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Fabienne Berrée, Abdelmadjid Debache, Yoann Marsac, Bertrand Carboni. A new access to 2-hydroxymorpholines through a three-component Petasis coupling reaction. *Tetrahedron Letters*, 2001, 42 (21), pp.3591-3594. 10.1016/S0040-4039(01)00515-9 . hal-03985915

HAL Id: hal-03985915

<https://hal.science/hal-03985915>

Submitted on 13 Feb 2023

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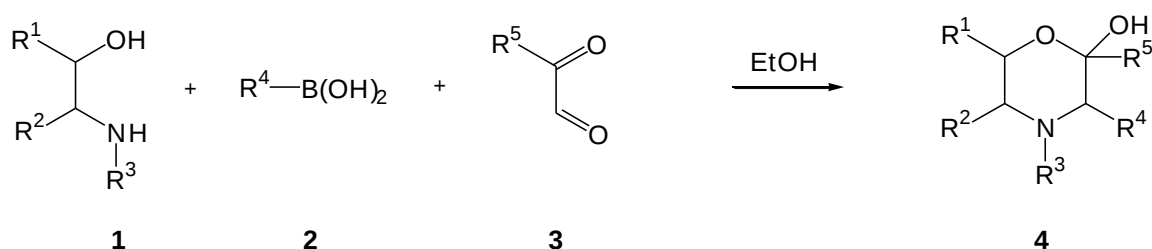
A new access to 2-hydroxymorpholines through a three-component Petasis coupling reaction.

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Abstract – 2-Hydroxymorpholines bearing a variety of substituents were prepared via the one-pot three-component reaction of a 1,2-aminoalcohol, an organoboronic acid and a glyoxal derivative.

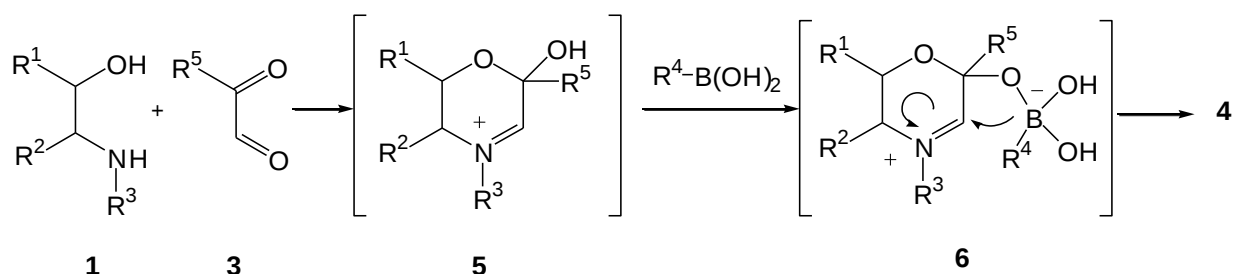
The 2-hydroxymorpholine ring has been identified as a central structural element of a number of biologically active compounds.ⁱ For example, a series of potent, orally active neurokinine-1 antagonists based on this morpholine core were recently disclosed.ⁱⁱ Morpholin-2-ones, their oxidation products, have been also proven to be important intermediates in the stereocontrolled synthesis of non-proteinogenic α -amino acids.ⁱⁱⁱ Main reported preparations of 2-hydroxymorpholines include condensation of a 1,2-aminoalcohol with α -hydroxy-^{iv} or α -halogenoketone,^v reaction of an α -aminoketone with an epoxide^{vi} and reduction of morpholin-2-ones.^{vii} Addition of organolithium, organozinc or alkylcopper reagents, respectively to N-cyanomethyl-1,3-oxazolidines^{viii} or 2-hydroxy-3-phenylthiomorpholines^{ix} have been also successfully used in non-racemic series. We report herein a new efficient one-pot synthesis of substituted 2-hydroxymorpholines from an aminoalcohol **1**, a boronic acid **2** and a glyoxal derivative **3** (Scheme 1).



