Microwave-Assisted Neat Procedure for the Petasis Reaction

Pierrick Nun, Jean Martinez, Frédéric Lamaty*

Institut des Biomolécules Max Mousseron, UMR 5247 CNRS-Universités Montpellier 1 et 2, Université Montpellier, 2, Place Eugène Bataillon, 34095 Montpellier Cedex 05, France
Fax +33(4)67143847; E-mail: Frederic.lamaty@univ-montp2.fr

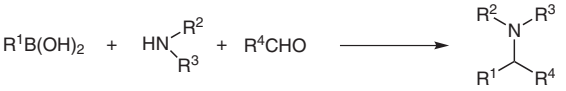
Received 26 February 2010; revised 2 March 2010

Abstract: A new solvent-free microwave-assisted procedure for the Petasis multicomponent reaction was developed. This method is the first application of the borono-Mannich reaction in solvent-free conditions and proved its applicability to various boronic acids and secondary amines. Results are very good in term of yields with shorter reaction time than the classical methods. Because of the efficiency of the method, full conversion of the starting materials towards the expected product was achieved, starting from stoichiometric quantities of reactants, avoiding the usual solvent-consuming column chromatography on silica gel. No purification step other than an aqueous washing was required.

Key words: microwave irradiation, Petasis borono-Mannich reaction, green chemistry, solvent-free

Microwave activation has emerged as a powerful technique in organic synthesis to accelerate the preparation of molecules.[1] Many examples have demonstrated that this technique can be adapted to most organic transformations. Reactions are generally faster, consequently cleaner, and sometimes more selective. Furthermore, the focused heating generated by the microwave enables high temperature to be reached in a short time.

Because of an increasing interest in developing the use of environmentally benign reagents and conditions, a possible approach is to elaborate solvent-free procedures.[2] Problems of safety and toxicity could thus be avoided, in addition to be more economically profitable. Solvent-free microwave activated procedures have so far mostly involved the use of heterogeneous system: inorganic solid support such as alumina, silica gel, or montmorillonite. Nevertheless, when solvent-free procedures are developed, very often a purification step, expensive in solvent, is needed.[3] Microwave activation of neat equimolar amounts of reactants leading to a full conversion of the expected product, thus avoiding a purification step by column chromatography could provide a valuable approach to the development of organic reactions. Motivated by our recent results in the development of solvent-free procedures,[4] we present herein our results concerning the development of such a procedure for the Petasis reaction. Petasis or borono-Mannich reaction is a three-component reaction classically involving a boronic acid, an amine, and an aldehyde[5] (Scheme 1).



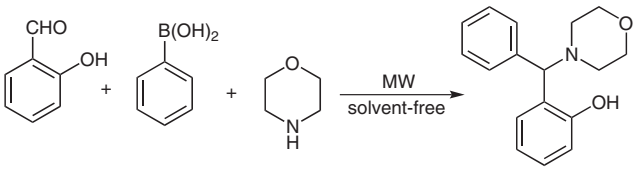
Scheme 1

The two most commonly used aldehydes are glyoxylic acid and salicylaldehyde, but different hydroxy aldehydes also proved their applicability,[6–8] especially to develop an asymmetric version of the reaction.[9] The presence of an hydroxy group or other coordinating group is essential to form a boronate, which can then form the new carbon–carbon bond after reaction with the in situ prepared imine.[6,8,10]

New methods were recently developed in order to improve reaction time, reactivity, and to reduce the environmental impact. We can quote here the use of water,[11] ionic liquids,[12] hexafluoroisopropanol,[13] organotrifluoroborates[14] boronates,[15] or thioureas.[16] Generally, the reaction time needed 24 hours for completion at room temperature. The use of microwaves was described,[17,18] but even if reaction time could be drastically reduced to 10 minutes at 120 °C, isolated yields were low (mostly inferior to 50%).

