# THE BORONIC ACID MANNICH REACTION: A NEW METHOD FOR THE SYNTHESIS OF GEOMETRICALLY PURE ALLYLAMINES

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Abstract: Reaction of vinyl boronic acids with the adducts of secondary amines and paraformaldehyde gives tertiary allylamines with the same geometry. This simple and practical method was used for the synthesis of geometrically pure naftifine, a potent antifungal agent.

The increasing need for the treatment of opportunistic fungal infections, particularly in patients with AIDS, cancer and other immunocompromised conditions, has focused much recent attention on the development of orally active antifungal agents.[1] A unique class of compounds with promising antifungal properties are the allylamine derivatives,[2] which are potent inhibitors of squalene epoxidases. Among these, naftifine[3] (1) is a very active topical antimycotic, terbinafine[4] (2) is a very effective oral antifungal agent, while NB-598 (3) inhibits cholesterol biosynthesis.[5]

1   2   3
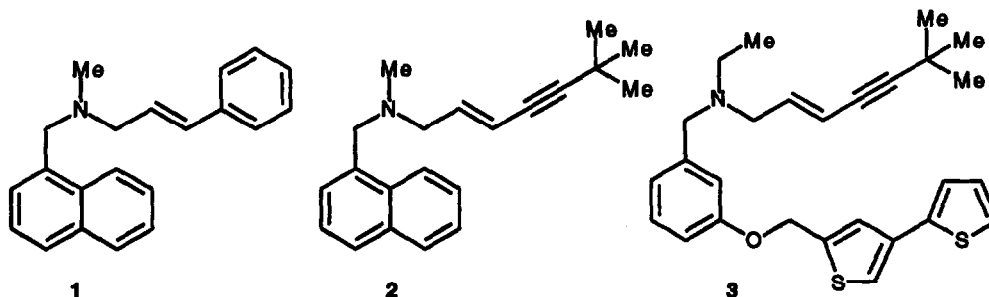
The diverse biological activity and synthetic utility of allylamines, have led to an increasing number of methods for the synthesis of this important functionality.[6] Although a number of synthetic approaches were reported, many of these give mixtures of regio- and stereo- isomers,[7] which are often difficult to separate. One of the most general methods for the synthesis of all kinds of amines is the addition of nucleophiles to imines and iminium salts (Mannich reaction).[8] Among the nucleophiles commonly used for this purpose are: enols and enolates,[8a] allyl and propargyl organometallics,[8b] activated aromatic rings,[8c] and alkynes.[6cd,8d] The use of vinylic nucleophiles to form allylamines in this way, however, has been rather limited, with the exception of vinyl silanes which are very effective in intramolecular variants of this process.[8d] We report herein a new practical method for the synthesis of geometrically pure allylamines, based on the participation of vinyl boronic acids in the Mannich reaction.

Vinyl and aryl boronic acids or boronates have found numerous synthetic applications in recent years, particularly in the Suzuki coupling reaction[9] with vinyl and aryl palladium intermediates. Geometrically pure vinyl boronic acids are easily prepared by hydroboration of alkynes with catecholborane followed by hydrolysis,[10] or by other methods.[11] In comparison with the boronates and other vinyl nucleophiles, the boronic acids are much easier to handle since they are stable to air and water. Furthermore, the boronic acid leaving group is water-soluble and easily removed.

The attractive features of vinyl boronic acids as a source of vinyl nucleophiles has prompted us to study their participation in the Mannich reaction for the synthesis of allylamines. Our initial studies involved reactions with the condensation products of a secondary amine (4) with paraformaldehyde. Under these conditions,[8a] the amine is converted to a hydroxy amine adduct (5) which can be transformed to the iminium salt (6) or the diamine (7). We have found that the amine-paraformaldehyde adduct reacts with vinyl boronic acids (8) to give an allylamine product (9) with complete retention of the geometry of the olefinic bond, similarly to the Suzuki coupling process.[9] The boronic acids were prepared by condensation of catecholborane (10) with terminal alkynes (11), followed by hydrolysis of the boronates (12).[10] Since the hydroboration proceeds regioselectively and exclusively in a cis-fashion, the boronic acids (8), and hence the allylamine products (9), are geometrically pure with 100% E-configuration. Although the boronates (12) also participated in the Mannich reaction, the by-product catechol required additional purification steps.