Scheme 1

N.A. Petasis has previously developed the *in situ* assembling of amines, aldehydes and alkenyl- or aryl boronic acids.^x Other authors later described related reactions,^{xi} but, to our knowledge, glyoxal and its derivatives have never been applied in such approaches. It was probably due to the high reactivity of these bifunctional compounds and the difficulty to stop the reaction after a first addition. C. Agami and coworkers have developed very elegant and efficient approaches based on the use of a masked form of glyoxal.^{xii}

On the basis of these results and considering the probable mechanism of the borono-Mannich reaction,^{xiii} we envisioned to use *in situ* generated heterocyclic iminium ions **5** as reactants in the synthesis of 2-hydroxymorpholines. One of the aldehyde functions is now masked as an hemiacetal while the second one is converted to an iminium group which can react with an appropriate nucleophile, in this case a boronic acid (Scheme 2). The presence of the hydroxyl group could also favour an intramolecular addition *via* the formation of a tetracoordinate boron complex **6**. The use of organoboron compounds is especially valued due to their easily accessibility, their tolerance for a broad range of functional groups, and their air and water stability compared with usual organometallics reagents.^{xiv}

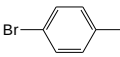


Scheme 2

1,2-Aminoalcohols were therefore directly engaged in a one-pot cyclisation procedure with boronic acid and glyoxal, its methyl- or phenyl- derivatives (Scheme1). In all cases, the formation of the expected 2-hydroxymorpholines **4** occurred (Table 1).^{xv} As outlined in the Table 1, the reaction proceeded readily with satisfactory yields and was compatible with the presence of various substituents in different positions of the 2-hydroxymorpholine core. A mixture of diastereoisomers was always obtained with a ratio depending on R¹-R⁵.

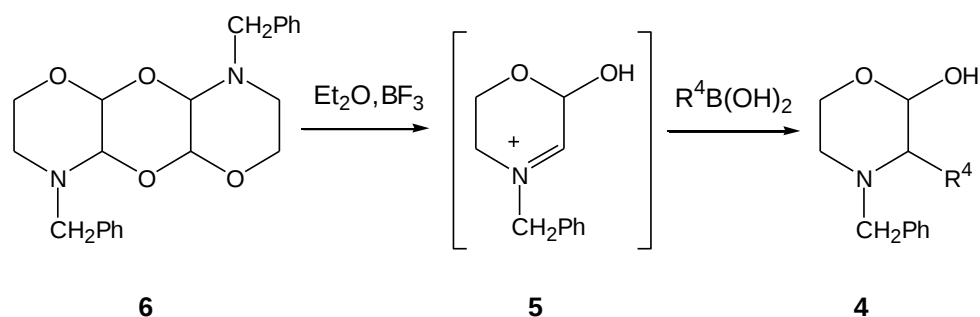
Table 1
Synthesis of 2-hydroxymorpholines **4**

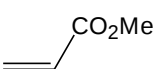
Compound	R ¹	R ²	R ³	R ⁴	R ⁵	Yield (%) ^a	d.r. ^b
4a	H	H	PhCH ₂	Ph	H	70	87:13
4b	H	H	PhCH ₂		H	50	80:20
4c	H	H	PhCH ₂		H	66	55:45

4d	H	H	PhCH ₂		H	56	75/25
4e	Me	H	Me	Ph	H	65	^c
4f	H	Ph	Me	Ph	H	86	^c
4g	H	H	PhCH ₂	Ph	Me	57	85/15
4h	H	H	PhCH ₂		Me	59	54/46
4i	H	H	PhCH ₂		Me	52	76/24
4j	H	H	PhCH ₂	Ph	Ph	92	89/11
4k	H	H	PhCH ₂		Ph	53	83/17

^a Yield of isolated product after purification by column chromatography. ^b Determined by ¹H NMR. (R⁴=aryl, relative stereochemistry *trans* for the major diastereoisomers). ^c Mixture of four diastereoisomers

Generating **5** from perhydro-4,8-dimethyl-4,8-diaza-1,5,9,10-tetraoxanthracene **6** ^{xvi} corroborated the existence of such a cyclic iminium as an intermediate in the synthesis of **4**. This route offers the supplementary advantage to prevent the presence of amine in the reaction mixture during the addition of the boronic acid. Thus, if no expected 2-hydroxymorpholine was obtained in the one pot procedure from an activated alkenyl boronic acid **2** (R⁴=CH=CH-CO₂Me),^{xvii, xviii} the addition proceeded in good yield when **6** was used as precursor in the presence of boron trifluoride etherate (Scheme 3).^{xix}



