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Microwave-Assisted Preparation of Aryltetrazoleboronate Esters

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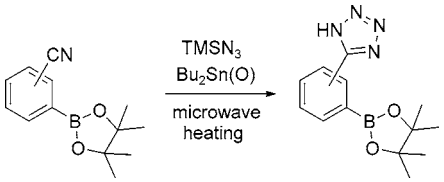
ABSTRACT



The addition of azido trimethylsilane to arylnitrileboronate esters is shown to proceed rapidly in dimethoxyethane to give aryltetrazoleboronate esters in moderate to good yields, with dibutyltin oxide as catalyst.

The growing demand for fast organic transformations within the synthetic community has resulted in considerable attention in the area of microwave-assisted organic synthesis.[1] The rapid and homogeneous heating observed in microwave-assisted organic synthesis is a clear advantage over conventional thermal techniques. The dramatic reduction in reaction time obtained with microwave heating has recently been coupled with automation to further improve the preparative efficiency of this powerful technique.

The tetrazole functional group is of particular interest in medicinal chemistry due to its potential role as a bioisostere of the carboxyl group.[2] Tetrazoles can be regarded as nitrogen analogues of carboxylic acids. Both groups have similar steric requirements and pK_a's, which contribute to the overall observed bioisosterism. Generally, a more favorable pharmacokinetic profile (i.e., increased biological absorption and greater metabolic stability) can be obtained by the bioisosteric replacement of carboxylic acids with tetrazoles while still retaining the desired pharmacological effect.

Several methods[3] for the preparation of tetrazoles from nitriles have been documented in the literature. Most methods require long reaction times measured in hours or days. However, Alterman and Hallberg[4] have reported the microwave-assisted preparation of tetrazoles from nitriles, requiring only minutes for complete conversion.

In support of our therapeutic projects, we required a fast, efficient route to aryltetrazoleboronic acids. It is well-known, however, that boronic acids tend to be difficult to derivatize by solution-phase methods. Difficulties can be attributed, in part, to their troublesome isolation and purification. As a result, chemical transformations on arylboronic acids[5] are

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(3) (a) Mihina, J. S.; Herbst, R. M. *J. Org. Chem.* **1950**, *15*, 1082−1092. (b) Finnegan, W. G.; Henry, R. A.; Lofquist, R. *J. Am. Chem. Soc.* **1958**, *80*, 3908−3911. (c) Grzonka, Z.; Liberek, B. *Rocz. Chem.* **1971**, *45*, 967−980. (d) Dunica, J. V.; Pierce, M. E.; Santella, J. B., III. *J. Org. Chem.* **1991**, *56*, 2395−2400. (e) Ostrovskii, V. A.; Poplavskii, V. S.; Koldobskii, G. I.; Erusalinkii, G. B. *Khim. Geterotsikl. Soedin.* **1992**, 1214−1217. (f) Huff, B. E.; Staszak, M. A. *Tetrahedron Lett.* **1993**, *34*, 8011−8014. (g) Wittenberger, S. J.; Donner, B. G. *J. Org.* Chem. **1993**, *58*, 4139−4141. (h) Kumar, A.; Narayanan, R.; Shechter, H. *J. Org. Chem.* **1996**, *61*, 4462−4465. (i) Koguro, K.; Oga, T.; Mitsui, S.; Orita, R. *Synthesis* **1998**, 910−914. (j) Curran, D. P.; Hadida, S.; Kim, S.-Y. *Tetrahedron* **1999**, *55*, 8997−9006. (k) Demko, D. P.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 7945−7950.

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(5) (a) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724. (b) Chen, D.; Qing, F.; Huang, Y. *Org. Lett.* **2002**, *4*, 1003−1005. (c) Gravel, M.; Thompson, K. A.; Zak, M.; Berube, C.; Hall, D. G. *J. Org. Chem.* **2002**, *67*, 3−15. (d) Spencer, J.; Burd, A. P.; Goodwin, C. A.; Merette, S. A. M.; Scully, M. F.; Adatia, T.; Deadman, J. J. *Tetrahedron* **2002**, *58*, 1551−1556. (e) Holland, R.; Spencer, J.; Deadman, J. J. *Synthesis* **2002**, *16*, 2379−2382.