This new method for allylamine synthesis is simple and experimentally convenient since it does not require anhydrous conditions or an inert atmosphere. At first, a mixture of a secondary amine and paraformaldehyde in dioxane or toluene is heated at 90°C for 10 min. Addition of the vinyl boronic acid to this mixture and stirring at 25°C for several hrs or for 30min at 90°C, gives the allylamine in high yield. A simple acid-base extraction, removes any unreacted vinyl boronic acid, and affords the allylamine product in pure form. Several examples are given in the table.

The synthesis of naftifine (1) is typical: A slurry of N-methyl-N-1-naphthylmethyl amine (67 mg, 0.39 mmol), dioxane (1 ml) and paraformaldehyde (12 mg, 0.39 mmol) was heated to 90°C. After 10 min, the solution became clear and TLC indicated conversion of the amine into a new spot. To this cooled solution was added (E)-styryl-boronic acid (87 mg, 0.58 mmol), and more dioxane (1 ml) and the mixture was heated for 10 min at 90°C, followed by TLC. Upon cooling the mixture was acidified with 2N HCl and washed three times with ether. Addition of 3N NaOH to bring the pH to 14, followed by extraction with ether, drying of the ether layer over $NaSO_4$, filtration and removal of the solvents gave pure naftifine (1) as a yellow viscous liquid (81 mg, 82%).[12]

The mechanism of this Boronic Acid Mannich (BAM) reaction is not completely clear at this time. In the absence of acid it is unlikely that significant amounts of the iminium salt (6) are generated[8a] and therefore this intermediate may not be involved. Also, vinyl boronic acids do not add readily to preformed iminium salts, such as Eschenmoser's salt ($Me_2N^+=CH_2$ I^-), whereas they react rapidly with diamines such as 7. Presumably, attack on the boron by the hydroxyl or amino group in 5 and 7, would activate the vinyl group as a nucleophile and the methylamino moiety as an electrophile, triggering a carbon-carbon bond forming process.
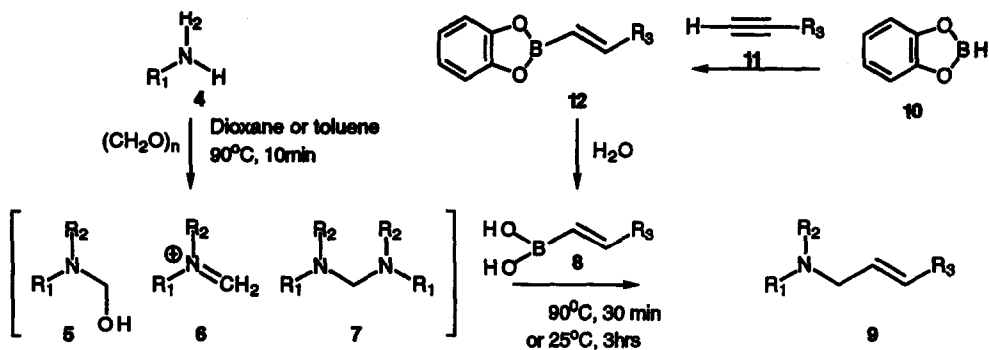
Secondary Amine	Boronic Acid	Allylamine	Yield (100% E)
			89%
			75%
			81%
			84%
			96%
			82%

In summary, we have found that vinyl boronic acids can participate as nucleophiles in the Mannich reaction giving geometrically pure allylamines. Although we have reported only examples with E-vinyl boronic acids it is expected that Z- or disubstituted derivatives would behave similarly. The reaction works well with secondary amines and is much less efficient with amine salts or with primary amines. Also, preliminary results with aryl boronic acids showed that they behave similarly and afford benzylamines, but the reaction is less efficient under the same conditions. We are currently exploring the effect of substituents and base additives in this reaction. Similar reactions with other nonenolizable carbonyl compounds, that present an opportunity to develop asymmetric variants of this process, are also under investigation.

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12. ^{1}H NMR (250 MHz, CDCl$_3$) δ: 8.38-8.35 (m, 1H); 7.91-7.80 (m, 2H); 7.58-7.26 (m, 9H); 6.63 (d, J=15.9 Hz, 1H); 6.43 (dt, J=15.8 Hz, J=6.5 Hz, 1H); 3.99 (s,2H); 3.32 (d, J=6.5 Hz, 2H); 2.32 (s, 3H); ^{13}CNMR (63 MHz, CDCl$_3$) δ: 137.06; 134.82; 133.82; 132.60; 132.42; 128.49; 128.38; 127.88; 127.55; 127.39; 127.31; 126.25; 125.83; 125.52; 125.05; 124.58; 60.35; 60.06; 42.42; MSEI; m/z (abund.) 287.30 (39); 196.30 (37); 141.30 (100); 117.30 (31); 115.30 (51).