Cl_2 could be the water solubility of what we considered was 1-phenyl-1*H*-benzotriazole 3-oxide. This notion was supported by the improved 77% yield that was obtained when the reaction mixture was directly chromatographed, without aqueous workup (entry 4). Replacement of pyridine with either Et_3N or 2,2′-bipyridine gave inferior results. Lowering the amount of $Cu(OAc)_2$ (entries 7 and 8) also proved to be detrimental, clearly indicating the need for a stoichiometric amount (98% $Cu(OAc)_2$ costs < $1/mol).

Whereas evidence pointed to the product of this Cu-mediated transformation to be 1-phenyl-1*H*-benzotriazole 3-oxide, confirmation was necessary. Therefore, the product was crystallized and analyzed crystallographically (Figure 2).[41] This unequivocally indicated that the product was the expected *N*-oxide and not the *O*-aryl product.

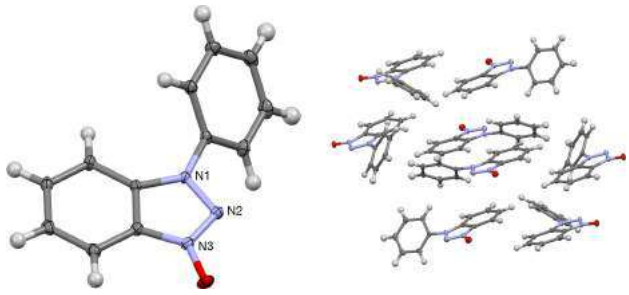


Figure 2. X-ray crystallographic structure of 1-phenyl-1*H*-benzotriazole 3-oxide (**1**) and crystal packing (thermal ellipsoids are shown at the 50% probability level).

Having established both reaction conditions and the structure of the product from the arylation step, we proceeded to evaluate the generality of the reaction. Several aryl boronic acids were reacted with BtOH and these data are summarized in Figure 3. Some comparisons to the previous report[40] are

perhaps instructive. Our reactions were typically conducted with 1.1 equiv. of the aryl boronic acid (except where indicated within parenthesis in Figure 3 and 4 equiv. of pyridine, in CH_2Cl_2 *at room temperature*, in the presence of molecular sieves. The reported reactions were conducted with 3 equiv. of the aryl boronic acid and 10 equiv. of pyridine, in 1,4-dioxane at 40 °C, in the presence of Na_2SO_4.[40] The product yields with phenyl and 2-naphthylboronic acid under both sets of conditions, were comparable (**1**: 77% in both cases, **10**: 73% here *versus* 68% reported[40]). Thus, excess aryl boronic acid may not always be necessary, however, we observed yields to improve with excess aryl boronic acid in some cases where yields were low (**9**, **13**, and **15**). Notably, in both reports, a stoichiometric amount of $Cu(OAc)_2$ was necessary.

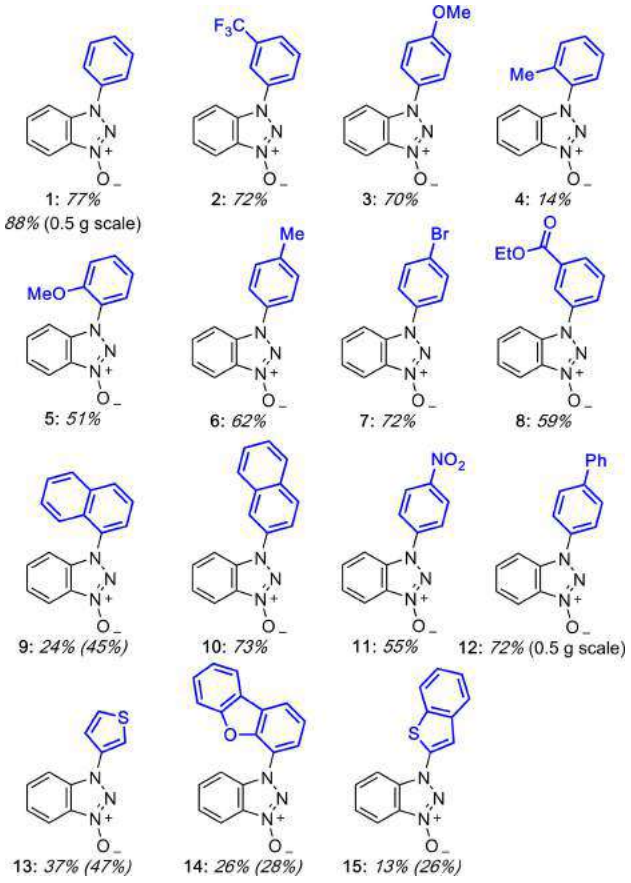


Figure 3. Products and yields from the reactions of BtOH with 1.1 equiv. of aryl boronic acids (yields in parentheses are from reactions with 2 equiv. of the boronic acid).

