Preparation of *n*-Butyl-2-(2'-triphenylmethyltetrazol-5-yl)phenylborinic Acid

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Understanding the mechanism of formation of an impurity in the key step of the synthesis of Losartan (**1**) helped devise a procedure to synthesize the title compound in high yield.

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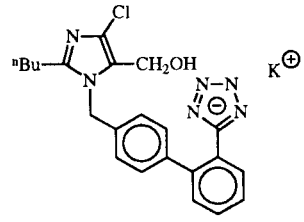
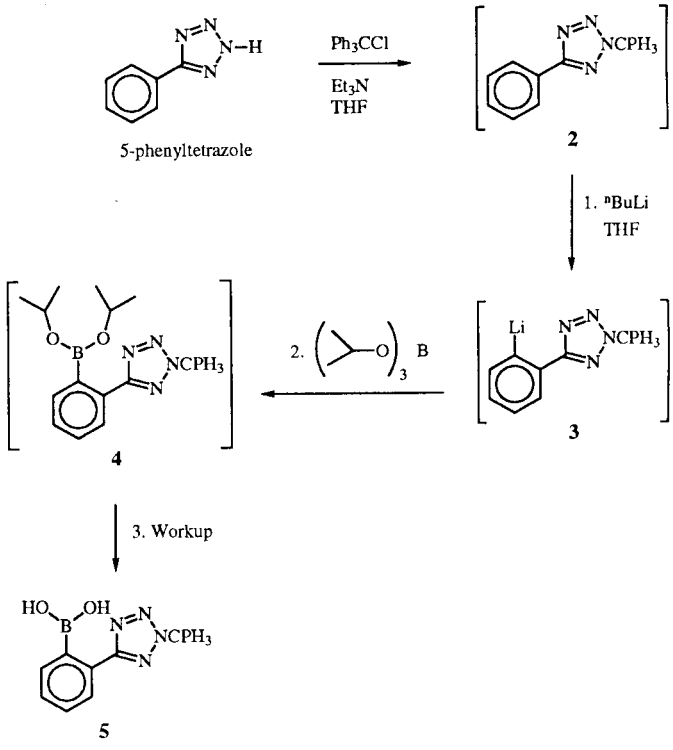
Over the past 30 years several components of the renin-angiotensin system have been pursued as theraputic targets, *e.g.* angiotensin converting enzymes, and renin inhibitors. These enzyme inhibitors lower plasma concentrations of the vasoconstrictor angiotensin II. Recently, a highly efficient, convergent approach to the angiotensin II receptor antagonist Losartan (**1**) [1] was published [2]. This methodology overcomes many of the drawbacks associated with previously reported syntheses such as handling of azide derivatives, disposals of heavy metals, use of halogenated solvents, and starting with expensive raw materials. In the synthesis of one of the key intermediates of this new process, 2-(2'-triphenylmethyltetrazol-5-yl)-phenylboronic acid (**5**), an impurity was generated and was identified as *n*-butyl-2-(2'-triphenylmethyl-tetrazol-5-yl)phenylborinic acid (**9**). Our effort to elucidate the structure and prepare the compound is the focus of this report.



Losartan® **1**

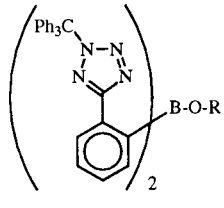
Scheme 1



The synthesis of **5** is summarized in Scheme 1; 5-phenyltetrazole was first protected with the trityl group. The reaction mixture was filtered to remove triethylamine hydrochloride. Compound **2** contained in the filtrate was then lithiated on the tetrazole-bearing phenyl ring with *n*-butyllithium to generate exclusively the *ortho*-lithiated compound **3**. This lithium salt was treated with triisopropyl borate to yield the boronic acid **5** after hydrolytic work up. Compound **9** was found as an impurity in the product.

Before its identification as **9**, the impurity was suspected to be generated by two moles of lithium salt **3** attacking one triisopropyl borate to form the diarylborinate ester **6** which would hydrolyze to form **7** upon work up. To enhance the chance for this to happen, the lithium salt slurry was treated with only half an equivalent of triisopropyl borate. Analyses of the reaction mixture by hplc showed area percents of 41% **5**, 44% **2**, and 11% impurity; another reaction mixture showed 43% **5**, 45% **2**, and 7% impurity. These data suggested that the lithium salt **3** did not readily attack a triisopropyl borate molecule twice.