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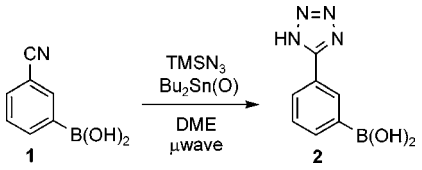
quite limited in scope. Therefore, we deemed a contribution in this area appropriate.

Initially, we investigated the reaction of 3-cyanophenylboronic acid **1** with azidotrimethylsilane in the presence of dibutyltin oxide. Several sets of conditions were screened under microwave heating, and the results are summarized in Table 1. Among the conditions tested, entries 5 and 6

Table 1. Optimization of Reaction Conditions



entry	$TMSN_3$ (equiv)	$Bu_2Sn(O)$ (equiv)	*T* (°C)	time (min)	convn[a] (%)
1	1	0.05	110	10	25
2	2	2.00	110	10	31
3	2	0.10	110	10	55
4	2	0.10	130	10	55
5	2	0.10	150	10	60
6	2	0.10	160	10	60

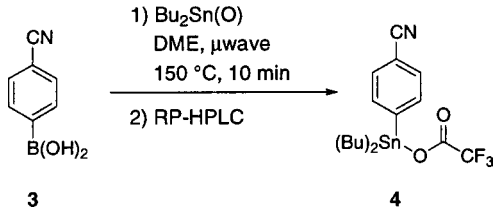
[a] Determined by integration of an HPLC total absorption chromatogram from 190 to 360 nm.

were found to be the most effective. The conversion of **1** to 3-tetrazolephenylboronic acid **2** was improved from 25% (Table 1, entry 1) to 55% (entry 3) at 110 °C by using 2 equiv of $TMSN_3$ and 10 mol % $Bu_2Sn(O)$. A slight improvement was realized with increasing temperature, resulting in 60% conversion at 150 °C (entry 5).

The inability to realize complete conversion to tetrazole **2**, despite higher dibutyltin oxide loading, forced us to consider whether the dibutyltin oxide was consumed by reaction with the boronic acid. Consumption of dibutyltin oxide would presumably result in the premature termination of the catalytic cycle since it is proposed[3h] to be operative in the addition of trimethylsilyl azide to nitriles. The most obvious possible products from this reaction would be insertion of the tin oxide into the boronic acid cyclic trimer to form a trioxastannadiborinane[6] or formation of a four membered diorganotin borate.[7]

Heterocycles that contain an Sn−O−B−C bonding arrangement are known,[8] but their chemical behavior has not been extensively studied. In fact, the thermally driven reaction of dialkyltin oxides with arylboronic acids has been shown to provide three different products, each with Sn−O−B−C links.[6a,9] We were led to investigate this reaction in greater detail because of our belief that formation of these adducts would be reversible under our tetrazole-forming reaction conditions and thus not explain the incomplete conversion to tetrazole **2**. Our model system, to this end, involved the reaction of 4-cyanophenylboronic acid **3** with dibutyltin oxide (Scheme 1).

Scheme 1. Preparation of Dibutylaryltin Trifluoroacetate **4**



We quickly discovered that a one-to-one ratio of **3** to the tin oxide was necessary for complete consumption of the boronic acid. Although the reaction was quite clean by LC/MS analysis, the mass spectra were not consistent with any expected products and we were unable to isolate the purified product of this reaction by recrystallization, silica, or Florosil chromatography. A further complication was that the crude compound slowly decomposed as determined by ^1H NMR analysis under ambient conditions.