Compound	R ⁴	Yd (%)	d.r.
4a	Ph	94	73/27
4l		76	60/40

Scheme 3

In conclusion, we have developed a novel and practical method for the one pot preparation of 2-hydroxymorpholines. The overall protocol is practical and quite efficient. By employing a perhydro-4,8-diaza-1,5,9,10-tetraoxanthracene as starting material, amine-sensitive boronic acid can also be used to afford 2-hydroxymorpholine in good yield. Further studies of this reaction are currently under investigation.

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- xv Typical procedure for the one-pot synthesis of **4a-4k**. A mixture of boronic acid (1 mmol), glyoxal (1 mmol) and 1,2-aminoalcohol (1 mmol) in ethanol (5 mL) was stirred at room temperature for 24 h. The solvent was removed in vacuo and the product was isolated by flash chromatography using 30% ethyl acetate in heptane to give **4**. Selected data: **4b** (major isomer) : white solid from isopropylether; mp 159-160°C; ¹H NMR (200MHz : CDCl₃) δ 2;35 (td, *J* 3.8 and 11.5, 1H), 2.79 (dt, *J* 1.9 and 11.8, 1H), 2.99 (d, *J* 13.5, 1H), 3.48 (d, *J* 8.9 , 1H), 3.78 (s, 1H), 3.83 (d, *J* 5.6, 1H), 3.84-4.00 (m, 2H), 3.93 (s, 3H), 4.66 (dd, *J* 7.4 and 8.8, 1H), 6.98 (d, *J* 8.2, 1H); 7.10 (td, *J* 1 and 7.5, 1H), 7.26-7.38 (m, 6H); 7.80 (dd, *J* 1.7 and 7.5, 1H). ¹³C NMR (50MHz : CDCl₃) δ 50.8, 55.6, 58.5, 63.9, 64.4, 98.6, 110.7, 121.2, 126.8, 127.9, 128.1, 128.4, 128.6, 128.7, 138.4, 158.1. Anal. calcd for C₁₈H₂₁NO₃ : C, 72.21; H, 7.07; N, 4.68. Found: C, 72.03; H, 7.24; N, 4.43.
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- xviii This failure may be attributed to a competitive Michael addition of the amine to the activated double bond.
- xix To a solution of perhydro-4,8-dimethyl-4,8-diaza-1,5,9,10-tetraoxoanthracene **6** (1 mmol) and boronic acid (2 mmol) in dry CH₂Cl₂ (20 mL), at -78°C was added dropwise Et₂O.BF₃ (4.5 mmol). The solution was stirred at -78°C for 0.5 h, warmed to room temperature and stirred overnight. After addition of NaHCO₃ sat. (15 mL), the mixture was extracted with CH₂Cl₂ (3x30 mL). The organic phases were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography using 30% ethyl acetate in heptane to afford **4l**: (major isomer) ¹H NMR (200MHz : CDCl₃) δ 2.24 (td, *J* 3.3 and 8.6, 1H), 2.69 (dt, *J* 3.3 and 11.6, 1H), 2.94 (dd, *J* 5.3 and 8.8, 1H), 3.20 (d, *J* 13.4 , 1H), 3.56-4.04 (m, 4H), 3.75 (s, 3H), 4.68 (d, *J* 5.4, 1H), 6.16 (d, *J* 15.9, 1H), 7.03 (dd, *J* 1.5 and 15.9, 1H), 7.24-7.33 (m, 5H). ¹³C NMR (50MHz : CDCl₃) δ 48.6, 51.6, 59.2, 62.4, 67.2, 94.3, 125.9, 127.2, 128.3, 128.8, 137.3, 144.6, 166.1. HRMS 277.1317 (calcd. for C₁₅H₁₉NO₄ : 277.1314).

Graphical abstract

A new access to 2-hydroxymorpholines through a three-component Petasis coupling reaction.

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