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Microwave-assisted synthesis of the Schöllkopf chiral auxiliaries: (3*S*)- and (3*R*)-3,6-dihydro-2,5-diethoxy-3-isopropyl-pyrazine

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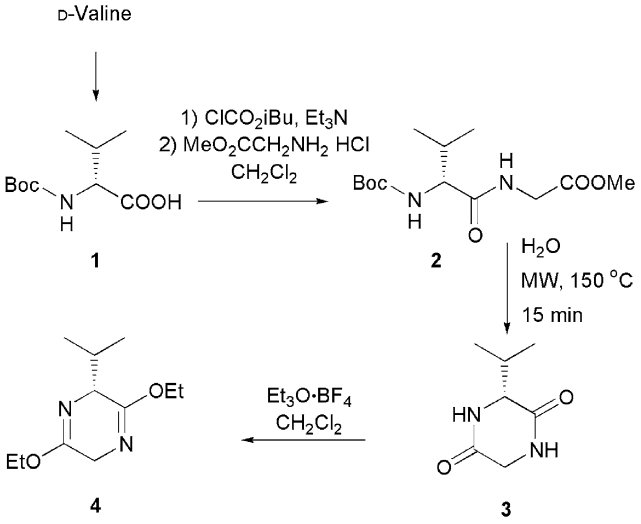
Abstract—A practical and efficient methodology for the laboratory scale preparation of Schöllkopf's bis-lactim ether chiral auxiliaries (3*S*)- and (3*R*)-3,6-dihydro-2,5-diethoxy-3-isopropyl-pyrazine has been developed. The key step is the preparation of the 2,5-diketopiperazine derivative by microwave-assisted heating in water. The protocol avoids reactions at low temperature and the use of high boiling solvents. Only inexpensive and readily available starting materials are required. The bis-lactim ethers were produced in high yields on a multigram scale.

The development of new methods for the synthesis of both natural and unnatural α-amino acids has attracted considerable attention over the past decades. Such amino acids are important tools in both chemistry and biology, either as free amino acids or as components of more complex entities.[1] Work in this area has focused upon the asymmetric synthesis of α-amino acids or α,α-disubstituted amino acids by the alkylation of achiral enolates of glycine or alanine derivatives, respectively. Many different cyclic glycine and alanine chiral templates have been described, with Schöllkopf's bis-lactim ethers **4** being one of the most used.[2] The synthesis of the Schöllkopf ethers has been reported by several groups.[3] Although these synthetic procedures seem straightforward, we have experienced several drawbacks using these protocols, including the use of highly toxic phosgene or triphosgene, the need for extensive purification and the requirement for freshly prepared alkylating agent for the final alkylation step. Recently, Chen et al.[4] addressed some of these problems by using isobutyl chloroformate instead of phosgene to prepare the valine anhydride intermediate. Herein, we report a highly efficient microwave-assisted laboratory-scale protocol for the generation of **4** by employing inexpensive and readily available starting materials and minimum purification.

Our synthetic strategy to (3*R*)-3,6-dihydro-2,5-diethoxy-3-isopropyl-pyrazine is outlined in Scheme 1. The corresponding 3*S* isomer was prepared by the same protocol starting from L-valine. D-Valine was converted to Boc-D-valine in a quantitative yield. The dipeptide Boc-D-Val-Gly-OMe **2** was synthesised (on a 0.124 mol scale) by a mixed anhydride approach using isobutyl



Scheme 1. Synthesis of (3*R*)-3,6-dihydro-2,5-diethoxy-3-isopropyl-pyrazine (**4**).

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chloroformate.[4] Aqueous workup, evaporation of the solvent and drying under reduced pressure afforded **2** as a white powder which was used in the next step without any further purification.