Usually, the Petasis borono-Mannich reaction requires a purification using a preparative TLC and more generally a solvent-consuming column chromatography. We chose to develop a solvent-free method for the borono-Mannich reaction, but without any use of solid support in order to simplify the purification of the final product. We limited our investigations to a neat procedure involving an equimolar amount of the three reactants (amine, aldehyde,

Table 1 Optimization of Reaction Conditions



Entry	Temp (°C)	Time	Conversion (%)[a]
1	90	2 h	87
2	120	2 h	99
3	150	45 min	99
4	120 (oil bath)	2 h	84

[a] Measured by ^{1}H NMR spectroscopy.

SYNTHESIS 2010, No. 12, pp 2063–2068
Advanced online publication: 09.04.2010
DOI: 10.1055/s-0029-1218727; Art ID: Z04910SS

boronic acid). To our knowledge, there is no example of such reaction in solvent-free conditions and especially using microwave irradiation with a simplified purification procedure.

Our first efforts focused on the optimization of the reaction conditions using the reaction between phenyl boronic acid, morpholine, and salicylaldehyde. Results are presented in Table 1. Reactants are introduced in the microwave vial without any addition of solvent. A temperature of 90 °C is not enough to obtain a full conversion in two hours (Table 1, entry 1) but at 120 °C and 150 °C the reaction is complete after two hours and 45 minutes, respectively. Heating the reaction mixture at 120 °C with a classical oil bath led to an appreciable conversion of 84%, but inadequate with our solvent-free procedure.

We finally chose to conduct the reaction at 120 °C for two hours (Table 1 entry 2) rather than 150 °C for 45 minutes (Table 1 entry 3), at a temperature more compatible with most organic structures. These conditions were applied to a wide range of boronic acids and secondary amines to prove the versatility of our method (Table 2).

Table 2 Reaction of Boronic Acids with Amines and Salicylaldehyde

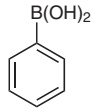
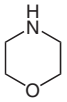
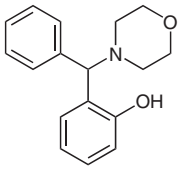
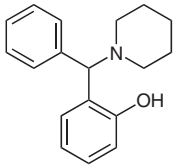
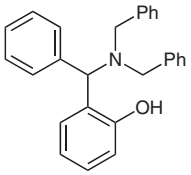
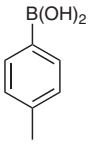
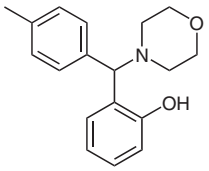
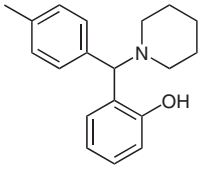
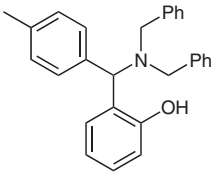
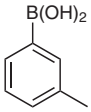
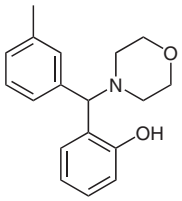
Boronic acid		Amine		Product		Isolated yield (%)
1a		**2a**		**3**		78
		2b		**4**		85
		2c		**5**		85
1b		**2a**		**6**		87
		2b		**7**		82
		2c		**8**		92
1c		**2a**		**9**		78

Table 2 Reaction of Boronic Acids with Amines and Salicylaldehyde (continued)