1-Hydroxy-1*H*-benzotriazoles are relatively straightforward to access[28,42] and so reactions of substituted benzotriazoles with various aryl boronic acids were investigated. Generally good yields were observed with 6-chloro BtOH and a superior yield was

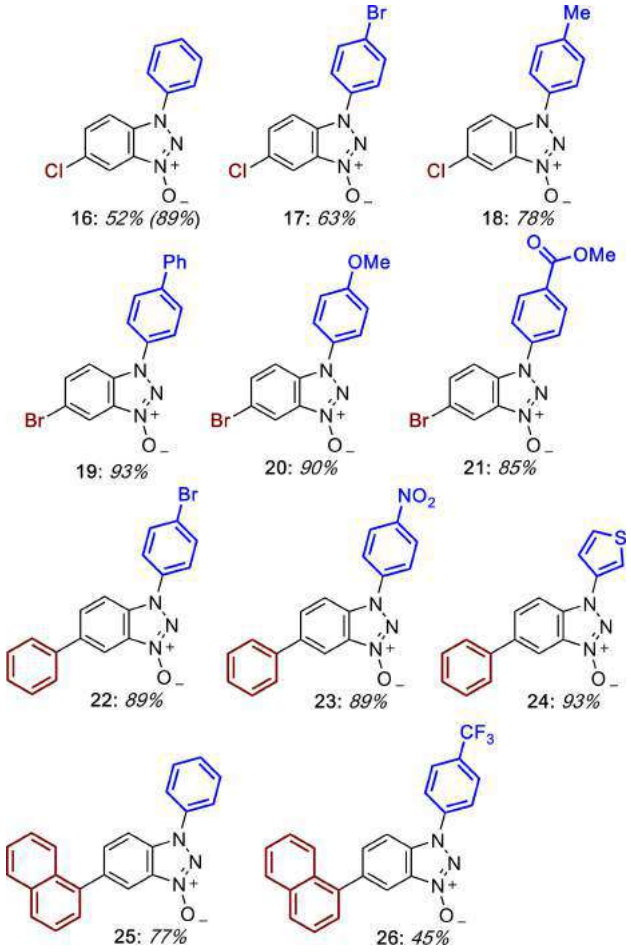
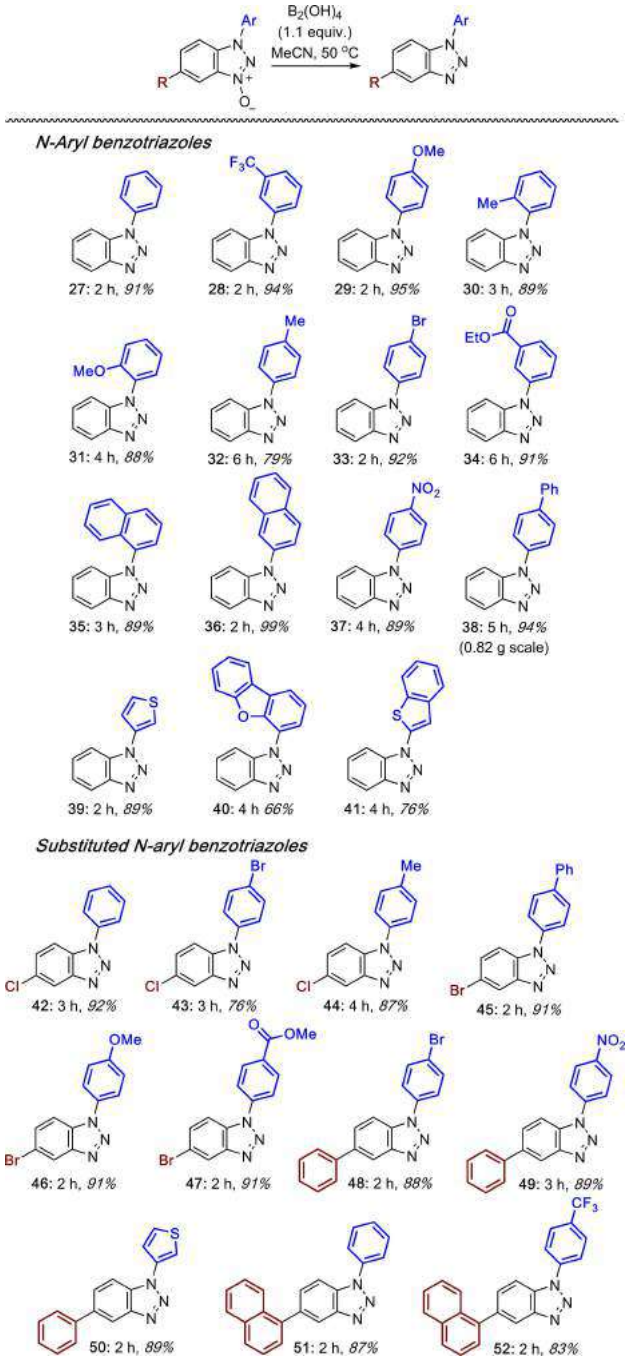


