Pergamon

Tetrahedron Letters 42 (2001) 3591–3594

TETRAHEDRON LETTERS

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

Fabienne Berrée,[a] Abdelmadjid Debache,[b] Yoann Marsac[a] and Bertrand Carboni[a,*]

[a]*Synthèse et Electrosynthèse Organique, UMR CNRS 6510, Bat 10A, Institut de Chimie, Université de Rennes 1, Campus de Beaulieu, F-35042 Rennes CEDEX, France*

[b]*Institut de Chimie, Université de Constantine, 25000 Constantine, Algeria*

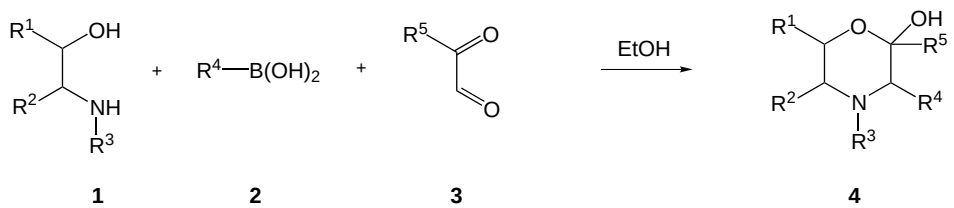
Received 26 March 2001

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.[1] For example, a series of potent, orally active neurokinine-1 antagonists based on this morpholine core were recently disclosed.[2] Morpholin-2-ones, their oxidation products, have also been proven to be important intermediates in the stereocontroled synthesis of non-proteinogenic α-amino acids.[3] The main reported preparations of 2-hydroxymorpholines include condensation of a 1,2-aminoalcohol with α-hydroxy-[4] or α-halogenoketone,[5] reaction of an α-aminoketone with an epoxide[6] and reduction of morpholin-2-ones.[7] Addition of organolithium, organozinc or alkylcopper reagents, respectively, to *N*-cyanomethyl-1,3-oxazolidines[8] or 2-hydroxy-3-phenylthiomorpholines[9] have also been 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).

Petasis has previously developed the in situ assembling of amines, aldehydes and alkenyl or aryl boronic acids.[10] Other authors later described related reactions,[11] 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 stopping the reaction after a first addition. Agami and co-workers have developed very elegant and efficient approaches based on the use of a masked form of glyoxal.[12]

On the basis of these results and considering the probable mechanism of the borono-Mannich reaction,[13] we envisioned the use of 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.[14]



1 **2** **3** **4**

Scheme 1.

* Corresponding author. Fax: (33) 2 99 28 69 78; e-mail: bertrand.carboni@univ-rennes1.fr

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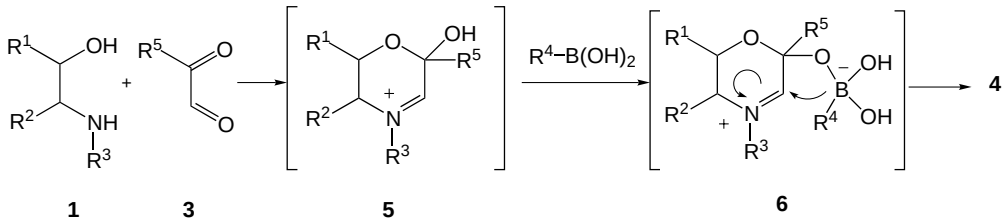
PII: S0040-4039(01)00515-9



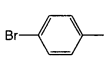
Scheme 2.

1,2-Aminoalcohols were therefore directly engaged in a one-pot cyclisation procedure with boronic acid and glyoxal, its methyl or phenyl derivatives (Scheme 1). In all cases, the formation of the expected 2-hydroxymorpholines **4** occurred (Table 1).[15] 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 R^1–R^5.

