Rapid Entry to 1,4-Diazepane-2,5-dione from β-Amino Acids

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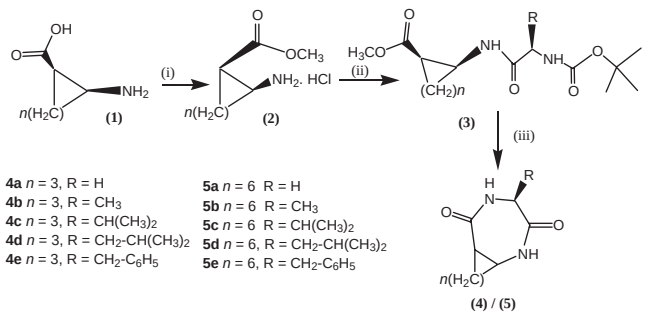
A versatile method for the synthesis of conformationally constrained 1,4-diazepane-2,5-dione from β-amino acids is described. These heterocyclic compounds will be useful as a new platform for the synthesis of conformationally constraint peptidomimetics.

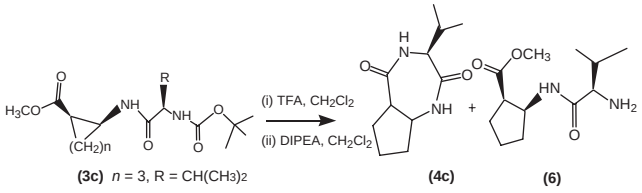
The development of new approaches for the construction of number of heterocycles continues to be essential for accessing natural products and their structural analogues. Among them, 1,4-diazepane-2,5-dione[1] scaffolds have gained over the years an ongoing interest for synthetic and clinical studies mainly as novel inhibitors of LFA-1[2] and HDM2 antagonists.[3] In this regard, use of β-amino acids are well known for the synthesis of various class of bioactive compounds.[4] Although several methods have been reported for designing and synthesis of six member diketopiperazine[5] rings, but there are very few reports concerning the seven member diazepane ring.[6] As a part of our ongoing efforts directed towards the synthesis of bioactive molecules and heterocyclic compounds, our attention was directed towards the synthesis of constrained 1,4-diazepane-2,5-dione using β-amino acids. Herein, we present a new general and versatile synthesis of 1,4-diazepane-2,5-dione from β-amino acids.

Our synthetic approach is illustrated in Scheme 1. β-Amino ester hydrochloride salt has been synthesized by the reported method,[7] which was further coupled with N-protected amino acids to afford **4a**–**4e** and **5a**–**5e** in excellent yields. The reaction was monitored by TLC (CCl_4:MeOH (6:4)). Under the conditions described several N-protected amino acids were effectively and quantitatively coupled with amino ester hydrochloride proving the efficiency of the coupling reaction. Further to optimize the reaction conditions for cyclization various methods[8] have been tried, using 2-(2-*tert*-butoxycarbonylamino-3-methylbutyrylamino)cyclopentanecarboxylic acid methyl ester (**3c**) as a model compound to give 3-isopropyloctahydrocyclopenta-[*e*][1,4]diazepine-2,5-dione (**4c**). The first attempt was made with the use of classical Mitsunobu condition[9] using DEAD/PPh_3 (1:1) in THF at room temperature. Cyclization occurred after 24 h and the product **4c** could be isolated in 30% yield after column chromatography. The other compound recovered in reaction mixture was unreacted 2-(2-amino-3-methylbutyryl-amino)cyclopentanecarboxylic acid methyl ester (**6**). The presence of **6** was also confirmed even when hindered di-*tert*-butyl azodicarboxylate (DTAD) was used, suggested that dipeptide **3c** was reluctant to cyclization probably because of the preferential transoid conformation assumed by the peptide bond. Excellent yields (70–87%) of the final products, however, could be obtained by using *N*,*N*-diisopropylethylamine DIPEA.[10] **4c** was achieved in 73% yield with the formation of smaller amount of **6** which could also be recharged further (Scheme 2). Under these conditions, several compounds were effectively and quantitatively cyclized to give functionalized 1,4-diazepane-2,5-diones (**4a**–**4e** and **5a**–**5e**) (Table 1).



Scheme 1. Reagents and conditions (i) $SOCl_2$, anhydrous MeOH. (ii) $(C_2H_5)_3N$, EDC, HOBT, CH_3CN, BocNH–R(CH)–COOH. (iii) TFA, DIPEA, CH_2Cl_2.