Figure 4. Products and yields from the reactions of 6-substituted BtOH derivatives with 1.1 equiv. of aryl boronic acids (yield in parentheses is from reaction with 2 equiv. of the boronic acid).

obtained in a reaction with 2 equiv. of $PhB(OH)_2$. 6-Bromo BtOH reacted very well with just 1.1 equiv. of the three boronic acids. With 6-phenyl BtOH high yields were attained with all three boronic acids and, notably, excellent yields were obtained with *p*-nitrophenylboronic acid and 3-thienylboronic acid. The latter gave a modest yield with BtOH.

At this stage we decided to reduce all (26) 1-aryl-1*H*-benzotriazole 3-oxides. 1-Hydroxy-1*H*-benzotriazoles were reduced by $B_2(OH)_4$ and Et_3N, under generally mild conditions.[28] In the present cases, because the products of the arylation reactions are already *N*-oxides, they were reduced with only $B_2(OH)_4$. The reduction products are shown in Scheme 3 and as can be seen from the reduction of **12** to **38**, this reaction is also scalable.

Although the X-ray structure of compound **1** had hinted at the regiochemical outcome of these reactions, as a second step the ^{1}H NMR data for 5-chloro-1-(*p*-tolyl)-1*H*-benzotriazole (**44**) were compared to



Scheme 3. Reduction of the 1-aryl-1*H*-benzotriazole 3-oxides with $B_2(OH)_4$.

those reported for 6-chloro-1-(*p*-tolyl)-1*H*-benzotriazole, and these are distinctly different.[43] As definitive proof of the regiospecificity of this chemistry, compound **44** was crystallized and a crystal structure was obtained (Figure 5).[44] This conclusively demonstrated the location of the aryl group relative to the halogen atom, substantiating our initial hypothesis that the *N*-hydroxyl group directs the arylation step, and that it can be used as a removable handle for the regiospecific *N*-arylation of benzotriazoles.

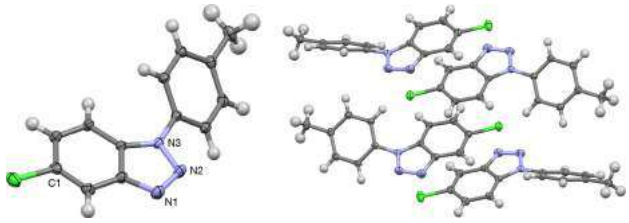
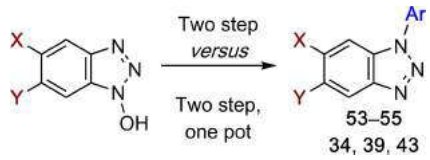


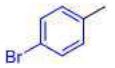
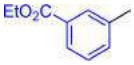
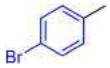
Figure 5. X-ray crystal structure of 5-chloro-1-(*p*-tolyl)-1*H*-benzotriazole (**44**) and crystal packing (thermal ellipsoids are shown at the 50% probability level).

