Tetrahedron Letters 50 (2009) 4925–4929

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# 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

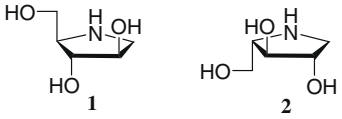
*Keywords:*
Amination
Bismesylate
Pyrrolidine
Microwave irradiation

ABSTRACT

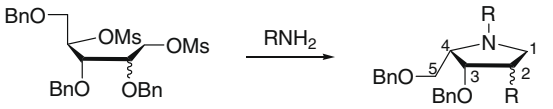
Microwave-assisted bismesylate amination is an efficient method of synthesizing pyrrolidine ring derivatives and provides a good to excellent product yield.



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 inhibitors[2] 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 carbohydrates[5] and non-carbohydrates.[6] However, the preparations of pyrrolidine analogues[7] are multistep procedures and provide low yield and/or poor stereoselectivity. Among these, construction of the pyrroline 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 pyrrolodine analogues is necessary. Microwave-assisted reaction conditions[9] are well known and greatly increase yields, but their application in the field of carbohydrate research has not been yet widespread. To demonstrate the efficiency 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




**3a** R = OBn down
**3b** R = OBn up

**4** R = OBn down
**5** R = OBn up

**Scheme 1.**

* Corresponding author. Fax: +886 4 7211 190.
*E-mail address:* antai@cc.ncue.edu.tw (A.-T. Wu).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.06.062

**Table 1**
Comparative amination of dimesylate **3** under microwave irradiation and under conventional conditions[10]

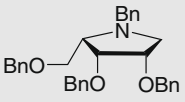
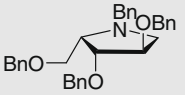
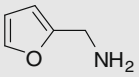
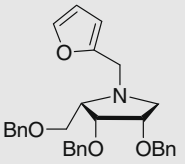
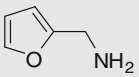
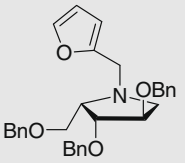
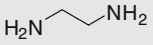
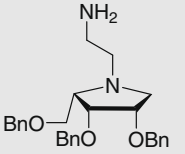
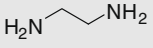
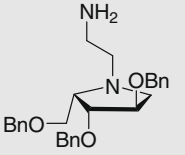
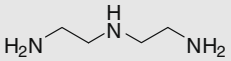
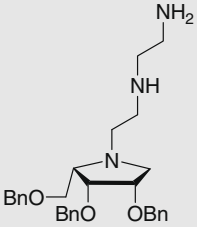
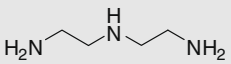
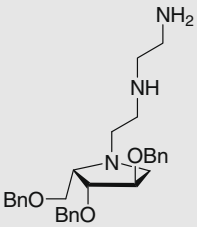
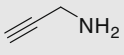
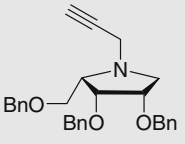
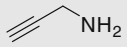
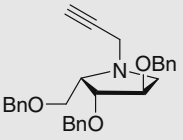
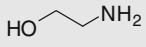
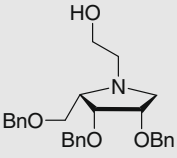
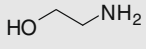
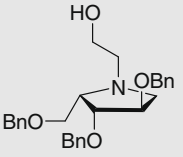
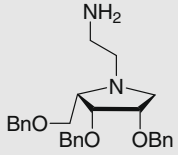
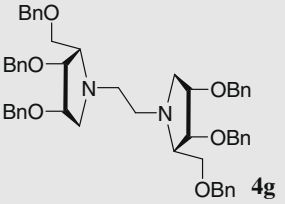
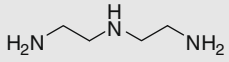
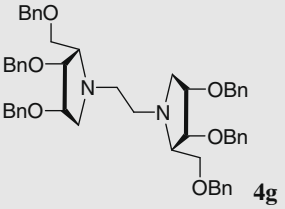
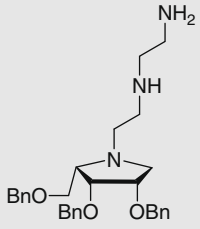
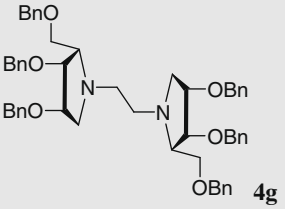
| Entry | Reactant | Product | Temp (°C) | Microwave | | Conventional | |
|---|---|---|---|---|---|---|---|
| | | | | Time (min) | Yield (%) | Time (min) | Yield (%) |
| 1[a] | $BnNH_2$ |  **4a** | 120 | 20 | 99 | 120 | 58 |
| 2[a] | $BnNH_2$ |  **5a** | 120 | 20 | 97 | | |
| 3[a] |  |  **4b** | 120 | 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*)

