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Petasis boronic acid–Mannich reactions of substituted hydrazines: synthesis of α-hydrazinocarboxylic acids†

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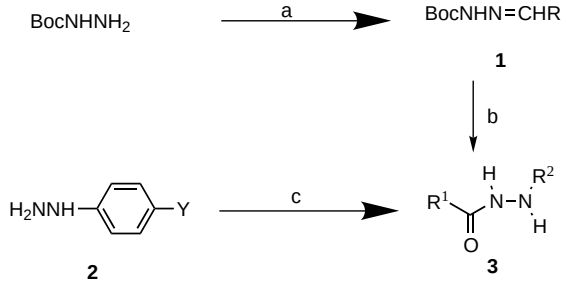
Abstract—*N*-1-(Carbamate protected)-*N*-2-(alkyl or aryl substituted) hydrazines can serve as amine substrates for the Petasis boronic acid–Mannich reaction, providing a practical synthetic route for the preparation of α-hydrazinocarboxylic acids. The scope and limitations of this method have been examined. © 2002 Published by Elsevier Science Ltd.

The Petasis boronic acid–Mannich reaction is a practical method for the preparation of α-amino acids.[1,2] Furthermore, it has been used for the synthesis of combinatorial libraries, because a wide variety of amines and aryl boronic acids can be readily condensed in a multi parallel fashion on solid supports.[3] Indeed, the Petasis boronic acid–Mannich reaction is ideally suited for combinatorial chemistry because: (1) it is a multi-component condensation;[4] (2) an increasing variety of boronic acids and amines are commercially available, and (3) it proceeds at ambient temperature in a wide range of solvents. The reaction is most efficient with alkenyl and electron-rich aromatic boronic acids, secondary amines, and sterically hindered primary amines, although anilines, unprotected amino acids, and peptides can also participate.[1a,b] Due to our interests in α-hydrazinocarboxylic acids as building blocks for the synthesis of combinatorial libraries of heterocycles for drug discovery,[5] we have investigated the scope and limitations of using substituted hydrazines as amine components in the Petasis boronic acid–Mannich reaction. To our knowledge hydrazines have not previously been studied as substrates for this reaction.[1–3]

Methods for the preparation of α-hydrazinocarboxylic acids have received considerable attention due to their wide utility as building blocks for the synthesis of β-turn,[6] γ-turn,[7] and α-helix[8] peptidomimetics, as well as antibiotics,[9] protease inhibitors,[10] antivirals,[11] and chiral α-amino acids.[12] In this letter, we report a mild, practical, and novel method for the synthesis of α-hydrazinocarboxylic acids using the Petasis boronic acid–Mannich reaction.

Substituted hydrazines were prepared by two methods (Scheme 1). Various aldehydes were condensed with $BocNHNH_2$ and the resulting hydrazones **1** were reduced either by catalytic hydrogenation or $NaBH_3CN$ to provide a series of Boc-protected alkyl substituted hydrazines **3** ($R^1 = t$-BuO; R^2 = alkyl).[13] Alternatively, commercially available heteroaryl- or phenylhydrazines **2** (Y = H, NO_2) were regioselectively protected to provide *N*-1-Boc-*N*-2-(substituted aryl)-hydrazines **3** ($R^1 = t$-BuO; R^2 = aryl).[14]



Scheme 1. General routes to alkyl and phenyl substituted hydrazines. *Reagents and conditions*: (a) RCHO, abs. EtOH; (b) H_2, 10% Pd–C, abs. EtOH or $NaBH_3CN$, *p*-TsOH, THF; (c) $(Boc)_2O$, Et_2O.

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† This paper is dedicated to the memory of Professor Henry Rapoport, who (over many years) provided valuable insight and practical advice to our combinatorial chemistry projects.

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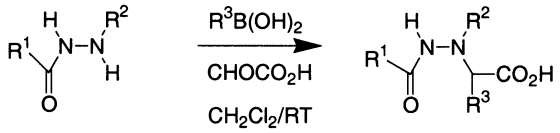
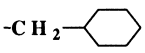
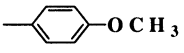
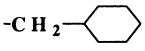
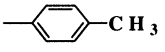
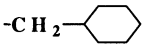
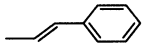
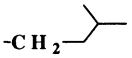
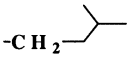
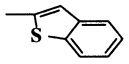
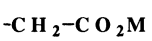
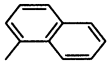
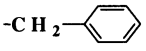
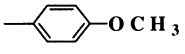
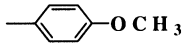
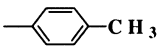
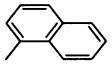
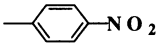
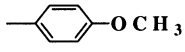
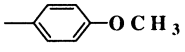
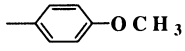
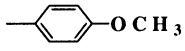
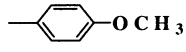
A variety of these substrates **3** were then subjected to standard Petasis boronic acid–Mannich reaction conditions, i.e. 1 equiv. each of **3**, glyoxylic acid monohydrate, and an organoboronic acid stirred at ambient temperature in CH_2Cl_2 for 48 h (Table 1).[15] When $R^1 = t$-BuO and R^2 = alkyl (**4a–g**), these reactions proceeded in satisfactory yields ranging from 60 to 99% after purification by flash chromatography. In the examples explored, yields did not vary appreciably due to variation of the arylboronic acid (**4a–c** and **4d–e**). Remarkably, when $R^1 = t$-BuO and R^2 = phenyl, **4h** was obtained in 99% yield. In this case, the reacting nitrogen atom is a poor nucleophile, because it is aniline-like and further deactivated inductively by the adjacent carbamate group. However, 4-nitrophenyl substituted hydrazine **3j**, which is further deactivated by an electron withdrawing substitutent, produced **4j** in only modest yield (LC-MS, 34%). Similarly, **3k** failed to give any of the desired product, **4k** (LC-MS).