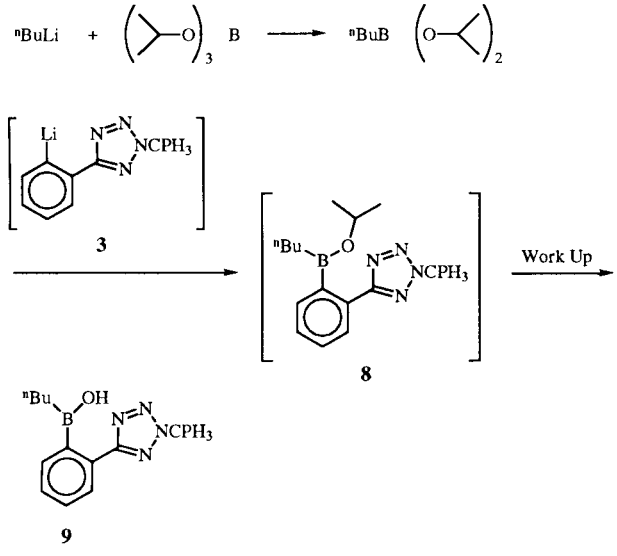
The clue as to how **9** was formed was unveiled in two



R = iPr **6**
R = H **7**

experiments in which excess amounts of *n*-butyllithium were charged to the solution of **2** and increased amounts of **9** were found in the reaction mixture by hplc assays. Thus when 1.25 and 2.0 equivalents of *n*-butyllithium were charged, assays of the reaction mixtures showed 15 and 51 area percents of **9** along with 80 and 23 area percents of **5** respectively. These data suggested the following mechanism for the formation of **9**: excess *n*-butyllithium attacked triisopropyl borate to give diisopropyl *n*-butylboronate which then reacted with **3** to yield **9** after hydrolytic work up. The preparation of pure **9** in 85% yield was thus achieved by preparation of diisopropyl *n*-butylboronate from *n*-butyllithium and triisopropyl borate in one flask, then cannulation of this solution to react with **3** prepared in a second flask.

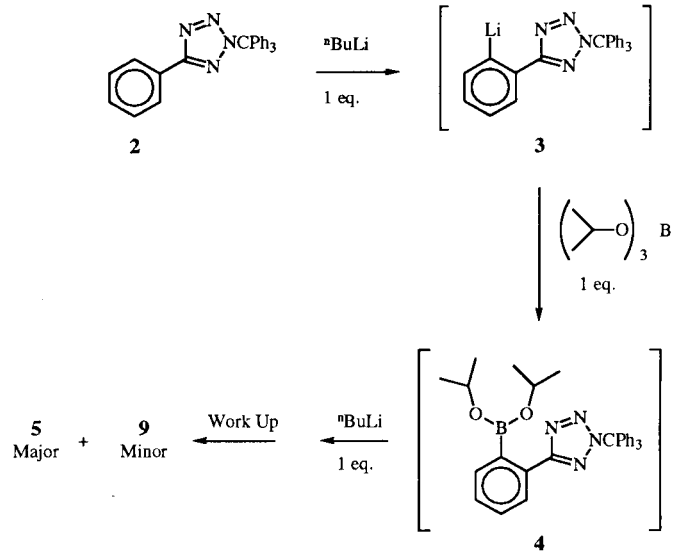
Scheme 2



An alternative route to synthesize **9** was explored but failed. As shown in Scheme 3, starting with isolated **2**, the diisopropyl 2-(2'-triphenylmethyltetrazol-5-yl)phenylboronate (**4**) was generated. A sample of this mixture was drawn and assayed to show area percents of 84% **5**, 8% **2**, and 8% impurity. One equivalent of *n*-butyllithium was then added to the mixture. A 30 minute sample was assayed to show 79% **5**, 6% **2**, and 11% impurity. An overnight sample was assayed to show 77% **5**, no **2**, and 12% impurity. This data showed only a marginal increase in the amount of impurity by one extra equivalent of *n*-butyllithium and thus it was not likely that the impurity was generated by *n*-butyllithium attacking **4**. Conversely, it showed the boron atom in diisopropyl 2-(2'-triphenylmethyltetrazol-5-yl)phenylboronate (**4**) was well shielded from further attack by *n*-butyllithium or another lithium salt **3**.