We also investigated reactions of 5,6-dichloro BtOH.[30] In this case, while performing the arylation and reduction as separate reactions, we observed that 5,6-dichloro-1-aryl-1*H*-benzotriazole 3-oxides were difficult to purify and were possibly prone to degradation. Thus, we decided to evaluate the arylation and reduction as a two-step, one-pot process (Table 2, entries 1–3). In three cases, after the *N*-arylation step (with 1.1 equiv. of each aryl boronic acid), the solvent was evaporated and the reduction was performed with $B_2(OH)_4$ in MeCN. In the phenyl case (**53**), a significant improvement in yield was observed, while modest yield improvements were observed in the 2-naphthyl (**54**) and *p*-bromophenyl (**55**) cases. The three final products were obtained without any difficulty. On the basis of the above observations three other two-step, one-pot reactions were conducted with 1.1 equiv. of the aryl boronic acids to assess if there was any advantage to be gained with the latter. Compounds **34**, **39** and **43** were selected (Table 2, entries 4–6) due to the somewhat lower yields observed in the arylation step in these cases. The results indicate that no major yield advantage was gained *via* the two-step, one-pot approach, and that this may be beneficial when the intermediate *N*-oxide is prone to degradation.

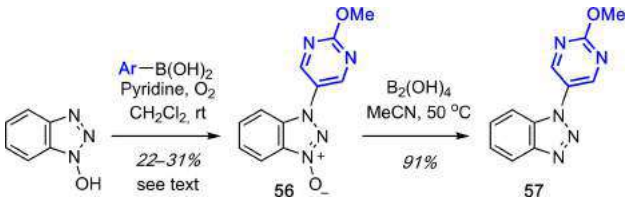
As seen in Figure 1, azaheterocycles at the *N*1 position of a benzotriazole result in compounds with biological activity. Therefore, we decided to introduce a pyrimidine motif *via* the use of 2-methoxypyrimidine-4-boronic acid (Scheme 4). Cautioned by the lower yields observed in the reactions of heteroaryl boronic acids, two reactions were conducted: (a) one with 1.1 equiv. of the pyrimidine boronic acid, at room temperature over 24 h, and (b) the second with 2 equiv. of the boronic acid, also at room temperature, but over 48 h, due to the limited solubility of the boronic acid. As in reactions of BtOH with heteroaryl boronic acids (Figure 3), yields were modest (22% and 31%) with the higher equivalence giving the better yield. Nevertheless, this demonstrates that physiologi-

Table 2. Synthesis of six *N*-aryl-1*H*-benzotriazoles *via* two-step and two-step, one-pot processes.



Entry	X and Y	Ar =	Product	Two step	Two step, one pot
1	X = Y = Cl		**53**	45%	62%
2	X = Y = Cl		**54**	34%	39%
3	X = Y = Cl		**55**	20%	26%
4	X = Y = H		**34**	54%	50%
5	X = Y = H		**39**	33%	34%
6	X = H, Y = Cl		**43**	48%	42%

cally important motifs can be introduced *via* this methodology.



Scheme 4. Synthesis of an *N*-aryl benzotriazole containing a biologically relevant pyrimidine motif.

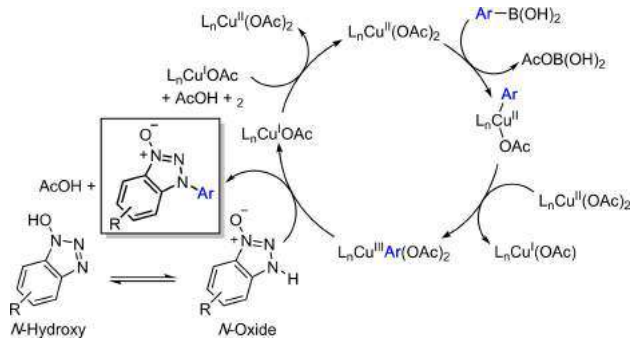
Because these reactions were conducted in a non-polar solvent, we anticipated the *N*1-OH→*N*3 prototropy to be minor and thus, the hydroxyl form to be the major component under the reaction conditions. It is known that substituents on the benzotriazole can influence the extent of this tautomerism but, generally, the *N*-hydroxy form remains major in EtOH, whereas the *N*-oxide predominates in water.[45] However, we were curious to assess the energy differences between the *N*-hydroxy and *N*-oxide tautomers in a set of representative examples, in *vacuo*, in CH_2Cl_2 (the reaction solvent), and in water. For this we chose BtOH, 6-Cl-BtOH, 5,6-di-Cl-BtOH, 6-Ph-BtOH, and the corresponding *N*-oxides. DFT computations were conducted using the B3LYP/6-311++(d,p) basis set and the results are shown in Table 3 (see the Supporting Information for details).

Table 3. Free energy differences between the *N*-oxide and *N*-hydroxy forms ($G_{N\text{-oxide}} - G_{N\text{-hydroxy}}$) in kcal/mol of 1-hydroxy-1*H*-benzotriazole and its derivatives.