Dipeptide **2** was then converted to 2,5-diketopiperazine **3**. This is normally done in two steps: (1) removal of the Boc-group from dipeptide **2** under acidic conditions, followed by (2) cyclisation to form 2,5-diketopiperazine **3** by heating.[3] Cledera et al.[5] reported a quantitative yield for the preparation of **3** by heating neat dipeptide **2** at 200 °C. However, this procedure only gave a moderate yield on a multigram scale.[4] We reasoned that by using microwave-assisted heating, both removal of the Boc group and cyclisation of the dipeptide could be achieved in one step, avoiding the reduction in yield by prolonged thermal heating at 200 °C. Furthermore, we have recently demonstrated the advantages of using microwave-assisted heating combined with water as solvent for the solution phase synthesis of 2,5-diketopiperazines.[6] A suspension of dipeptide **2** (6.67 mmol) in water was heated at 150 °C using microwave irradiation for 15 min in a sealed vial. TLC showed complete conversion. The pressure in the reaction vial almost exceeded the upper pressure range for the instrument (20 bars), due to the generation of CO_2 gas during the thermal breakdown of the Boc protecting group. In order to scale up the reaction further, a large scale instrument for microwave-assisted synthesis was employed. Several experiments were conducted by increasing the amount of **2** suspended in water and heating at 200 °C for 15 min in a sealed container. It was found that 12 g batches of **2** could efficiently be converted to 2,5-diketopiperazine **3**[7] without exceeding the 20 bar pressure limit. Seven batches (7×41.6 mmol) were pooled, the solvent was evaporated and the residue dried under vacuum. The crude product was recrystallised from ethanol:chloroform (3:1 v/v) to afford a white powder in 73% yield.

In the final step of the synthesis, bis-O-alkylation of 2,5-diketopiperazine **3** was carried out to afford the bis-lactim ether **4**. Bis-O-methylation is normally achieved with $Me_3O{\cdot}BF_4$; however, the quality of $Me_3O{\cdot}BF_4$ is of great importance and this reaction works best with freshly prepared reagent.[3a] The preparation of $Me_3O{\cdot}BF_4$ involves the use of gaseous Me_2O and although a protocol for kilogram-scale preparation of this oxophilic alkylating agent is available,[3a] we decided to test the commercially available $Et_3O{\cdot}BF_4$ to generate **4**. One advantage of using $Et_3O{\cdot}BF_4$ is that the reaction mixture becomes homogeneous, and not a two-phase mixture of thick floating oil and solvent, as is the case with $Me_3O{\cdot}BF_4$. 2,5-Diketopiperazine **3** (28.8 mmol) and $Et_3O{\cdot}BF_4$ (97 mmol) were dissolved in dichloromethane and stirred at room temperature. TLC showed complete reaction after 5 days. The pH of the reaction mixture was adjusted to pH 9 during the workup in order to minimise acid-catalysed hydrolysis of the bis-lactim ether. Purification by flash chromatography afforded **4** as an oil.[8] The overall yield starting from D-valine was 71%. ^1H and ^{13}C NMR spectra were in full agreement with the published data.[3a]

In conclusion, we have developed an efficient and straightforward protocol for the preparation of bis-lactim ether **4** from D-valine. The key step is the preparation of 2,5-diketopiperazine **3** in water by microwave-assisted heating. The protocol involves only one chromatographic purification step.