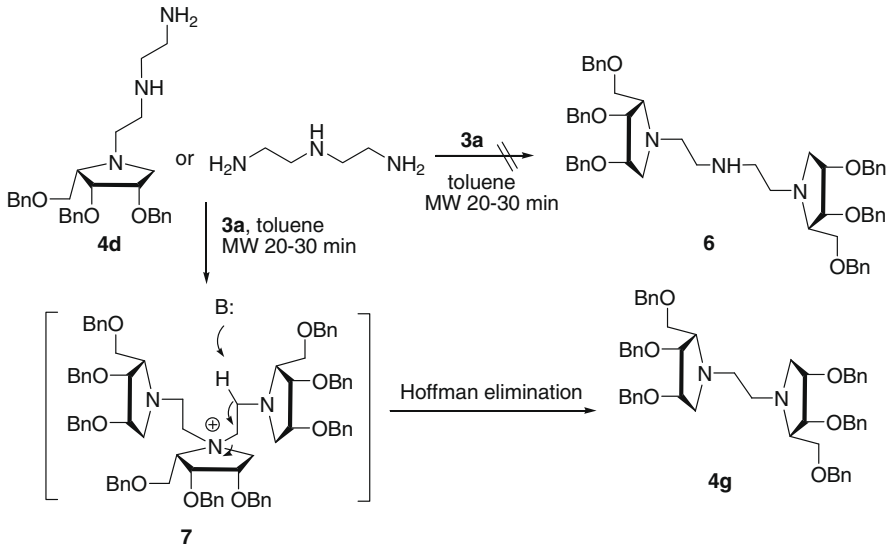
| Entry | Reactant | Product | Temp (°C) | Microwave | | Conventional | |
|---|---|---|---|---|---|---|---|
| | | | | Time (min) | Yield (%) | Time (min) | Yield (%) |
| 10[a] |  |  **5e** | 84 | 60 | 70 | | |
| 11[a] |  |  **4f** | 120 | 10 | 97 | 4320 | — |
| 12[a] |  |  **5f** | 120 | 10 | 95 | | |
| 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.

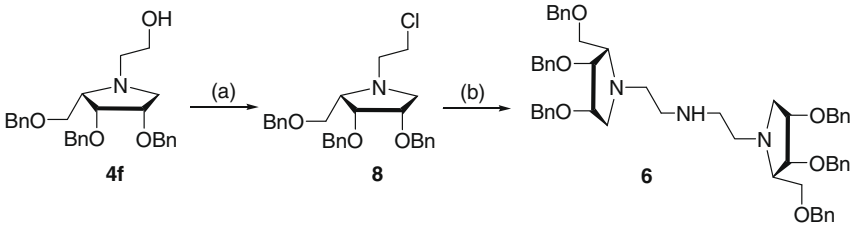
(300 W) for 10 min, producing the corresponding N-alkylated pyrrolidine derivative (**4a**–**f**, entries 1, 3, 5, 7, 9, and 11).[10] The amination of dimesylate **3b** with various alkylamines was also performed under microwave conditions, producing an excellent yield of products (**5a**–**f**, entries 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 desired 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**.

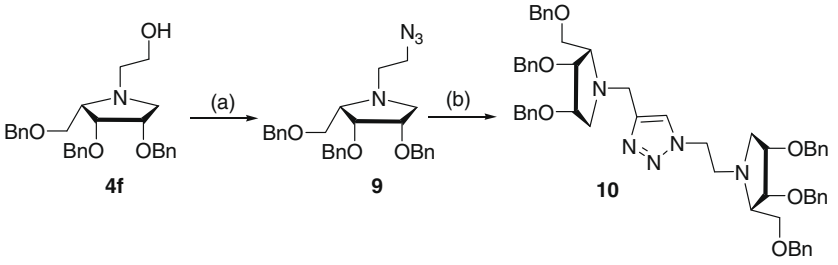
Compound **6** can be obtained using the N-alkylated derivative **4f** as the starting material. When **4f** underwent standard mesylation in the presence of triethylamine or pyridine, it produced an unexpected chloride derivative **8** (62%) instead of the mesyl deriv-




**Scheme 2.**




**Scheme 3.** Reagents and conditions: (a) MsCl, TEA; $CH_2Cl_2$; (b) **4c**, TEA, $CH_3CN$.




**Scheme 4.** Reagents and conditions: (a) $HN_3$, THF; (b) Cu(0), **4e**, MeOH.

ative. Compound **6** can be successfully obtained by treatment of **8** with **4c** and TEA in $CH_3CN$ 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 $CH_3CN$, 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 ($HN_3$) in THF produced the azido derivative **9**. Compound **9** was treated with **4e** and copper(I) catalyst in ethanol under reflux[12] 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.

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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.

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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 $CH_2Cl_2$ ($3 \times 10$ mL). The organic layer was washed with brine, dried over $MgSO_4$, 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 $CH_2Cl_2$ ($3 \times 10$ mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum.
11. *Characterization data of compound* **4g**: a yellow syrup. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.39–7.19 (m, 15H, Ph), 4.74, 4.63 (AB, $J$ = 12.0 Hz, 2H, $PhCH_2$), 4.58 (s, 2H, $PhCH_2$), 4.49 (s, 2H, $PhCH_2$), 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); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ 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 ($PhCH_2$), 72.8 ($PhCH_2$), 71.6 ($PhCH_2$), 70.0 (C-1), 64.8 (C-2), 55.7 (C-5), 54.5 (C-6); HRMS (FAB): calcd for $C_{54}H_{61}N_2O_6$ (M+H), $m/z$ 833.4530; found $m/z$ 833.4527.
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