We were surprised to find that preparative reversed-phase chromatography provided a clean stable compound, which allowed us to obtain full characterization data. It was not until we completed a single-crystal X-ray diffraction analysis that we became confident in the structure assigned to **4** (Figure 1).

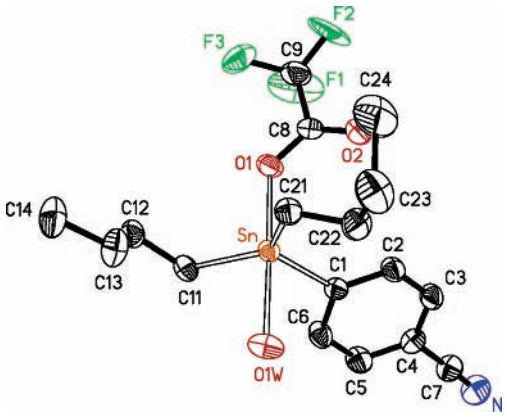


Figure 1. X-ray crystal structure of **4**.

It appears that under the microwave conditions **3** undergoes ipso replacement of boron by dibutyltin oxide. The resulting tin hydroxide, of limited stability,[10] is converted[11] to the trifluoroacetate during reversed-phase purification. To our knowledge, this ipso replacement of boron by tin is unreported in the chemical literature.

(6) (a) Brown, P.; Mahon, M. F.; Molloy, K. C. *J. Chem. Soc., Dalton Trans.* **1992**, *24*, 3503−3509. (b) For a related compound, see: Beckmann, J.; Jurkschat, K.; Pieper, N.; Schurmann, M. *Chem. Commun.* **1999**, *12*, 1095−1096.

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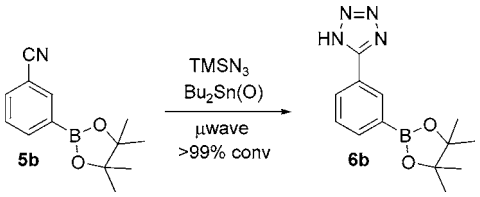
(8) (a) Coles, S. J.; Hibbs, D. E.; Hursthouse, M. B.; Beckett, M. A.; Owen, P.; Varma, K. S. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2002**, *E58*, m65−67. (b) Beckett, M.; Owen, P.; Varma, K. S. *J. Organomet. Chem.* **1999**, *588*, 107−112.

The disordered trifluoroacetate group as well as a coordinated water molecule are clearly visible from the X-ray structure (Figure 1). The Sn−O bond lengths of 2.220 and 2.344 Å correlate well with related structures.[12] In addition, the Sn−C bond lengths range from 2.131 to 2.140 Å, which also compares well to related compounds. The crystal structure also implies a hydrogen-bonding network of the water molecule to a neighboring molecules' nitrogen atom and another neighboring molecules' trifluoroacetate carbonyl oxygen.

To circumvent the above-mentioned impediments, it was clear that an alternate approach would be needed. We envisioned that protection of the boronic acid as the pinacol ester may help to alleviate the problem at hand. The pinacolboronate ester was readily prepared by allowing the boronic acid in DME to react with a slight excess of pinacol in the presence of magnesium sulfate. Filtration of this reaction slurry provides a solution of the boronate ester, which could be used directly in our tetrazole formation reactions. Indeed, when the pinacol ester **5b** was subjected to the conditions found in entry 5 of Table 1 the formation of the tin-containing byproduct was not observed and the percent conversion was improved to 78% (Scheme 2). After

Scheme 2. Preparation of Aryltetrazole Boronate[a]



[a] Percent conversion determined by integration of an HPLC total absorption chromatogram from 190 to 360 nm.

further investigation, it was found that when the reaction was subjected to a second reaction cycle greater than 99% conversion could be obtained. In a typical experiment,[13] a mixture of 2 equiv of $TMSN_3$ and **5b** in DME was irradiated at 150 °C for 10 min in the presence of 10 mol % $Bu_2Sn(O)$. After the addition of an additional 2 equiv of $TMSN_3$ and 10 mol % $Bu_2Sn(O)$, the mixture was subjected to another microwave heating cycle (150 °C, 10 min) to complete the reaction. Interestingly, the *N*-(trimethylsilyl)tetrazole species that is associated with the reaction between nitriles and alkylsilyl azide reagents was never observed; only the 1*H*-tetrazole was detected, most likely due to a trace amount of water present in the reaction.