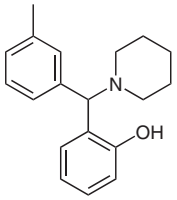
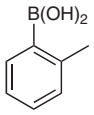
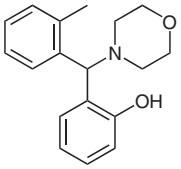
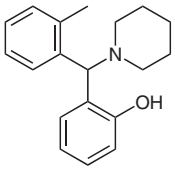
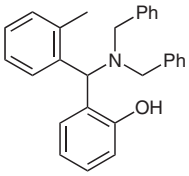
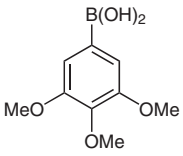
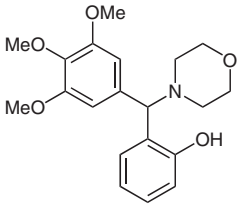
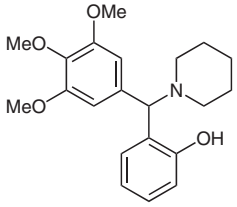
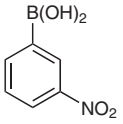
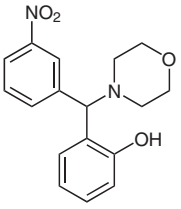
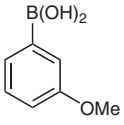
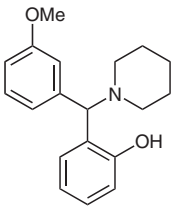
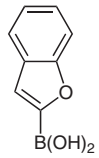
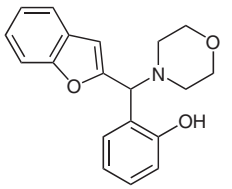
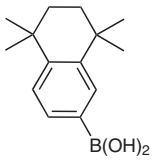
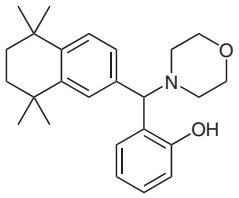
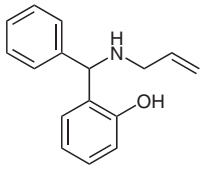
Boronic acid		Amine	Product		Isolated yield (%)
		2b	**10**		82
1d		**2a**	**11**		72
		2b	**12**		87
		2c	**13**		90
1e		**2a**	**14**		92
		2b	**15**		89
1f		**2a**	**16**		87
1g		**2b**	**17**		80

Table 2 Reaction of Boronic Acids with Amines and Salicylaldehyde (continued)

Boronic acid	Amine	Product	Isolated yield (%)
1h 	**2a**	**18** 	95
1i 	**2a**	**19** 	96
1a	**2d** 	**20** 	44

This method provided a large variety of compounds, always in high yields (>72%). Various secondary amines could be used. Boronic acids bearing either an electron-donating or -withdrawing group gave excellent results. We obtained in all cases high conversions with the exclusive formation of the expected product. In order to eliminate salts and the eventual traces of starting reactants, the crude mixture was washed with an aqueous solution of 0.5 N NaOH. This basic washing eliminates in the aqueous phase the boron salts as well as traces of boronic acid (formation of boronates) and salicyladehyde. The product can then be recovered in a pure form and with only few milliliters of ethyl acetate as solvent. The use of glyoxylic acid instead of salicyladehyde gave no conversion in the expected product. With primary amines such as allylamine the conversion to the amine **20** was only 44% and mainly imine was observed. These results are in accordance with those described by Petasis et al.[6] and by McLean et al.[17] for primary amines, observing only poor conversions and the intermediate imine as the main compound.

The practicability and power of the method is well illustrated in the synthesis of benzofuran derivative **18**. This compound has been prepared previously using a microwave-assisted Petasis reaction in a low yield of 23% due to its decomposition during the purification step (column chromatography on silica gel).[17] The same compound could be prepared in 95% yield using the method described herein.

In conclusion, we have developed the first microwave-assisted neat method for the Petasis reaction. A large range of compounds could be prepared including fragile products in two hours at 120 °C and without purification by column chromatography. The use of microwave irradiation permitted to reduce the reaction time and the formation of secondary products, hence providing a simplification of the procedure.