X, Y	ΔG_{vacuo}	$\Delta G_{CH_2CL_2}$	ΔG_{H_2O}
H, H	−0.10	−3.46	−4.32
H, Cl	1.11	−2.64	−3.57
Cl, Cl	0.822	−2.63	−3.51
H, Ph	0.23	0.70	0.21

These data indicate that even in CH_2Cl_2, a solvent of modest dielectric constant ($\varepsilon = 9.08$), the *N*-oxide form is preferred for BtOH as well as its 6-Cl and 5,6-di-Cl derivatives, and this preference increases in water ($\varepsilon = 78.54$). However, these computations indicate a slight preference for the *N*-oxide form of BtOH *in vacuo*, but in the remaining three cases the *N*-hydroxy form is preferred. 6-Ph-BtOH is the exception, where under all conditions a preference for the *N*-hydroxy form is seen. Thus, the notion that substituents influence the tautomerism is supported by these computations but they also seem to indicate that the tautomerism could be altered in either direction.

On the basis of the mechanism proposed for the etherification of *p*-cresol with MeOH,[46] we anticipate a pathway as shown in Scheme 5. This proceeds by formation of an aryl-Cu^{II} species followed by oxidation to an aryl-Cu^{III} by another Cu^{II}, reaction of the aryl-Cu^{III} species with BtOH, reductive-elimination from the Cu^{III} intermediate, and a reoxidation of the formed Cu^{I} to Cu^{II}.



Scheme 5. A proposed catalytic cycle for the *N*-arylation of 1-hydroxy-1*H*-benzotriazoles.

In previous work,[40] species leading up to reductive elimination were evaluated by DFT computations. An *N*-coordinated intermediate that would produce the *N*-oxide product was slightly higher in energy (by 0.2 kcal/mol) than the corresponding *O*-coordinated species that would lead to *O*-arylation. However, the transition state leading to *N*-arylation was lower in energy (by 3 kcal/mol) as compared to that leading to

O-arylation. Also, the *N*-oxide product is lower in energy (by 5.9 kcal/mol) than the *O*-aryl isomer. We now offer a computational perspective into the *N*-hydroxy/*N*-oxide tautomerism of BtOH, which is also a part of this overall process.

3 Conclusions

Herein, we have demonstrated a facile approach to the *regiospecific* *N*-arylation of 1*H*-benzotriazoles, which involves a Cu-mediated reaction with aryl boronic acids. We believe that the *N*1-OH→*N*3 prototropy in 1-hydroxy-1*H*-benzotriazoles, even in non-polar solvents, can be utilized to capture the *N*-oxide tautomer with aryl boronic acids. This arylation can then drive the reaction forward. This hypothesis is consistent with the formation of 1-aryl-1*H*-benzotriazole 3-oxides as intermediates. Facile reduction of these *N*-oxides with $B_2(OH)_4$ then yields the *N*1-aryl benzotriazoles. Thus, the hydroxyl moiety functions as an easily disposable arylation-directing group, rendering this a regiospecific *N*-arylation. Both our results and those previously published[40] indicate that the reaction requires stoichiometric $Cu(OAc)_2$, but our reactions can be conducted at room temperature with nearly stoichiometric amounts of aryl boronic acids in most cases. In some cases where yields were lower, these could be improved by increasing the boronic acid stoichiometry to 2 equiv. The present data and those published[40] indicate that contrary to the anticipated formation of *O*-aryl ethers,[39] as from reactions of phenols with aryl boronic acids,[36,37] *N*-arylation is the operative mechanism in the reactions of 1-hydroxy-1*H*-benzotriazoles. As shown here, this can be exploited for the regiospecific *N*-arylation of benzotriazoles.

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References

[1] a) Y. Ren, L. Zhang, C.-H. Zhou, R.-X. Geng, *Med. Chem.* **2014**, *4*, 640–662; b) X.-M. Peng, G.-X. Cai, C.-H. Zhou, *Curr. Top. Med. Chem.* **2013**, *13*, 1963–2010; c) B. V. Suma, N. N. Natesh, V. Madhavan, *J. Chem. Pharm. Res.* **2011**, *3*, 375–381.

[2] *The Chemistry of Benzotriazole Derivatives*, Top. Curr. Chem., Springer International Publishing, Switzerland, **2014**, vol. 43.