Table 1. Petasis boronic acid–Mannich reactions of substituted hydrazines



3 **4**

Compound	R^1	R^2	R^3	Yield[a]
4a	t-BuO			99%
4b	t-BuO			74%
4c	t-BuO			86%
4d	t-BuO			89%
4e	t-BuO			60%
4f	t-BuO			70%
4g	t-BuO			86%
4h	t-BuO			99%
4i	t-BuO			85%
4j	t-BuO			34%
4k	t-BuO			0%
4l[b]	t-BuO	—H		71%
4m	BnO	—CH_2CO_2Et		60%
4n	H_2N			20%

[a]All yields refer to pure, isolated products. All compounds have been characterized by LC-MS, HNMR, and CNMR; [b]Pre-formed $BocNHN{=}CHCO_2H$ was condensed with the arylboronic acid.

Since building blocks of structure **4** ($R^2=H$) were of interest to us for combinatorial library production,[5] we wondered if they could be prepared from the unsubstituted hydrazine, **3** ($R^1=t$-BuO; $R^2=H$). However, when $BocNHNH_2$ was subjected to the same Petasis boronic acid–Mannich reaction conditions, a complex mixture of products was obtained (LC-MS). Nevertheless, the desired product **4l** could be prepared in 71% yield by first pre-forming the presumed intermediate, $BocNHN{=}CHCO_2H$ and then adding an aryl boronic acid in CH_2Cl_2 at ambient temperature. Furthermore, **4l** could also be obtained by catalytic debenzylation of **4g**. Using this protective group strategy, **4l** was obtained (H_2 balloon, 10% Pd–C, abs. EtOH) in 71% yield after purification by flash chromatography. As expected, the Boc group in **3** could be replaced by a CBZ, e.g. **4m** was obtained cleanly in 60% yield. And finally, the commercially available semicarbazide **3n** was examined. Although the expected product **4n** was obtained, the yield was poor (LC-MS, 20%) and formed as a complex mixture of products.

In summary, we have demonstrated that *N*-1-(carbamate protected)-*N*-2-(alkyl or aryl substituted) hydrazines can serve as amine substrates for the Petasis boronic acid–Mannich reaction providing a practical synthetic route for the preparation of α-hydrazinocarboxylic acids. Further studies related to the utility of products **4** as intermediate building blocks for a tandem Petasis-Ugi multicomponent condensation have been disclosed[16] and complete experimental details will be reported in due course.

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15. **General procedure for the Petasis boronic acid–Mannich reaction of substituted hydrazines 3 to prepare α-hydrazinoacids 4**: to a stirred mixture of glyoxylic acid monohydrate (0.41 g, 4.4 mmol) in CH_2Cl_2 (23 mL) was added *N*-1-Boc-*N*-2-(cyclohexylmethyl)-hydrazine (1.0 g, 4.4 mmol) followed by 4-methoxyphenylboronic acid (0.67 g, 4.4 mmol). The resulting mixture was stirred at ambient temperature for 48 h and after this time, the CH_2Cl_2 was removed under reduced pressure. The residue was purified by chromatography (silica gel, 40% EtOAc:hexanes) to give 1.75 g (99%) of **4a** as a hydroscopic white solid: $R_f=0.18$ (50% EtOAc:hexanes); analytical HPLC: Polaris C18 column (4.6×250 mm, 3 micron particle size), mobile phase 0.1% aqueous phosphoric acid/CH_3CN linear gradient over 30 min, 1 mL/min, one peak detected by ELS and UV at 215 nm, $t_R=18.4$ min; H NMR ($CDCl_3$, 300 MHz): δ 0.75–1.80 (m, 11H), 1.40 (s, 9H), 2.40–2.65 (m, 2H), 3.84 (s, 3H), 4.57 (s, 1H), 5.2 (br s, 1H), 6.93 (d, 2H), 7.21 (d, 2H); C NMR ($CDCl_3$, 75 MHz): δ 26.21, 26.29, 26.76, 28.40, 31.43, 31.67, 35.86, 55.57, 72.60, 72.89, 82.21, 114.42, 131.31, 131.76, 157.26, 160.19, 172.69; LCMS (ELSD): 393 ($M+H^+$).
16. Presented in part at Cambridge Healthtech Institute's Seventh Annual 'High Throughput Organic Synthesis' Symposium, February 13–15, 2002, San Diego, CA.