Effect of the nature of tertiary amines on cyclization was also studied. It was found that all esters described racemises more slowly in the presence of hindered amine i.e. DIPEA in comparison to that of less hindered amine i.e. triethylamine. Understandably, removal of amide proton is less susceptible to steric hindrance then the removal of the proton from the α carbon atom of the ester. Moreover, it provides an expedient route for the stereoselective synthesis of the desired products



Scheme 2. Synthesis of 1,4-diazepane-2,5-dione core.

Table 1. Synthesis of 1,4-diazepane-2,5-dione (4a–4e and 5a–5e)

Entry	Products[a]	Time/h	Yield[b]/%
1	**4a**	24	70
2	**4b**	24	70
3	**4c**	24	73
4	**4d**	24	75
5	**4e**	23	70
6	**5a**	18	85
7	**5a**	18	80
8	**5b**	18	86
9	**5c**	18	85
10	**5d**	18	84
11	**5e**	18	87

[a]All compounds have been characterized by IR, NMR, and MS. [b]Isolated yields after purification by column chromatography.

with excellent yield and purity. It is well evident from the Table 1 that the reactivity of the substrate increases with the ring size, this may be essentially because of the ring strain present in the eight member ring which results in less stability and more reactivity (**5a**–**5e**) then five member rings (**4a**–**4e**). Most of the reactions proceeded smoothly and excellent yield were obtained in appropriate reaction time. Typical experimental procedures for the synthesis of **4a**–**4e** and **5a**–**5e** and the spectroscopic data for the selected compounds are summarized in references.[11,12]

In summary, a simple and an efficient method for the synthesis of 1,4-diazepane-2,5-diones from β-amino acids have been developed. This strategy may also be employed for the elongation of peptide chain or to increase the molecular diversity. Further elaboration of these products to potentially useful building block is actually underway in our laboratory and will be reported in due course.

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11 *Typical procedures for the synthesis of* **4c**. To a stirred solution of the *N-tert*-butoxycarbonyl protected β-amino ester (13.3 mmol) in CH_2Cl_2, TFA was added (2 mL). The reaction mixture was stirred at room temperature for 45 min and concentrated under reduced pressure to give oil, which was redissolved in minimum quantity of CH_2Cl_2 (10 mL) and DIPEA (diisopropylethylamine 2 mL) was added, the mixture was stirred at rt for 24 h. The reaction mixture was concentrated under reduced pressure to give brown viscous liquid. Purification by flash chromatography on silica and elution with CCl_4:MeOH (6:4) gave pure product in 73% yield.
12 All compounds described gave satisfactory analytical and spectroscopic data. Analytical data for selected compounds have been reported here. **5e**, viscous oil, IR 3213, 1735 cm^{-1} ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (m, 8H), 1.51 (m, 2H), 1.53 (m, 2H), 3.02 (td, $J = 9$ Hz, 4 Hz, 1H), 3.60 (m, 1H), 3.98 (dd, $J = 16$ Hz, 7 Hz, 1H), 4.46 (dd, $J = 16$ Hz, 7.1 Hz, 1H), 4.92 (m, 1H), 7.06 (m, 1H), 7.12 (m, 2H), 7.21 (m, 2H) 8.1 (br, NH, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.51, 25.02, 26.82, 29.61, 30.03, 32.91, 37.61, 45.61, 49.11, 58.12, 125, 127.11, 127.32, 128.1, 128.4, 140.2, 175, 178.55. ESI-MS m/z 301 $(M + H)^+$. **4c**, viscous oil, IR 3218, 1737 cm^{-1} ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 (d, $J = 7.1$ Hz, 3H), 0.95 (d, $J = 6.7$ Hz, 3H), 1.51 (m, 2H), 1.73–1.75 (m, 4H), 2.68 (m, 1H), 3.07 (td, $J = 9$ Hz, 5 Hz, 1H), 3.80 (m, 1H), 4.56 (m, 1H), 8.02 (br, NH, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.21, 16.24, 17.3, 20.6, 28.01, 28.5, 48.02, 46.31, 62.81, 174.4, 178.5. ESI-MS m/z 211 $(M + H)^+$. **4b**, viscous oil, IR 3211, 1731 cm^{-1} ^1H NMR ($CDCl_3$, 400 MHz) δ 1.48 (d, $J = 7$ Hz, 3H), 1.50 (m, 2H), 1.73–1.75 (m, 4H), 3.08 (td, $J = 9$ Hz, 5 Hz, 1H), 3.83 (m, 1H), 4.72 (m, 1H), 8.01 (br, NH, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.21, 17.34, 20.6, 28.01, 46.21, 48.05, 52.81, 175.4, 178.2. ESI-MS m/z 183 $(M + H)^+$.

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