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Heterocyclic aldehydes as novel components in the boronic Mannich reaction

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Abstract

A range of heterocyclic aldehydes are shown for the first time to react in the boronic Mannich reaction to provide an expedient synthesis of new highly-functionalised small molecules. © 2000 Elsevier Science Ltd. All rights reserved.

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Petasis et al. have recently introduced a protocol for the synthesis of amino acids in one step by a three-component boronic Mannich reaction (BMR) based on simply mixing an aryl or alkenyl boronic acid, an amine and an aldehyde at room temperature.[1–4] We have exploited this reaction in the syntheses of new 2-ketopiperazine[5] and 2-keto-1,4-diazepine derivatives[6] designed as conformationally constrained amino acid mimics. Examining the literature it appears that while the boronic acid component has been varied somewhat (e.g. including thienyl, furyl and benzo[b]furyl derivatives)[2,3] and several amines (especially secondary amines)[2–4] react, all reported successful examples of the BMR involve glyoxylic acid or an α-hydroxyaldehyde as the functionalised aldehyde component.[7] A key issue, therefore, was to establish if different structural variants of the aldehyde input could take part in the BMR. Herein, we report that a range of heterocyclic aldehydes react in this protocol providing the rapid, multi-component assembly of a series of novel highly-functionalised small molecules.

We screened a range of heterocyclic aldehydes in conjunction with equimolar quantities of phenylalkenyl boronic acid **1**[8] and morpholine as the amine input (Scheme 1). The reactions were carried out in DMF:CH_2Cl_2 (4:6 v/v) at 50°C for 2 days. LCMS and ^{1}H NMR analysis of the crude product mixture established that products **2a**–**e** were formed. It is notable that all of the aldehydes which gave the BMR product **2** possessed a heteroatom α to the aldehyde group. Both π-deficient (*e.g.* 2-pyridyl) and π-rich (*e.g.* 2-furyl) aldehydes reacted. In contrast, several other aldehydes both with and without

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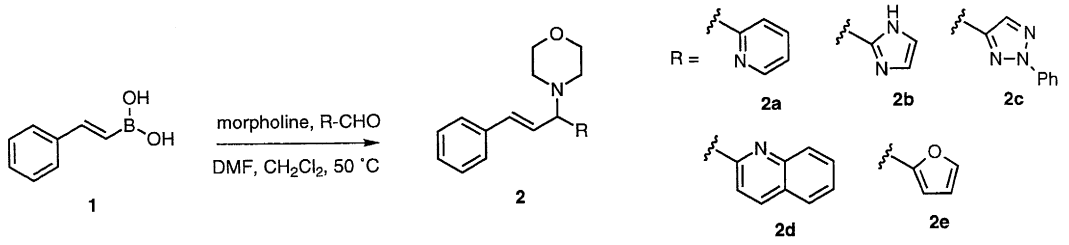
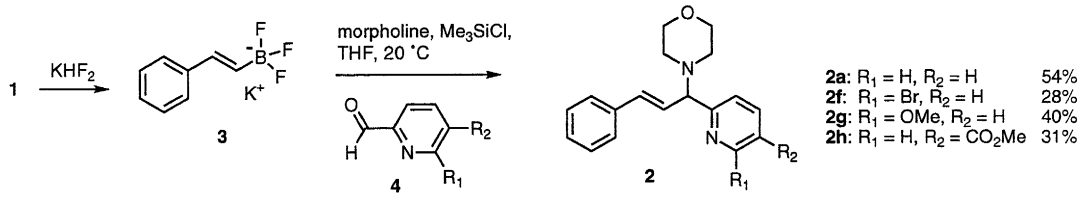
an α-heteroatom gave no detectable BMR product (e.g. benzaldehyde, pyridine-3-carboxaldehyde and pyridine-4-carboxaldehyde, pyrrole- and thiophene-2-carboxaldehyde derivatives).



Scheme 1. Reaction of alkenyl boronic acid **1** with morpholine and various heterocyclic aldehydes

However, yields of these reactions according to the standard protocol[1–3] were usually low, e.g. the preparation of pyridine derivative **2a** yielded only 10% of the desired product after purification. Therefore, we decided to investigate the use of the more reactive trifluoroborate derivative **3** (Scheme 2) which can easily be obtained following a procedure by Vedejs et al.[9] Upon addition of trimethylsilyl chloride, trifluoroborate salts such as **3** are easily converted in situ into the corresponding reactive tricoordinated difluoroboranes.[9]



Scheme 2. Preparation of pyridine derivatives **2a**, **f**–**h** using alkenyl trifluoroborate salt **3**

Reactions performed on a preparative scale with a series of pyridine-2-carboxaldehyde derivatives (Scheme 2), namely the parent system and its 6-bromo,[10] 6-methoxy[11] and 5-methoxycarbonyl[12] derivatives, afforded the products **2a**, **2f**, **2g** and **2h**, respectively, in the purified yields shown, thereby establishing that this is a simple and practically useful approach to these interesting multi-functional small molecules.

The crucial role in the mechanism of the BMR played by the α-heteroatom in the aldehyde component is not yet clear, but it might be involved in chelation events with the boron atom. We have, however, definitely established that a wider structural diversity of products than hitherto appreciated can be readily obtained by the BMR, and this should have far-reaching consequences for the synthetic utility of this new multi-component reaction.

Typical experimental procedure: Potassium alkenyl trifluoroborate **3** (210 mg, 1.0 mmol) was added to a solution of pyridine-2-carboxaldehyde **4** (1.0 mmol) and morpholine (1.0 mmol) in THF (10 ml). Finally, trimethylsilyl chloride (2.0 mmol) was added and the reaction stirred overnight at room temperature. The reaction mixture was poured into brine, extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, the solvent removed in vacuo and the residue purified by column chromatography on silica gel eluting with a mixture of methanol in CH_2Cl_2 containing 0.5% acetic acid. **2a**: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.61 (m, 1H, pyr), 7.74 (m, 1H, pyr), 7.57 (m, 1H, pyr), 7.18–7.40 (m, 6H, phenyl, pyr), 6.78 (d, 1H, *J*=15.8, C*H*phenyl), 6.39 (dd, 1H, *J*=15.8, 9.2, C*H*=CHphenyl), 4.38 (d, 1H, *J*=9.2, C*H*pyr), 3.80 (m, 4H, OCH_2), 2.84–2.89, 2.57–2.61 (2m, 2×2H, NCH_2). HRMS-EI calcd for $C_{18}H_{20}N_2O$: 280.1576; found: 280.1578.

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