All reagents were purchased from Aldrich Chemical Co. and used without further purification. NMR analyses were performed on Bruker Avance DPX 200 (200 MHz for ^{1}H NMR and 50 MHz for ^{13}C NMR) and Bruker Avance AM 300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) spectrometers. Chemical shifts are reported in ppm and calibrated using residual undeuterated solvents as an internal reference. Mass spectra (electrospray ionization mode, ESI-MS) were recorded on a Micromass Q-TOF quadrupole mass spectrometer fitted with an electrospray interface. The mass spectrometer was calibrated in the positive- and negative-ion ESI modes. The samples were dissolved in a mixture H_2O–MeCN (50:50 v/v). High-resolution mass spectra (HRMS) were recorded on a Jeol JMS DX300-SX 102 in positive mode using NBA (3-nitrobenzylalcohol) or GT (mixture of glycerol–thioglycerol, 50:50 v/v) as matrix. Microwave-assisted reactions were performed in sealed vessels with a Biotage Initiator 60 EXP® instrument.

Reaction of Boronic Acids with Amines; General Procedure

The appropriate boronic acid (0.5 mmol) was introduced in a 2 mL microwave vial, and then salicylaldehyde (0.5 mmol, 53 μL) and the respective amine (0.5 mmol) were successively added. The reaction vessel was sealed and submitted to microwave irradiation at 120 °C during 2 h in a Biotage Initiator microwave oven. After cooling to r.t., EtOAc (5 mL) was added and the mixture washed with aq 0.5 M NaOH (5 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo, to afford the expected product (Table 2).

2-[Morpholino(phenyl)methyl]phenol (3)[11]

Yield: 104.9 mg (78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42–2.77 (m, 4 H), 3.71–3.88 (m, 2 H), 4.45 (s, 1 H), 6.79 (t, *J* = 7.5 Hz, 1 H), 6.91 (d, *J* = 8.1 Hz, 1 H), 6.99 (t, *J* = 7.7 Hz, 1 H), 7.12–7.25 (m, 1 H), 7.27–7.54 (m, 5 H), 11.79 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.24, 66.91, 76.68, 117.06, 119.78, 124.82, 127.77, 128.14, 128.32, 128.44, 129.42, 139.30, 156.11.

MS (ESI): m/z = 270.16 $[M + H]^+$.

2-[Phenyl(piperidin-1-yl)methyl]phenol (4)
Yield: 113.4 mg (85%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22–1.59 (m, 7 H), 2.12–2.49 (m, 3 H), 4.39 (s, 1 H), 6.59 (t, J = 7.3 Hz, 1 H), 6.78 (t, J = 7.9 Hz, 2 H), 7.01 (dt, J = 8.8, 1.6 Hz, 1 H), 7.12–7.25 (m, 3 H), 7.27–7.34 (m, 2 H), 12.51 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.13, 26.11, 52.54, 76.48, 116.86, 119.02, 125.57, 127.83, 128.45, 128.81, 129.20, 139.45, 157.15.

MS (ESI): m/z = 268.3 $[M + H]^+$.

HRMS: m/z calcd for $C_{18}H_{22}NO$: 268.1701; found: 298.1697.

2-[(Dibenzylamino)(phenyl)methyl]phenol (5)[17]
Yield: 161.0 mg (85%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.32 (d, J = 13.3 Hz, 2 H), 3.89 (d, J = 13.3 Hz, 2 H), 5.05 (s, 1 H), 6.78 (t, J = 7.4 Hz, 1 H), 6.72 (d, J = 7.3 Hz, 1 H), 6.87 (d, J = 8.0 Hz, 1 H), 7.08 (t, J = 6.8 Hz, 1 H), 7.15–7.45 (m, 15 H), 12.09 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.76, 68.27, 116.72, 119.04, 124.52, 127.75, 128.55, 128.73, 128.86, 129.40, 129.67, 129.79, 130.61, 131.58, 134.54, 136.92, 157.55.

MS (ESI): m/z = 380.2 $[M + H]^+$.