[3] a) K. H. G. Verschueren, K. Pumpor, S. Anemülller, S. Chen, J. R. Mesters, R. Hilgenfeld, *Chem. Biol.* **2008**, *15*, 597–606; b) C.-Y. Wu, K.-Y. King, C.-J. Kuo, J.-M. Fang, Y.-T. Wu, M.-Y. Ho, C.-L. Liao, J.-J. Shie, P.-H. Liang, C.-H. Wong, *Chem. Biol.* **2006**, *13*, 261–268; c) M. Bretner, A. Baier, K. Kopaska, A. Najda, A. Schoof, M. Reinholz, A. Lipniacki, A. Piasek, T. Kulikowski, P. Borowski, *Antiviral Chem. Chemother.* **2005**, *16*, 315–326; d) K. Kopańska, A. Najda, J. Żebrowska, L. Chomicz, J. Piekarczyk, P. Myjak, M. Bretner, *Bioorg. Med. Chem.* **2004**, *12*, 2617–2624; e) K.-L. Yu, Y. Zhang, R. L. Civiello, K. F. Kadow, C. Cianci, M. Krystal, N. A. Meanwell, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2141–2144; f) P. Borowski, J. Deinert, S. Schalinski, M. Bretner, K. Ginalski, T. Kulikowski, D. Shugar, *Eur. J. Biochem.* **2003**, *270*, 1645–1653; g) G. Caliendo, G. Greco, P. Grieco, E. Novellino, E. Perissutti, V. Santagada, D. Barbarulo, E. Esposito, A. De Blasi, *Eur. J. Med. Chem.* **1996**, *31*, 207–213; h) G. Caliendo, R. Di Carlo, G. Greco, R. Meli, E. Novellino, E. Perissutti, V. Santagada, *Eur. J. Med. Chem.* **1995**, *30*, 77–84.

[4] a) W. D. Thomas, J. Powers, E. J. Sullivan, S. Punna, A. Novack, C. Hu, A. M. K. Pennell, P. Zhang, A. Melikian, T. T. Charvat, S. Ungashe, *Aust. Pat. Appl.* **2009**, AU 2008302672A1; b) D. Mo, W. Shi, X. Ma, H. Bi, G. Su, C. Chen, N. Zou, *Faming Zhuanlo Shenqing* **2016**, CN 105820132A.

[5] F. Ohsawa, S. Yamada, N. Yakushiji, R. Shinozaki, M. Nakayama, K. Kawata, M. Hagaya, T. Kobayashi, K. Kohara, Y. Furusawa, C. Fujiwara, Y. Ohta, M. Makishima, H. Naitou, A. Tai, Y. Yoshikawa, H. Yasui, H. Kakuta, *J. Med. Chem.* **2013**, *56*, 1865–1877.

[6] W. S. Palmer, M. Alam, H. B. Arzeno, K.-C. Chang, J. P. Dunn, D. M. Goldstein, L. Gong, B. Goyal, J. C. Hermann, J. H. Hogg, G. Hseih, A. Jahangir, C. Janson, S. Jin, R. U. Kammlott, A. Kuglstatter, C. Lukas, C. Michoud, L. Niu, D. C. Reuter, A. Shao, T. Silva, T. A. Trejo-Martin, K. Stein, Y.-C. Tan, P. Tivitmahaisoon, P. Tran, P. Wagner, P. Weller, S.-Y. Wu, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1486–1492.

[7] P. S. Narinder, K. Rajesh, N. P. Deo, S. Sarita, S. Om, *Int. J. Biol. Chem.* **2011**, *5*, 193–199.

[8] S. K. Awasthi, N. Mishra, S. K. Dixit, A. Singh, M. Yadav, S. S. Yadav, S Rathaur, *Am. J. Trop. Med. Hyg.* **2009**, *80*, 764–768.

[9] N. Mishra, P. Arora. B. Kumar, L. C. Mishra, A. Bhattacharya, S. K. Awasthi, V. K. Bhasin, *Eur. J. Med. Chem.* **2008**, *43* 1530–1535.

[10] a) M. Finšgar, I. Milošev, *Corros. Sci.* **2010**, *52*, 2737–2749; b) N. K. Allam, A. A. Nazeer, *J. Appl. Electrochem.* **2009**, *39*, 961–969; c) M. M. Antonijevic, M. B. Petrovic, *Int. J. Electrochem. Sci.* **2008**, *3*, 1–28.

[11] S. Weiss, J. Jakobs, T. Reemtsma, *Environ. Sci. Technol.* **2006**, *40*, 7193–7199.

[12] R. D. Theys, G. Sosnovsky, *Chem. Rev.* **1997**, *97*, 83–132.

