



Microwave-assisted synthesis of pyrrolidine derivatives

Yuan-Chun Chang^a, Jiun-Ly Chir^b, Shuan-Yi Tsai^a, Wei-Fu Juang^a, An-Tai Wu^{a,*}

^a Department of Chemistry, National Changhua University of Education, Changhua 50058, Taiwan

^b Biotechnology Center in Southern Taiwan, Academia Sinica, Tainan County 744, Taiwan

ARTICLE INFO

Article history:

Received 13 April 2009

Revised 2 June 2009

Accepted 12 June 2009

Available online 16 June 2009

Keywords:

Amination

Bismesylate

Pyrrolidine

Microwave irradiation

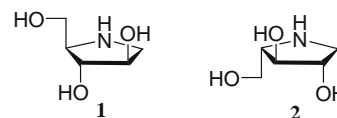
ABSTRACT

Microwave-assisted bismesylate amination is an efficient method of synthesizing pyrrolidine ring derivatives and provides a good to excellent product yield.

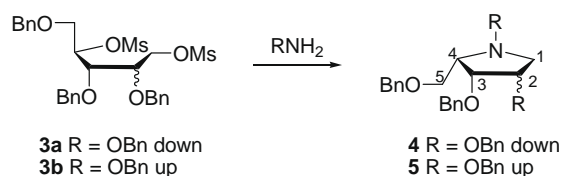
© 2009 Elsevier Ltd. All rights reserved.

Polyhydroxylated pyrrolidines,¹ a sub-class of iminosugars that naturally occurs in plants and microorganisms, have attracted attention due to their significant biological activities. Many of them are potent glycosidase and glycosyltransferase inhibitors² because their structures mimic the transition states of an enzyme-catalyzed reaction. The hydroxylated pyrrolidine analogues, such as 1,4-dideoxy-1,4-imino-D-arabinitol (DAB1) **1**, show potent inhibitory potential and a broad inhibitory spectrum toward mammalian glucosidases, including α -glucosidase II, α -mannosidases I and II, intestinal isomaltase, and trehalase.³ In addition, 1,4-dideoxy-1,4-imino-L-arabinitol (LAB1) **2**, the L isomer of **1**, shows potent inhibition toward the α -L-arabinofuranosidase III of *Monilinia fructigena*.⁴ Therefore, many synthetic approaches have focused on the preparation of analogues of polyhydroxylated pyrrolidines **1** derived from carbohydrates⁵ and non-carbohydrates.⁶ However, the preparations of pyrrolidine analogues⁷ are multistep procedures and provide low yield and/or poor stereoselectivity. Among these, construction of the pyrrolidine ring through amination of benzylamine with dimesylate analogues to afford N-benzyl pyrrolidine derivatives has been reported.⁸ However, under conventional conditions, this kind of transformation often requires a long reaction time and high temperature to allow the substitution to take place and, at best, the product yield is low. Therefore, finding a practical method to synthesize pyrrolidine analogues is necessary. Microwave-assisted reaction conditions⁹ are well known and greatly increase yields, but their application in the field of carbohydrate research has not been yet widespread. To demonstrate the effi-

ciency of this approach, this study explores the use of microwave irradiation to develop an efficient and rapid procedure for preparing N-substituted pyrrolidine analogues. These compounds may lead to precursors of potent glycosidase inhibitors.



N-Substituted pyrrolidine analogues were synthesized by the amination of dimesylate **3a** with various alkylamines (Scheme 1). Heating dimesylate **3a** with various alkylamines under reflux conditions in the absence of solvent produced some of the desired products (**4a–e**), but only at a low yield (Table 1, entries 1, 3, 5, 7, and 9). However, when 2-aminoethanol was applied under conventional conditions, the amination reaction could not produce the desired product **4f** even with an extended reaction time (entry 11). The conversion was markedly improved when the reaction was performed under microwave conditions in a microwave oven



Scheme 1.

* Corresponding author. Fax: +886 4 7211 190.

E-mail address: antai@cc.ncue.edu.tw (A.-T. Wu).