2-[Morpholino(*p*-tolyl)methyl]phenol (6)[11]
Yield: 123.1 mg (87%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.48–2.50 (m, 4 H), 3.09 (s, 3 H), 3.76–3.79 (m, 4 H), 4.40 (s, 1 H), 6.62 (dt, J = 7.4, 1.2 Hz, 1 H), 6.77 (dd, J = 8.1, 1.1 Hz, 1 H), 6.84 (dd, J = 7.5, 1.6 Hz, 1 H), 6.97–7.05 (m, 2 H), 7.17–7.24 (m, 2 H), 11.81 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.09, 52.2, 66.93, 76.50, 117.00, 119.61, 125.01, 128.47, 128.62, 129.25, 129.61, 136.27, 137.88, 156.12.

MS (ESI): m/z = 284.2 $[M + H]^+$.

2-[Piperidin-1-yl(*p*-tolyl)methyl]phenol (7)[11]
Yield: 115.7 mg (82%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04–1.79 (m, 6 H), 2.35 (s, 3 H), 2.41–2.50 (m, 4 H), 4.50 (s, 1 H), 6.73 (t, J = 6.3 Hz, 1 H), 6.91 (t, J = 8.1 Hz, 2 H), 7.11–7.19 (m, 3 H), 7.29–7.38 (m, 2 H), 12.51 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.12, 24.16, 26.13, 52.43, 76.10, 116.82, 119.01, 125.73, 128.26, 128.78, 129.17, 129.37, 137.53, 140.00, 157.20.

MS (ESI): m/z = 282.3 $[M + H]^+$.

2-[(Dibenzylamino)(*p*-tolyl)methyl]phenol (8)[11]
Yield: 180.7 mg (92%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.49 (s, 3 H), 3.51 (d, J = 13.2 Hz, 2 H), 4.05 (d, J = 13.2 Hz, 2 H), 5.21 (s, 1 H), 6.75–6.84 (m, 1 H), 6.98 (d, J = 7.2 Hz, 1 H), 7.09 (d, J = 8.0 Hz, 1 H), 7.21–7.55 (m, 15 H), 12.29 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.30, 53.85, 67.82, 116.66, 119.09, 124.77, 127.68, 128.55, 128.72, 128.91, 129.20, 129.69, 129.89, 130.69, 132.53, 137.13, 138.09, 157.74.

MS (ESI): m/z = 394.23 $[M + H]^+$.

2-[Morpholino(*m*-tolyl)methyl]phenol (9)
Yield: 110.3 mg (78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 2.44–2.71 (m, 4 H), 3.71–3.88 (m, 4 H), 4.40 (s, 1 H), 6.78 (t, J = 7.3 Hz, 1 H), 6.91 (d, J = 8.1 Hz, 1 H), 6.98 (d, J = 7.4 Hz, 1 H), 7.07–7.33 (m, 5 H), 11.79 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.55, 52.25, 66.93, 76.91, 117.02, 119.58, 125.56, 128.33, 128.63, 129.11, 129.41, 138.60, 139.27, 156.10.

MS (ESI): m/z = 284.07 $[M + H]^+$.

HRMS: m/z calcd for $C_{18}H_{22}NO_2$: 284.1651; found: 284.1643.

2-[Piperidin-1-yl(*m*-tolyl)methyl]phenol (10)
Yield: 115.2 mg (82%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41–1.69 (m, 6 H), 2.35 (s, 3 H), 2.41–2.50 (m, 4 H), 4.46 (s, 1 H), 6.70 (dt, J = 7.5, 1.2 Hz, 1 H), 6.83–6.94 (m, 2 H), 7.01–7.29 (m, 5 H), 12.57 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.57, 24.15, 26.12, 52.54, 76.21, 116.85, 118.99, 125.66, 128.26, 128.61, 129.21, 129.44, 137.44, 140.00, 157.17.