[13] a) R. R. Kale, V. Prasad, P. P. Mohapatra, V. K. Tiwari, *Monatsh. Chem.* **2010**, *141*, 1159–1182; b) A. R. Katritzky, K. Suzuki, Z. Wang, *Synlett* **2005**, 1656–1665; c) A. R. Katritzky, B. V. Rogovoy, *Chem. Eur. J.* **2003**, *9*, 4586–4593; d) A. Paio, A. Zaramella, R. Ferritto, N. Conti, C. Marchioro, P. Seneci, *J. Comb. Chem.* **1999**, *1*, 317–325; e) A. R. Katritzky, S. Rachwal, G. J. Hitchings, *Tetrahedron* **1991**, 47, 2683–2732.
[14] See for examples: a) M. Kallitsakis, E. Loukopoulos, A. Abdul-Sada, G. J. Tizzard, S. J. Coles, G. E. Kostakis, I. N. Lykakis, *Adv. Synth. Catal.* **2016**, *359*, 138–145; b) M. J. Go, J. M. Lee, K. M. Lee, C. H. Oh, H. Chang, K. H. Park, S. H. Kim, M. Kim, H.-R. Park, M. H. Park, Y. Kim, J. Lee, *Polyhedron* **2014**, *67*, 286–294; c) W. Du, P. Wu, Q. Wang, Z. Yu, *Organometallics* **2013**, *32*, 3083–3090; d) A. K. Verma, R. R. Jha, R. Chaudhary, R. K. Tiwari, A. K. Danodia, *Adv. Synth. Catal.* **2013**, *355*, 421–438; e) W. Yan, X. Ye, N. G. Akhmedov, J. L. Peterson, X. Shi, *Org. Lett.* **2012**, *14*, 2358–2361.
[15] For some recent examples, see: a) K. J. Okolotowicz, P. Bushway, M. Lanier, C. Gilley, M. Mercola, J. R. Cashman, *Bioorg. Med. Chem.* **2015**, *23*, 5282–5292; b) H. Kakuta, N. Yakushiji, R. Shinozaki, F. Ohsawa, S. Yamada, Y. Ohta, K. Kawata, M. Nakayama, M. Hagaya, T. Oohashi, H. Yasui, Y. Yoshikawa, *ACS Med. Chem. Lett.* **2012**, *3*, 427–432; c) M. Chen, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 4247–4250; d) K. A. Nolan, M. P. Humphries, J. Barnes, J. R.; Doncaster, M. C. Caraher, N. Tirelli, R. A. Bryce, R. C. Whitehead, I. J. Stratford, *Bioorg. Med. Chem.* **2010**, *15*, 696–706.
[16] E. Łukasik, Z. Wróbel, *Synlett* **2014**, *25*, 1987–1990.
[17] a) L. Campbell-Verduyn, P. H. Elsinga, L. Mirfeizi, R. A. Dierckx, B. L. Feringa, *Org. Biomol. Chem.* **2008**, *6*, 3461–3463; b) F. Shi, J. P. Waldo, Y. Chen, R. C. Larock, *Org. Lett.* **2008**, *10*, 2409–2412.
[18] R. K. Kumar, M. A. Ali, T. Punniyamurthy, *Org. Lett.* **2012**, *13*, 2102–2105.
[19] J. Zhou, J. He, B. Wang, W. Yang, H. Ren, *J. Am. Chem. Soc.* **2011**, *133*, 6868–6870.
[20] P. López-Alvarado, C. Avendaño, J. C. Menéndez, *J. Org. Chem.* **1995**, *60*, 5678–5682.
[21] J. C. Antilla, J. M. Baskin, T. E. Barder, S. L. Buchwald, *J. Org. Chem.* **2004**, *69*, 5578–5587.
[22] H.-G. Lee, J.-E. Won, M.-J. Kim, S.-E. Park, K.-J. Jung, B. R. Kim, S.-G. Lee, Y.-J. Yoon, *J. Org. Chem.* **2009**, *74*, 5675–5678.
[23] C. Mukhopadhyay, P. K. Tapaswi, R. J. Butcher, *Org. Biomol. Chem.* **2010**, *8*, 4720–4729.
[24] Q.-L. Liu, D.-D. Wen, C.-C. Huang, Q.-L. Li, Y.-M. Zhu, *Helv. Chim. Acta* **2010**, *93*, 1350–1354.
[25] R. R. Kale, V. Prasad, H. A. Hussain, V. K. Tiwari, *Tetrahedron Lett.* **2010**, *51*, 5740–5743.