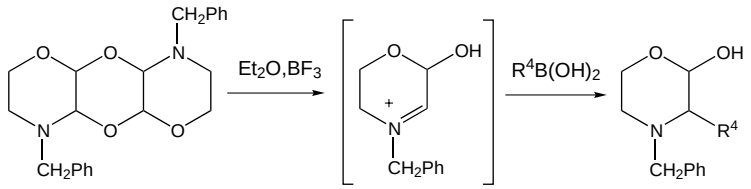
Generating **5** from perhydro-4,8-dimethyl-4,8-diaza-1,5,9,10-tetraoxoanthracene **6**[16] corroborated the existence of such a cyclic iminium as an intermediate in the synthesis of **4**. This route offers the supplementary advantage to prevent the presence of amine in the reaction mixture during the 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** (R^4=CH=CH–CO_2Me),[17,18] the addition proceeded in good yield when **6** was used as precursor in the presence of boron trifluoride etherate (Scheme 3).[19]

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

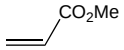
Table 1. Synthesis of 2-hydroxymorpholines **4**

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 ^{1}H NMR. (R^4=aryl, relative stereochemistry *trans* for the major diastereostereoisomers). [c] Mixture of four diastereoisomers



6 5 4

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

Scheme 3.

efficient. By employing a perhydro-4,8-diaza-1,5,9,10-tetraoxoanthracene 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.