MS (ESI): m/z = 282.12 $[M + H]^+$.

HRMS: m/z calcd for $C_{19}H_{24}NO$: 282.1858; found: 298.1841.

2-[Morpholino(*o*-tolyl)methyl]phenol (11)
Yield: 101.8 mg (72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.51–2.59 (m, 5 H), 2.62–2.89 (m, 2 H), 3.71–3.88 (m, 4 H), 4.95 (s, 1 H), 6.77 (dt, J = 7.4, 1.2 Hz, 1 H), 6.92 (dd, J = 8.1, 1.1 Hz, 1 H), 6.97 (dd, J = 7.6, 1.5 Hz, 1 H), 7.12–7.23 (m, 4 H), 7.61–7.68 (m, 1 H), 11.98 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.55, 52.25, 66.93, 76.91, 117.02, 119.58, 125.56, 128.33, 128.63, 129.11, 129.41, 138.60, 139.27, 156.10.

MS (ESI): m/z = 284.16 $[M + H]^+$.

HRMS: m/z calcd for $C_{18}H_{22}NO_2$: 284.1651; found: 284.1647.

2-[Piperidin-1-yl(*o*-tolyl)methyl]phenol (12)
Yield: 122.2 mg (87%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41–1.69 (m, 6 H), 2.41–2.69 (m, 7 H), 5.01 (s, 1 H), 6.75 (t, J = 7.5 Hz, 1 H), 6.89–6.99 (m, 2 H), 7.09–7.28 (m, 4 H), 7.59–7.70 (m, 1 H), 12.52 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.04, 25.54, 27.61, 53.35, 71.17, 118.17, 120.06, 126.00, 128.55, 128.78, 129.36, 129.73, 137.74, 139.50, 158.52.

MS (ESI): m/z = 282.18 $[M + H]^+$.

HRMS: m/z calcd for $C_{19}H_{24}NO$: 282.1858; found: 298.1847.

2-[(Dibenzylamino)(*o*-tolyl)methyl]phenol (13)
Yield: 176 mg (90%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3 H), 3.79 (d, J = 13.7 Hz, 2 H), 3.99 (d, J = 13.6 Hz, 2 H), 5.48 (s, 1 H), 6.75–6.84 (m, 1 H), 6.98 (d, J = 7.2 Hz, 1 H), 7.09 (d, J = 8.0 Hz, 1 H), 7.21–7.55 (m, 15 H), 11.98 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.16, 53.01, 53.38, 64.38, 116.85, 119.38, 124.77, 127.68, 128.55, 128.72, 128.91, 129.20, 129.69, 129.89, 130.69, 132.53, 137.13, 138.09, 167.01.

MS (ESI): m/z = 394.21 $[M + H]^+$.

HRMS: m/z calcd for $C_{28}H_{28}NO$: 394.2171; found: 394.2161.

2-[Morpholino(3,4,5-trimethoxyphenyl)methyl]phenol (14)
Yield: 165.7 mg (92%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38–2.72 (m, 4 H), 3.68–3.89 (m, 13 H), 4.28 (s, 1 H), 6.63–6.71 (m, 1 H), 6.75 (dt, J = 7.3, 1.2 Hz, 1 H), 6.87 (dd, J = 8.1, 1.1 Hz, 1 H), 6.96 (dd, J = 7.6, 1.6 Hz, 1 H), 7.09–7.18 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.23, 56.11, 60.82, 66.88, 105.22, 117.06, 119.83, 124.83, 128.73, 129.31, 135.19, 137.67, 153.85, 161.56.

MS (ESI): *m*/*z* = 360.1 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{20}H_{26}NO_5$: 360.1811; found: 360.1807.