Table 1
Comparative amination of dimesylate **3** under microwave irradiation and under conventional conditions¹⁰

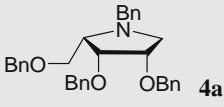
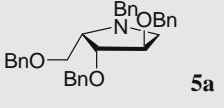
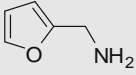
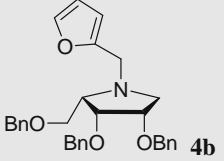
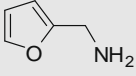
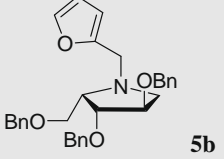
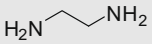
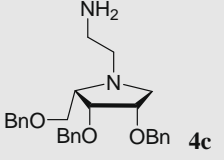
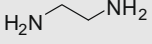
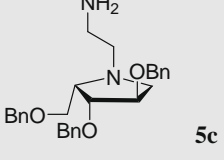
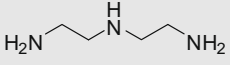
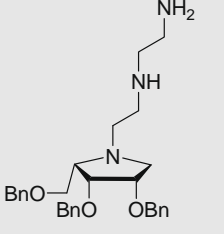
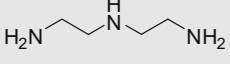
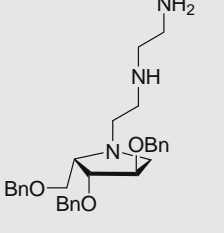
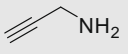
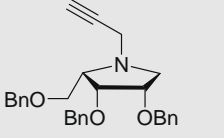
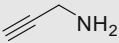
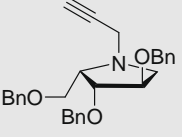
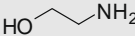
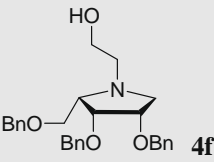
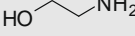
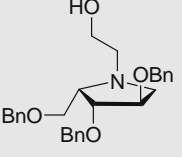
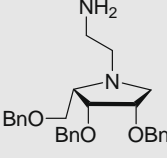
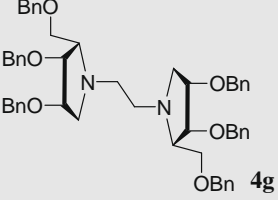
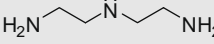
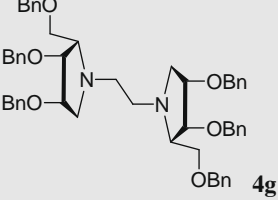
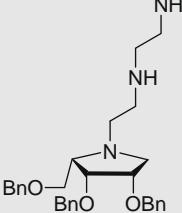
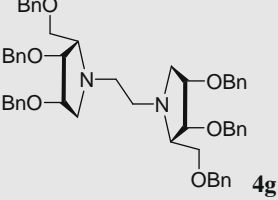
Entry	Reactant	Product	Temp (°C)	Microwave		Conventional	
				Time (min)	Yield (%)	Time (min)	Yield (%)
1 ^a	BnNH ₂	 4a	120	20	99	120	58
2 ^a	BnNH ₂	 5a	120	20	97		
3 ^a		 4b	120	10	99	90	75
4 ^a		 5b	120	10	93		
5 ^a		 4c	116	10	99	600	67
6 ^a		 5c	116	10	96		
7 ^a		 4d	120	10	99	60	85
8 ^a		 5d	120	10	99		
9 ^a		 4e	84	60	76	1110	36

Table 1 (continued)

Entry	Reactant	Product	Temp (°C)	Microwave		Conventional	
				Time (min)	Yield (%)	Time (min)	Yield (%)
10 ^a		 5e	84	60	70		
11 ^a		 4f	120	10	97	4320	—
12 ^a		 5f	120	10	95		
13 ^a	 4c	 4g	120	30	—	4320	—
14 ^b		 4g	120	20	78	4320	—
15 ^b	 4d	 4g	120	30	64	4320	—

^a This reaction was performed under solvent-free conditions. (—) = no reaction.