For comparison, the reaction outlined in Scheme 2 was also conducted under conventional thermal techniques. Utilizing the same conditions as the microwave-assisted reaction [i.e., 150 °C (sealed tube), 10 min, 2 cycles] we observed similar percent conversion (90%) conventionally as compared to the reaction when it was conducted with microwave heating (99%). However, under refluxing conditions the reaction required more than 22 h for complete conversion. Overall, these comparisons demonstrated that microwave heating was a more effective and convenient method than conventional thermal techniques.

Ten different arylnitrile boronates **5** were selected as starting materials and utilized for the synthesis of a set of aryltetrazole boronates. The nitrile boronates were either commercially available or prepared from the requisite bromide by one of the following methods: (1) metal−halogen exchange and trapping with 2-isopropoxypinacol borolane[14] or (2) palladium-catalyzed boronation with bis-(pinacolato)diboron.[15] The crude reaction mixtures were analyzed via HPLC with a 0.05% formic acid modifier.[16]

All of the nitrile boronates were smoothly converted to the corresponding tetrazoles in moderate to good yields (Table 2). However, in the case of 2-hydroxybenzonitrile, pinacol ester **6h**, it was discovered that three reaction cycles were required for complete conversion. Although there was no clear correlation between the aryl substituents and the reaction outcome, the reaction did prove to tolerate a variety of functionalities.

Product isolation was accomplished by either Florisil flash chromatography or aqueous workup.[17] Florisil chromatography was found to be our preferred method of isolation. It allowed the complete reaction solution to be directly loaded

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(13) **General Procedure.** A microwave vial was charged with (3-cyanophenyl)boronic acid, pinacol ester (344 mg, 1.5 mmol), azidotrimethylsilane (0.40 mL, 3.0 mmol), dibutyltin oxide (37 mg, 0.15 mmol), and DME (2.2 mL). The reaction mixture was heated to 150 °C for 10 min in a CEM Explorer microwave. After the mixture was cooled to room temperature, additional azidotrimethylsilane (0.40 mL, 3.0 mmol) and dibutyltin oxide (37 mg, 0.15 mmol) were added, and the mixture was reheated for 10 min at 150 °C. The reaction solution was loaded onto a Florisil column (35 g) and eluted with 20% CH_2Cl_2/heptane → 10% methanol/CH_2Cl_2 to furnish the product (3-tetrazolephenyl)boronic acid, pinacol ester **6b** (342 mg, 83%). ^{1}H NMR (DMSO-d_6): δ 8.37 (s, 1H), 8.16 (d, 1H, J = 7.9 Hz), 7.80 (d, 1H, J = 7.2 Hz), 7.58 (t, 1H, J = 7.6 Hz), 1.34 (s, 12H). ^{13}C NMR (DMSO-d_6): δ 156.5, 136.1, 132.6, 129.6, 128.8, 125.6, 83.9, 24.7. HRMS: *m/z* $(M + H)^+$ calcd for $C_{13}H_{17}BN_4O_2$ 273.1523, found 273.1519.