2-[Piperidin-1-yl(3,4,5-trimethoxyphenyl)methyl]phenol (15)
Yield: 158.2 mg (89%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37–1.72 (m, 6 H), 2.27–2.53 (m, 4 H), 3.79 (s, 3 H), 3.83 (s, 3 H), 4.31 (s, 1 H), 6.61–6.72 (m, 2 H), 6.83 (d, *J* = 7.2 Hz, 1 H), 6.91 (d, *J* = 7.5 Hz, 1 H), 7.05–7.13 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.12, 25.81, 52.56, 56.09, 60.82, 105.23, 116.87, 119.08, 125.65, 128.70, 129.08, 135.56, 137.45, 153.05, 153.23, 156.94.

MS (ESI): *m*/*z* = 358.2 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{21}H_{28}NO_4$: 358.2018; found: 358.2014.

2-[Morpholino(3-nitrophenyl)methyl]phenol (16)
Yield: 136.3 mg (87%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32–2.81 (m, 4 H), 3.69–3.90 (m, 4 H), 4.53 (s, 1 H), 6.68 (t, *J* = 7.5 Hz, 1 H), 6.88 (d, *J* = 8.1 Hz, 1 H), 6.97 (d, *J* = 7.5 Hz, 1 H), 7.01–7.18 (m, 1 H), 7.42–7.58 (t, *J* = 8.0 Hz, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 8.17 (dd, *J* = 7.2 1.2 Hz, 1 H), 8.28 (s, 1 H), 11.32 (s,1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.70, 52.36, 66.72, 76.36, 117.52, 120.05, 123.18, 123.44, 123.61, 129.18, 129.39, 130.21, 134.23, 141.65, 148.46, 155.76.

MS (ESI): *m*/*z* = 314.9 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{17}H_{19}N_2O_4$: 315.1345; found: 315.1330.

2-[(3-Methoxyphenyl)(piperidin-1-yl)methyl]phenol (17)
Yield: 118.5 mg (80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31–1.69 (m, 7 H), 2.19–2.37 (m, 3 H), 3.67 (s, 3 H), 4.33 (s, 1 H), 6.59 (dt, *J* = 7.4, 1.2 Hz, 1 H), 6.69 (dd, *J* = 8.2, 2.5 Hz, 1 H), 6.75 (dd, *J* = 8.1, 1.1 Hz, 1 H), 6.80 (dd, *J* = 7.6, 1.5 Hz, 1 H), 6.85–6.95 (m, 2 H), 7.00 (dt, *J* = 7.7, 1.7 Hz, 1 H), 7.12 (t, *J* = 8.0 Hz, 1 H), 12.31 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.14, 26.11, 52.54, 55.17, 76.50, 112.86, 113.96, 116.86, 118.03, 121.03, 125.48, 128.33, 129.17, 129.69, 141.15, 157.10, 159.75.

MS (ESI): *m*/*z* = 298.11 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{19}H_{24}NO_2$: 298.1807; found: 298.1794.

2-[Benzofuran-2-yl(morpholino)methyl]phenol (18)[17]
Yield: 146.4 mg (95%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.49–2.93 (m, 4 H), 3.62–3.98 (m, 4 H), 4.86 (s, 1 H), 6.71–6.89 (m, 2 H), 6.91–7.01 (m, 2 H), 7.12–7.45 (m, 3 H), 7.47–7.68 (m, 2 H), 11.19 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.37, 66.94, 68.50, 106.44, 111.52, 116.97, 119.59, 121.63, 122.74, 123.06, 124.55, 127.89, 129.25, 129.54, 154.16, 154.93, 156.89.

MS (ESI): *m*/*z* = 310.1 $[M + H]^+$.

2-[Morpholino(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methyl]phenol (19)
Yield: 181.9 mg (96%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (m, 12 H), 1.61–1.71 (m, 4 H), 2.41–2.59 (m, 4 H), 3.70–3.82 (m, 4 H), 4.40 (s, 1 H), 6.73 (t, *J* = 7.5 Hz, 1 H), 6.85 (d, *J* = 7.3 Hz, 1 H), 6.96 (d, *J* = 7.2 Hz, 1 H), 7.09–7.24 (m, 4 H), 11.79 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.85, 34.21, 35.04, 51.95, 67.00, 76.55, 116.89, 119.42, 124.96, 125.47, 127.06, 128.54, 129.49, 135.51, 141.65, 144.60, 145.13, 156.42.