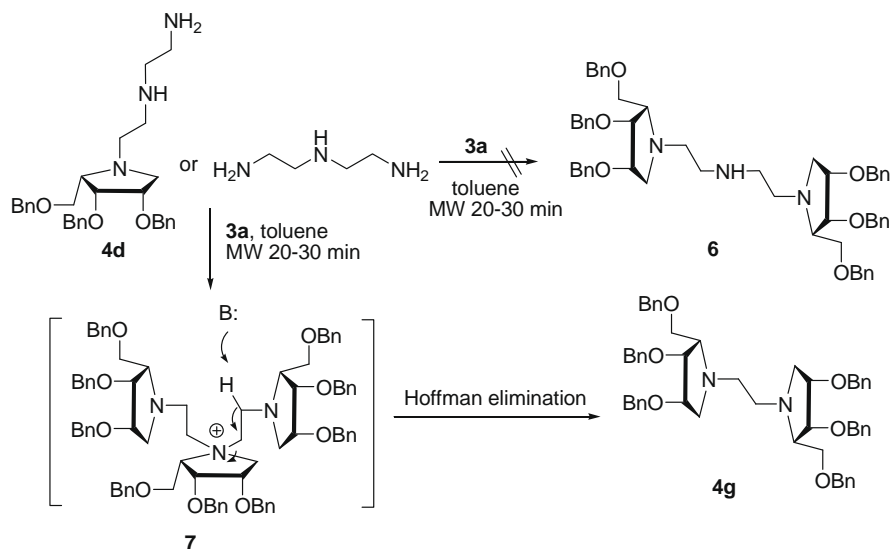
^b This reaction was performed in toluene. (—) = no reaction.

(300 W) for 10 min, producing the corresponding N-alkylated pyrrolidine derivative (**4a–f**, entries 1, 3, 5, 7, 9, and 11).¹⁰ The amination of dimesylate **3b** with various alkylamines was also performed under microwave conditions, producing an excellent yield of products (**5a–f**, entries 2, 4, 6, 8, 10, and 12). In both the synthesized N-alkylated pyrrolidine derivatives **4** and **5**, the synthetic processes did not change the absolute configurations at C(2) or C(3). However, the configuration at C(4) was inverted to that of the starting material, which resulted from a stereocontrolled cyclization process.

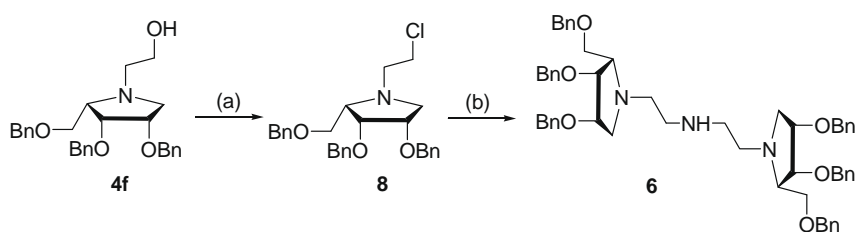
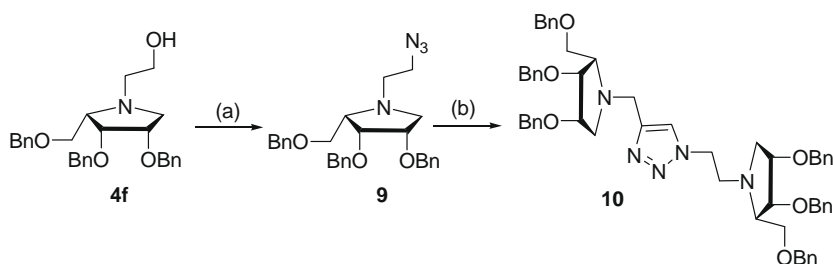
Based on these results, we attempted to extend this methodology to the synthesis of dimeric pyrrolidine derivatives using similar conditions, except for variations in the solvent (Table 1). Amination of **4c** with dimesylate **3a** in toluene under both types of heating conditions was not successful and did not yield the de-

sired product **4g** (Table 1, entry 13). Surprisingly, amination of **4d** or diethylenetriamine with dimesylate **3a** (3.0 equiv) in toluene for 20–30 min under microwave irradiation produced a Hoffman elimination product **4g** as the major product,¹¹ and none of the desired compound **6** (entries 14 and 15). In contrast, we could not obtain the Hoffman elimination product **4g** or **6** under conventional heating conditions. The proposed mechanism for this transformation is shown in Scheme 2. These results demonstrate that the microwave-assisted approach overcame steric problems and produced intermediate **7**, which underwent further elimination to produce **4g**.