This study helped refine the process for the production of **5** which is a key intermediate in the synthesis of Losartan (**1**).

Scheme 3



EXPERIMENTAL

General Methods.

All reactions that involved organolithium compounds were conducted under a dry nitrogen atmosphere using oven dried glassware and syringes. Tetrahydrofuran was dried over 3A sieves to < 60 ppm water. Hplc method: A 250 x 4 mm Nucleosil C18 column with 5 micron packing is used. The gradient mobile phase is A = 0.1% phosphoric acid (*p*H 2.5 +/- 0.1), B = acetonitrile, and C = methanol; changing from A:B:C = 40:50:10 at start to A:B:C = 20:70:10 at 10 minutes. The flow is 1.5 ml/minute with oven at 40°. Run time is 20 minutes. Samples are dissolved in acetonitrile with triethylamine (one drop per liter). Elemental analyses were performed by Quantitative Technologies, Inc. Melting points were determined on an Electrothermal apparatus and are uncorrected.

Butyl[2-[2'-(triphenylmethyl)-2H-tetrazol-5-yl]phenyl]borinic Acid (**9**).

To 30 ml of tetrahydrofuran cooled to -60° was added simultaneously 5.8 ml of triisopropyl borate (25 mmoles) and 15.6 ml of a 1.6 *M* solution of *n*-butyllithium (25 mmoles) in hexanes *via* syringe pump over 30 minutes. The reaction was held an additional 15 minutes at this temperature.

In another flask 9.72 g of 5-phenyl-2-triphenylmethyltetrazole **2** (25 mmoles) was dissolved in 54 ml of tetrahydrofuran. The solution was degassed three times with vacuum and nitrogen then cooled to -20°. To this solution was added a 1.6 *M* solution of *n*-butyllithium in hexanes until a red color persisted (approximately 2.0 ml, 3.2 mmoles) then an additional 15.6 ml of the 1.6 *M* solution of *n*-butyllithium (25 mmoles) was added over 10 minutes. The red slurry was held at -15 to -20° for 2.5 hours then the contents of the first flask were cannulated to this flask

and the reaction was held at -15° for 2 hours.

The reaction was quenched with 2.8 ml of acetic acid (50 mmoles) and the resulting gel was washed with 80 ml of a 14% aqueous solution of ammonium chloride containing 2 pellets of sodium hydroxide, then 80 ml of brine. The organic phase was dried (magnesium sulfate) and filtered. The filtrate was basified with 2 ml of triethylamine then evaporated to a viscous yellow oil which was pumped overnight to give a yellow foam, 10.4 g.

This foam was dissolved in 160 ml of tetrahydrofuran and then 50 ml of hexanes was added. The solution was concentrated until some solid appeared, then an additional 50 ml of hexanes was added. The mixture was cooled to 0° for 30 minutes and filtered to give a white solid, 4.7 g. A second and a third crop were collected in a similar manner, 4.2 g combined. In total an 85% yield was obtained, mp 121-122°; ir (potassium bromide): 3213, 2931, 1443, 1343, 749, 690 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 0.63-0.86 (m, 5H), 0.92-1.11 (m, 4H), 7.03-7.10 (m, 6H), 7.31-7.47 (m, 11 H), 7.80-7.95 (m, 1H), 9.38 (s, 1H); ^{13}C nmr (75.43 MHz, acetone-d_6): δ 14.3, 26.2, 26.5, 27.2, 81.8, 127.6, 128.3, 128.7, 128.9, 129.3, 131.1, 148.8, 205.8.

Anal. Calcd. for $C_{30}H_{29}N_4OB \cdot 1/2H_2O$: C, 74.85; H, 6.18; N, 11.64; B, 2.25. Found: C, 74.90; H, 6.04; N, 11.66; B, 2.01.

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