[26] K, Sun, Z. Zhu, J. Sun, L. Liu, X. Wang, *J. Org. Chem.* **2016**, *81*, 1476–1483.
[27] Z.-X. Wang, W.-M. Shi, H.-Y. Bi, X.-H. Li, G.-F. Su, D.-L. Mo, *J. Org. Chem.* **2016**, *81*, 8014–8021.
[28] V. Gurram, H. K. Akula, R. Garlapati, N. Pottabathini, M. K. Lakshman, *Adv. Synth. Catal.* **2015**, *357*, 451–462.
[29] H. P. Kokatla, P. F. Thomson, S. Bae, V. R. Doddi, M. K. Lakshman, *J. Org. Chem.* **2011**, *76*, 7842–7848.
[30] V. Basava, L. Yang, P. Pradhan, M. K. Lakshman, *Org. Biomol. Chem.* **2016**, *14*, 7069–7083.
[31] A. T. Londregan, D. W. Piotrowski, J. Xiao, *Synlett* **2013**, *24*, 2695–2700.
[32] R. Bosch, G. Jung, W. Winter, *Acta Crystallogr.* **1983**, *C39*, 1089–1092.
[33] K. Horiki, *Tetrahedron Lett.* **1977**, *18*, 1897–1900.
[34] A. R. Katritzky, N. Malhotra, W.-Q. Fan, E. Anders, *J. Chem. Soc. Perkin Trans. 2* **1991**, 1545–1547.
[35] B. D. Brink, J. R. DeFrancisco, J. A. Hillner, B. R. Linton, *J. Org. Chem.* **2011**, *76*, 5258–5263.
[36] D. M. T. Chan, K. L. Monaco, R. P. Wang, M. P. Winters, *Tetrahedron Lett.* **1998**, *39*, 2933 – 2936.
[37] D. A. Evans, J. L. Katz, T. R. West, *Tetrahedron Lett.* **1998**, *39*, 2937 – 2940.
[38] P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan, A. Combs, *Tetrahedron Lett.* **1998**, *39*, 2941 – 2944.
[39] P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, K. M. Averill, D. M. T. Chan, A. Combs, *Synlett* **2000**, 674–676.
[40] W.-M. Shi, F.-P. Liu, Z.-X. Wang, H.-Y. Bi, C. Liang, L.-P. Xu, G.-F. Su, D.-L. Mo, *Adv. Synth. Catal.* **2017**, *359*, 2741–2746.
[41] CCDC 1812840 (compound **1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via* www.ccdc.cam.ac.uk/data_request/cif.
[42] See for examples: a) N. J. Leonard, K. Golankiewicz, *J. Org. Chem.* **1969**, *34*, 359–365; b) J. Fu, Y. Yang, X.-W. Zhang, W.-J. Mao, X.-M. Zhang, H.-L. Zhu, *Bioorg. Med. Chem.* **2010**, *18*, 8457–8462.
[43] 500 MHz ^{1}H NMR data for 5-chloro-1-(*p*-tolyl)-1*H*-benzotriazole (**44**) in $CDCl_3$: 8.12 (s, 1H, ArH), 7.66–7.62 (m, 3H, ArH), 7.50 (d, J = 8.8 Hz, 1H, ArH), 7.42 (d, J = 7.2 Hz, 2H, ArH), 2.48 (s, 3H, Me). 300 ^{1}H NMR data for 6-chloro-1-(*p*-tolyl)-1*H*-benzotriazole in $CDCl_3$:[23] 8.05 (d, J = 8.6 Hz, 1H, ArH), 7.71 (d, J = 1.5 Hz, 1H, ArH), 7.61 (d, J = 8.3 Hz, 2H, ArH), 7.40 (2 d merged as a t, J = 8.3 and 8.6 Hz, 3H, ArH), 2.48 (s, 3H, Me).
[44] CCDC 1812841 (compound **44**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via* www.ccdc.cam.ac.uk/data_request/cif.
[45] F. T. Boyle, R. A. Y. Jones, *J. Chem. Soc. Perkin Trans. 2* **1973**, 160–164.
[46] A. E. King, T. C. Brunold, S. S. Stahl, *J. Am. Chem. Soc.* **2009**, *131*, 5044–5045.

FULL PAPER

The Disappearing Director: The Case of Directed *N*-Arylation *via* a Removable Hydroxyl Group

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