References

1. (a) Rekka, E.; Kourounakis, P. *Eur. J. Med. Chem.* **1989**, *24*, 179–185; (b) Kelley, J. L.; Musso, D. L.; Boswell, G. E.; Soroko, F. E.; Cooper, B. R. *J. Med. Chem.* **1996**, *39*, 347–349.
2. (a) Hale, J. J.; Mills, S. G.; MacCoss, M.; Shah, S. K.; Qi, H.; Mathre, D. J.; Cascieri, M. A.; Sadowski, S.; Strader, C. D.; MacIntyre, D. E.; Metzger, J. M. *J. Med. Chem.* **1996**, *39*, 1760–1762; (b) Hale, J. J.; Mills, S. G.; MacCoss, M.; Finke, P. E.; Cascieri, M. A.; Sadowski, S.; Ber, E.; Chicchi, G. G.; Kurtz, M.; Metzger, J.; Eiermann, G.; Tsou, N. N.; Tattersall, F. D.; Rupniak, N. M. J.; Williams, A. R.; Rycroft, W.; Hargreaves, R.; MacIntyre, D. E. *J. Med. Chem.* **1998**, *41*, 4607–4614; (c) Dorn, C. P.; MacCoss, M.; Hale, J. J.; Mills, S. G. US Patent 5512570; 1996; (d) Baker, R.; Elliott, J. M.; Stevenson, G. I.; Swain, C. J. US Patent 5985896, 1999.
3. (a) Anslow, A. S.; Harwood, L. M.; Lilley, I. A. *Tetrahedron: Asymmetry* **1995**, *6*, 2465–2468; (b) Harwood, L. M.; Tyler, S. N. G.; Anslowv, A. S.; MacGilp, I. D.; Drew, M. G. B. *Tetrahedron: Asymmetry* **1997**, *8*, 4007–4010; (c) Ma, D.; Ding, K. *Org. Lett.* **2000**, *2*, 2515–2517; (d) Chinchilla, R.; Falvello, L. R.; Galindo, N.; Najera, C. *J. Org. Chem.* **2000**, *65*, 3034–3041.
4. Griffin, C. E.; Lutz, R. E. *J. Org. Chem.* **1956**, *21*, 1131–1137.
5. (a) Cromwell, N. H.; Tsou, K. C. *J. Am. Chem. Soc.* **1949**, *71*, 993–995; (b) Lutz, R. E.; Jordan, R. H. *J. Am. Chem. Soc.* **1949**, *71*, 996–999.
6. (a) Easton, N. R.; Cassady, D. R.; Dillard, R. D. *J. Org. Chem.* **1963**, *28*, 448–451; (b) Stevens, C. L.; Mitarbo, J. *J. Org. Chem.* **1964**, *29*, 3146–3151.
7. Shafer, C. M.; Molinski, T. F. *J. Org. Chem.* **1996**, *61*, 2044–2050.
8. Marco, J. L.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1985**, *26*, 6345–6348.
9. Agami, C.; Couty, F.; Prince, B.; Puchot, C. *Tetrahedron* **1991**, *47*, 4343–4354.
10. (a) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445–446; (b) Prakash, G. K. S.; Mandal, M.; Schweizer, S.; Petasis, N. A.; Olah, G. A. *Org. Lett.* **2000**, *2*, 3173–3176; (c) Petasis, N. A.; Patel, Z. D. *Tetrahedron Lett.* **2000**, *41*, 9607–9611; (d) Petasis, N. A.; Boral, S. *Tetrahedron Lett.* **2001**, *42*, 539–542.
11. (a) Wang, Q.; Finn, M. G. *Org. Lett.* **2000**, *2*, 4063–4065; (b) Golebiowski, A.; Klopfenstein, S. R.; Chen, J. J.; Shao, X. *Tetrahedron Lett.* **2000**, *41*, 4841–4844; (c) Currie, G. S.; Drew, M. G. B.; Harwood, L. M.; Hughes, D. J.; Luke, R. W. A.; Vickers, R. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2982–2990; (d) Batey, R. A.; MacKay, D. B. *Tetrahedron Lett.* **2000**, *41*, 9935–9938; (e) Schienger, N.; Bryce, M. R.; Hansen, T. K. *Tetrahedron* **2000**, *56*, 10023–10030; (f) Thompson, K. A.; Hall, D. G. *Chem. Commun.* **2000**, 2379–2380.
12. (a) Agami, C.; Couty, F.; Puchot-Kadouri, C. *Synlett* **1998**, 449–456; (b) Agami, C.; Couty, F.; Lam, H.; Mathieu, H. *Tetrahedron* **1998**, *54*, 8783–8796; (c) Agami, C.; Couty, F.; Mathieu, H.; Pilot, C. *Tetrahedron Lett.* **1999**, *40*, 4539–4542.
13. Petasis, N. A.; Zavialov, I. A. *Advances in Boron Chemistry*; The Royal Society of Chemistry: Cambridge, 1997; pp. 179–182.
14. (a) Matteson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer: Berlin, 1995; (b) Vaultier, M.; Carboni, B. In *Comprehensive Organometallic Chemistry II*; Wilkinson, G.; Stone, F. G. A.; Abel, V. E., Eds.; Pergamon Press: Oxford, 1995; Vol. 11, pp. 191–276.
15. 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; ^{1}H NMR (200 MHz: $CDCl_3$) 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* 1.0 and 7.5, 1H), 7.26–7.38 (m, 6H); 7.80 (dd, *J* 1.7 and 7.5, 1H). ^{13}C NMR (50 MHz: $CDCl_3$) 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 $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.03; H, 7.24; N, 4.43.

16. Agami, C.; Couty, F.; Hamon, L.; Prince, B.; Puchot, C. *Tetrahedron* **1990**, *46*, 7003–7010.
17. Rasset-Deloge, C.; Pilar-Fresneda, M. P.; Vaultier, M. *Bull. Soc. Chem. Fr.* **1992**, *129*, 285–290.
18. This failure may be attributed to a competitive Michael addition of the amine to the activated double bond.
19. 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 CH_2Cl_2 (20 mL) at −78°C was added dropwise Et_2O,BF_3 (4.5 mmol). The solution was stirred at −78°C for 0.5 h, warmed to room temperature and stirred overnight. After addition of $NaHCO_3$ satd (15 mL), the mixture was extracted with CH_2Cl_2 (3×30 mL). The organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography using 30% ethyl acetate in heptane to afford **4l**: (major isomer) ^{1}H NMR (200 MHz: $CDCl_3$) 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). ^{13}C NMR (50 MHz: $CDCl_3$) 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 $C_{15}H_{19}NO_4$: 277.1314).