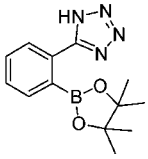
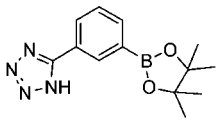
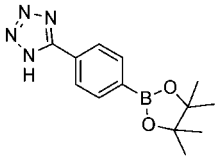
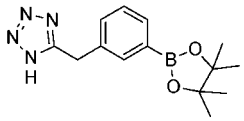
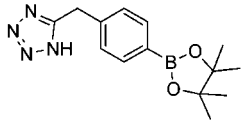
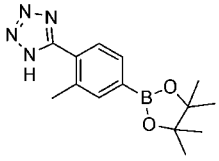
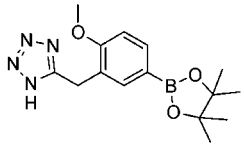
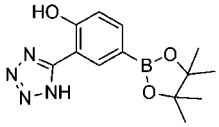
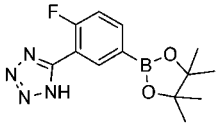
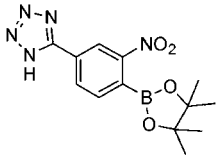
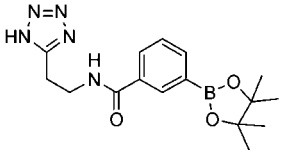
(14) Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179−13184.

(15) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508−7510.

(16) The use of 0.05% trifluoroacetic acid as a modifier resulted in hydrolysis of the pinacol ester functionality, during HPLC analysis.

(17) **Typical Aqueous Workup.** After completion of the reaction, the solvent was removed and the residue was taken up in ether. The ether was extracted with 2 N NaOH, and the combined aqueous layers were washed with ether. The aqueous layer was then acidified to pH 4, and the resulting precipitate was collected.

Table 2. Synthesis of Aryltetrazole Boronates **6**

entry	product		isolated yield (%)[a]
1		**6a**	65
2		**6b**	83
3		**6c**	84
4		**6d**	70
5		**6e**	65
6		**6f**	87
7		**6g**	93
8		**6h**	56
9		**6i**	85
10		**6j**	48
11		**6k**	60

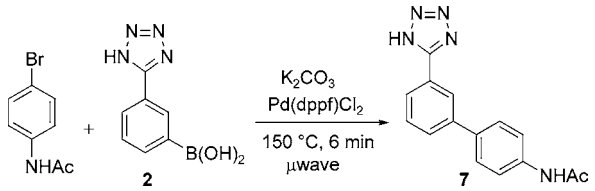
[a] Compounds **6a**−**f** were isolated by Florisil flash chromatography. Compounds **6g**−**k** were isolated by aqueous workup as free boronic acids.

onto the column, thus minimizing contact to toxic tin-containing compounds. In some cases, hydrolysis of the pinacol ester on Florisil was observed, which resulted in troublesome product recovery. In those cases, standard aqueous workup conditions were employed to isolate the free boronic acid.

This rapid method was easily transferred to larger scale applications. We found that the reaction could be run at higher concentration in a sealed 80 mL microwave vessel. In fact, when the reaction was scaled up to 15 mmol and conducted under identical microwave conditions the desired product, 3-tetrazolephenylboronic acid, was isolated in nearly quantitative yield.

To demonstrate the synthetic utility of these boronic acids we also conducted a palladium-catalyzed Suzuki coupling (Scheme 3). To our knowledge, previously reported cou-

Scheme 3. Suzuki Coupling of Unprotected Tetrazole



plings[18] with tetrazole-containing boronic acids required protection at the N-2 position. Apparently, in these cases tetrazole protection was deemed necessary as the free tetrazole acted as a poison with palladium catalysts. In our unprotected case, however, 3-tetrazolephenylboronic acid was coupled with 4-bromoacetanilide in the presence of $Pd(dppf)Cl_2$ to provide **7** in 74% unoptimized isolated yield.

In conclusion, we have developed a convenient method for the preparation and isolation of aryltetrazoleboronates. As part of our study, we demonstrated that protection of the boronic acid functionality as the pinacol ester greatly increased preparative efficiency. Furthermore, the use of microwave irradiation was shown to provide rapid access to aryltetrazoleboronate derivatives.

Supporting Information Available: Experimental procedures and characterization data (^1H and ^{13}C NMR) for all compounds, including X-ray data for compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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