Compound **6** can be obtained using the N-alkylated derivative **4f** as the starting material. When **4f** underwent standard mesylation in the presence of triethylamine or pyridine, it produced an unexpected chloride derivative **8** (62%) instead of the mesyl deriv-



Scheme 2.

Scheme 3. Reagents and conditions: (a) MsCl, TEA; CH₂Cl₂; (b) **4c**, TEA, CH₃CN.Scheme 4. Reagents and conditions: (a) HN₃, THF; (b) Cu(I), **4e**, MeOH.

ative. Compound **6** can be successfully obtained by treatment of **8** with **4c** and TEA in CH₃CN under conventional refluxing for 19 h, but the yield of **6** is low (36%). However, when this reaction was performed under microwave conditions at 80 °C for 20 min in CH₃CN, the yield improved to 57% (Scheme 3).

With compounds **4e** and **4f** in hand, we then attempted to synthesize the dimeric pyrrolidine derivative **10** using a triazole as a linker (Scheme 4). Treating **4f** with hydrazoic acid (HN₃) in THF produced the azido derivative **9**. Compound **9** was treated with **4e** and copper(I) catalyst in ethanol under reflux¹² for 12 h, producing the sugar triazole **10** (44%) with 1,4-regioselectivity. When this reaction was conducted under microwave conditions with 20 min irradiation, the yield improved to 65%.

In conclusion, this study shows that amination reactions of dimesylate **3** with various alkylamines can be substantially improved by microwave heating. This approach shortens reaction

times from 1.5–72 h to 10–30 min and the yields are also improved. Following subsequent deprotection, these compounds may lead to more potent glycosidase inhibitors and such work is currently underway.

Acknowledgment

This work was supported by the National Science Council of Taiwan.

References and notes

- Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680.
- (a) Wicki, J.; Williams, S. J.; Withers, S. G. *J. Am. Chem. Soc.* **2007**, *129*, 4530–4531; (b) Sears, P.; Wong, C. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300–2324; (c) Butters, T.; Dwek, R. A.; Platt, M. *Chem. Rev.* **2000**, *100*, 4683–4696; (d) Gloster,