Acknowledgements

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References and notes

1. For representative reviews on the preparation of optically active amino acids: (a) Williams, R. M. In *Synthesis of Optically Active α-Amino Acids*; Baldwin, J. E., Ed.; Organic Chemistry Series; Pergamon Press: Oxford, 1989; (b) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889; (c) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539; (d) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2708; (e) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517.
2. Abellan, T.; Chinchilla, R.; Galindo, N.; Guillena, G.; Najera, C.; Sansano, J. M. *Eur. J. Org. Chem.* **2000**, 2698, and references therein.
3. (a) Bull, S. D.; Davies, S. G.; Moss, W. O. *Tetrahedron: Asymmetry* **1998**, *9*, 321–327; (b) Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*, 4525.
4. Chen, J.; Corbin, S. P.; Holman, N. J. *Org. Process Res. Dev.* **2005**, *9*, 185.
5. Cledera, P.; Avendano, C.; Menendea, J. C. *Tetrahedron* **1998**, *54*, 12349.
6. Tullberg, M.; Grøtli, M.; Luthman, K. *Tetrahedron* **2006**, *62*, in press.
7. (3*R*)-Isopropylpiperazine-2,5-dione (**3**). A suspension of methyl *N*-(*tert*-butoxycarbonyl)-D-valyl-glycinate (2.0 g, 6.9 mmol) in water (20 ml) was heated at 150 °C by microwave irradiation (in a Biotage Initiater Microwave Synthesiser producing controlled radiation at 2450 MHz and using fixed hold-time) for 15 min in a sealed vial. The solvent was removed under reduced pressure and the residue dried under vacuum overnight. The crude product was recrystallised from ethanol:chloroform (3:1 v/v). The target compound was obtained as a white powder in 75% yield. In a typical large-scale experiment, a suspension of methyl *N*-(*tert*-butoxycarbonyl)-D-valyl-glycinate (12.0 g, 41.6 mmol) in water (150 ml) was heated at 200 °C by microwave irradiation (in a Biotage Advancer Microwave Synthesiser producing controlled radiation at 2450 MHz and using fixed hold-time) for 15 min in a sealed container. Work up and purification were carried out as described above. The resulting white powder was obtained in 73% yield. ^1H NMR (400 MHz, CD_3OD): δ 0.97 (d, $J = 6.9$ Hz, 3H, $CH(CH_3)_2$), 1.04 (d, $J = 6.9$ Hz, 3H, $CH(CH_3)_2$), 2.17–2.30 (m, 1H, $CH(CH_3)_2$), 3.72 (m, 1H, HNC*H*), 3.79 (d, $J = 19$ Hz, 1H, $NHCH_2$), 4.01 (d, $J = 19$ Hz, 1H, $NHCH_2$). ^{13}C NMR (100 MHz, CD_3OD): δ 16.0 ($CH(CH_3)_2$), 17.9 ($CH(CH_3)_2$), 33.2 ($CH(CH_3)_2$), 44.0 ($NHCH_2$), 60.5 (HNCH), 167.5 (CO), 172.8 (CO). NMR spectral data were consistent with the literature data.[4]
8. (3*R*)-3,6-Dihydro-2,5-diethoxy-3-isopropyl-pyrazine (**4**). In a typical experiment, a mixture of 3(*R*)-isopropylpiperazine-2,5-dione (4.5 g, 28.8 mmol) and $Et_3O{\cdot}BF_4$ (18.5 g, 97 mmol) in dichloromethane (150 ml) was stirred at room

temperature for 5 days. Commercially available $Et_3O{\cdot}BF_4$ was used in the alkylation step without prior purification. The solution was added in portions to a vigorously stirred mixture of $NaHCO_3$ (satd aq 150 ml) and dichloromethane (150 ml) at 5 °C, while the pH was adjusted to 8–9 by the addition of NaOH (3 M, 60 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2×100 ml). The combined organic phases were washed with brine (150 ml), dried with $MgSO_4$ and concentrated under vacuum to give crude **4** as a yellow oil. Flash column chromatography using hexane/ethyl acetate (9:1) as eluent yielded the pure product in 92% yield (5.6 g, 26.5 mmol) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (d, $J = 6.6$ Hz, 3H, $CH(CH_3)_2$), 1.02 (d, $J = 6.6$ Hz, 3H, $CH(CH_3)_2$), 1.24–1.29 (m, 6H, OCH_2CH_3), 2.18–2.27 (m, 1H, $CH(CH_3)_2$), 3.93–3.97 (m, 3H, HNCH and $NHCH_2$), 4.04–4.20 (m, 4H, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4 (OCH_2CH_3), 17.1 ($CH(CH_3)_2$), 19.1 ($CH(CH_3)_2$), 32.7 ($CH(CH_3)_2$), 46.9 ($NHCH_2$), 60.8 ($NHCH_2$), 61.1 (OCH_2CH_3), 162.0 (CO), 164.2 (CO). NMR spectral data were consistent with the literature data.[4]