MS (ESI): *m*/*z* = 380.3 $[M + H]^+$, 293.3.

HRMS: *m*/*z* calcd for $C_{25}H_{34}NO_2$: 380.2590; found: 380.2585.

Acknowledgment

We thank the Fondation d'Entreprise EADS for financial support.

References

(1) (a) Loupy, A. *Microwaves in Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, **2006**. (b) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, **2005**, 29–55. (c) Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* **2008**, 1125. (d) Appukkuttan, P.; Van der Eycken, E. *Eur. J. Org. Chem.* **2008**, 1133.
(2) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev.* **2009**, *109*, 4140.
(3) (a) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213. (b) Tanaka, K. *Solvent-Free Organic Synthesis*; Wiley-VCH: Weinheim, **2003**, 433. (c) Varma, R. S.; Naicker, K. P.; Kumar, D.; Dahiya, R.; Liesen, P. J. *J. Microwave Power Electromagn. Energy* **1999**, *34*, 113.
(4) (a) Colacino, E.; Nun, P.; Colacino, F. M.; Martinez, J.; Lamaty, F. *Tetrahedron* **2008**, *64*, 5569. (b) Declerck, V.; Nun, P.; Martinez, J.; Lamaty, F. *Angew. Chem. Int. Ed.* **2009**, *48*, 9318. (c) Nun, P.; Martinez, J.; Lamaty, F. *Synlett* **2009**, 1761.
(5) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583.
(6) Petasis, N. A.; Boral, S. *Tetrahedron Lett.* **2001**, *42*, 539.
(7) (a) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445. (c) Prakash, G. K. S.; Mandal, M.; Schweizer, S.; Petasis, N. A.; Olah, G. A. *Org. Lett.* **2000**, *2*, 3173. (d) Prakash, G. K. S.; Mandal, M.; Schweizer, S.; Petasis, N. A.; Olah, G. A. *J. Org. Chem.* **2002**, *67*, 3718.
(8) Schlienger, N.; Bryce, M. R.; Hansen, T. K. *Tetrahedron* **2000**, *56*, 10023.
(9) (a) Kaiser, P. F.; Churches, Q. I.; Hutton, C. A. *Aust. J. Chem.* **2007**, *60*, 799. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.
(10) Wang, Q.; Finn, M. G. *Org. Lett.* **2000**, *2*, 4063.
(11) Candeias, N. R.; Veiros, L. F.; Afonso, C. A. M.; Gois, P. M. P. *Eur. J. Org. Chem.* **2009**, 1859.
(12) Yadav, P. N.; Reddy, B. V. S.; Lakshmi, P. N. *J. Mol. Catal. A: Chem.* **2007**, *274*, 101.
(13) Nanda, K. K.; Trotter, B. W. *Tetrahedron Lett.* **2005**, *46*, 2025.
(14) Tremblay-Morin, J.-P.; Raeppel, S.; Gaudette, F. *Tetrahedron Lett.* **2004**, *45*, 3471.
(15) Jourdan, H.; Gouhier, G.; Van Hijfte, L.; Angibaud, P.; Piettre, S. R. *Tetrahedron Lett.* **2005**, *46*, 8027.
(16) Yamaoka, Y.; Miyabe, H.; Takemoto, Y. *J. Am. Chem. Soc.* **2007**, *129*, 6686.
(17) McLean, N. J.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2004**, *45*, 993.
(18) Follmann, M.; Graul, F.; Schäfer, T.; Kopec, S.; Hamley, P. *Synlett* **2005**, 1009.