- T. M.; Meloncelli, P.; Stick, R. V.; Zechel, D.; Vasella, A.; Davies, G. J. *J. Am. Chem. Soc.* **2007**, *129*, 2345–2354; (e) Caines, M. E. C.; Hancock, S. M.; Tarling, C. A.; Wrodnigg, T. M.; Stick, R. V.; Stutz, A. E.; Vasella, A.; Withers, S. G.; Strynadka, N. C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4474–4476.
3. (a) Wrodnigg, T. M. *Monatsh. Chem.* **2002**, *133*, 393–426; (b) Kato, A.; Adachi, I.; Miyauchi, M.; Ikeda, K.; Komae, T.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Wormald, M. R.; Fleet, G. W. J.; Asano, N. *Carbohydr. Res.* **1999**, *316*, 95–103.
4. (a) Scofield, A. M.; Fellows, L. E.; Nash, R. J.; Fleet, G. W. *Life Sci.* **1986**, *39*, 645–650; (b) Axamawaty, M. T. H.; Fleet, G. W. J.; Hannah, K. A.; Namgoong, S. K.; Sinnott, M. L. *Biochem. J.* **1990**, *266*, 245–249.
5. (a) Kim, J. H.; Yang, M. S.; Lee, W. S.; Park, K. H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2877–2880; (b) Kim, Y. J.; Kido, M.; Bando, M.; Kitahara, T. *Tetrahedron* **1997**, *53*, 7501–7508; (c) Overkleeft, H. S.; van Wiltenburg, J.; Pandit, U. K. *Tetrahedron* **1994**, *50*, 4215–4224; (d) Fleet, G. W. J.; Witty, D. R. *Tetrahedron: Asymmetry* **1990**, *1*, 119–136; (e) Fleet, G. W. J.; Smith, P. W. *Tetrahedron* **1986**, *42*, 5685–5692.
6. Zhou, X.; Liu, W.-J.; Ye, J.-L.; Huang, P.-Q. *Tetrahedron* **2007**, *63*, 6346–6357.
7. (a) Gautier-Lefebvre, I.; Behr, J.-B.; Guillerm, G.; Muzard, M. *Eur. J. Med. Chem.* **2005**, *40*, 1255–1261; (b) Chakraborty, C.; Dhavale, D. D. *Carbohydr. Res.* **2006**, *341*, 912–917; (c) Huang, Y.; Dalton, D. R. *J. Org. Chem.* **1997**, *62*, 372–376; (d) Kim, I. S.; Kim, S. J.; Lee, J. K.; Li, Q. R.; Jung, Y. H. *Carbohydr. Res.* **2007**, *342*, 1502–1509; (e) Joseph, C. C.; Regeling, H.; Zwanenburg, B.; Chittenden, G. J. F. *Carbohydr. Res.* **2002**, *337*, 1803–1807; (f) Lauritsen, A.; Madsen, R. *Org. Biomol. Chem.* **2006**, *4*, 2898–2905.
8. Behr, J.-B.; Guillerm, G. *Tetrahedron Lett.* **2007**, *48*, 2369–2372.
9. (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284; (b) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283; (c) Couri, M. R.; Luduvico, I.; Santos, L.; Alves, R.; Prado, M. A.; Gil, R. F. *Carbohydr. Res.* **2007**, *342*, 1096–1100; (d) Gadhwal, S.; Baruah, M.; Sandhu, J. S. *Chem. Commun.* **1999**, 1573–1574; (e) Loupy, A.; Pigeon, P.; Ramdani, M. *Tetrahedron* **1996**, *52*, 6705–6712; (f) Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. *Synthesis* **2003**, *18*, 2877–2881.
10. (a) *Conventional heating conditions*: a solution of **3** (0.883 mmol) in alkylamine (5 mL) was refluxed for 1.5–2 h. After cooling, the solvent was removed in vacuo. The mixture was diluted with water and extracted with CH₂Cl₂ (3 × 10 mL). The organic layer was washed with brine, dried over MgSO₄, and concentrated under vacuum. (b) *Microwave heating conditions*: a solution of **3** (1.83 mmol) in alkylamine (5 mL) was refluxed for 10–30 min by microwave irradiation (300 W) (Milestone Start S). After cooling, the mixture was diluted with water and extracted with CH₂Cl₂ (3 × 10 mL). The organic layer was washed with brine, dried over MgSO₄, and concentrated under vacuum.
11. *Characterization data of compound 4g*: a yellow syrup. ¹H NMR (CDCl₃, 300 MHz): δ 7.39–7.19 (m, 15H, Ph), 4.74, 4.63 (AB, *J* = 12.0 Hz, 2H, PhCH₂), 4.58 (s, 2H, PhCH₂), 4.49 (s, 2H, PhCH₂), 4.05 (dd, *J* = 8.4, 4.5 Hz, 1H, H-3), 3.99 (dd, *J* = 9.9, 5.1 Hz, 1H, H-4), 3.84 (dd, *J* = 9.0, 6.6 Hz, 1H, H-1a), 3.63 (dd, *J* = 9.3, 5.7 Hz, 1H, H-1b), 3.20 (dd, *J* = 10.5, 5.1 Hz, 1H, H-5a), 3.04 (dd, *J* = 12.3, 6.6 Hz, 1H, H-2), 3.01–2.88 (m, 1H, H-6a), 2.67 (dd, *J* = 10.5, 6.3 Hz, 1H, H-5b), 2.65–2.51 (m, 1H, H-6b); ¹³C NMR (CDCl₃, 75 MHz): δ 138.6 (Ph), 138.5 (Ph), 138.4 (Ph), 128.2 (Ph), 128.2 (Ph), 128.1 (Ph), 127.6 (Ph), 127.6 (Ph), 127.4 (Ph), 127.4 (Ph), 127.3 (Ph), 78.3 (C-3), 77.3 (C-4), 73.2 (PhCH₂), 72.8 (PhCH₂), 71.6 (PhCH₂), 70.0 (C-1), 64.8 (C-2), 55.7 (C-5), 54.5 (C-6); HRMS (FAB): calcd for C₅₄H₆₁N₂O₆ (M+H), *m/z* 833.4530; found *m/z* 833.4527.
12. Chandrasekhar, S.; Rao, C. L.; Nagesh, C.; Reddy, C. R.; Sridhar, B. *Tetrahedron Lett.* **2007**, *48*, 5869–5872.