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TETRAHEDRON: *ASYMMETRY*

Synthesis of chiral pyrrolidine and pyrrole derivatives through the chemoselective Dieckmann reaction of α,β-aminodiesters

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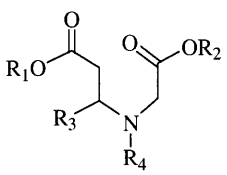
Abstract

α,β-Aminodiesters were allowed to react with *t*-BuOK in THF at −78°C. The chemoselectivity of the Dieckmann cyclization was controlled by the nature of the substituents R_3 and R_4, allowing the preparation of pyrrolidine or pyrrole derivatives.

Pyrrolidine derivatives present a diversity of pharmacological properties and potential pharmaceutical applications.[1] Different strategies have been developed to construct the pyrrolidine nucleus,[2] among them the Dieckmann reaction involving α,β-aminodiesters and related compounds as substrates.[3] Herein, we report the Dieckmann reaction of α,β-aminodiesters of type **1**. The chemoselectivity of the cyclization (formation of **2** or **3**) was shown to be dependent on the nature of the substituents R_3 and R_4.



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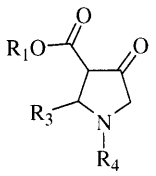

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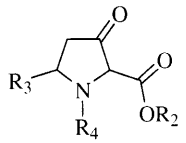

3

The synthesis of α,β-aminodiesters **1a**–**g** from enoates **4a**–**c** is shown in Scheme 1. Conjugate addition of benzylamine to **4a** led to adduct **5a** in good yield. This compound was then alkylated with $BrCH_2CO_2Et$ and $BrCH_2CO_2t$-Bu, furnishing, respectively, **1a** and **1b**. The N-debenzylated derivative **1c** was prepared from **1a** by hydrogenolysis.

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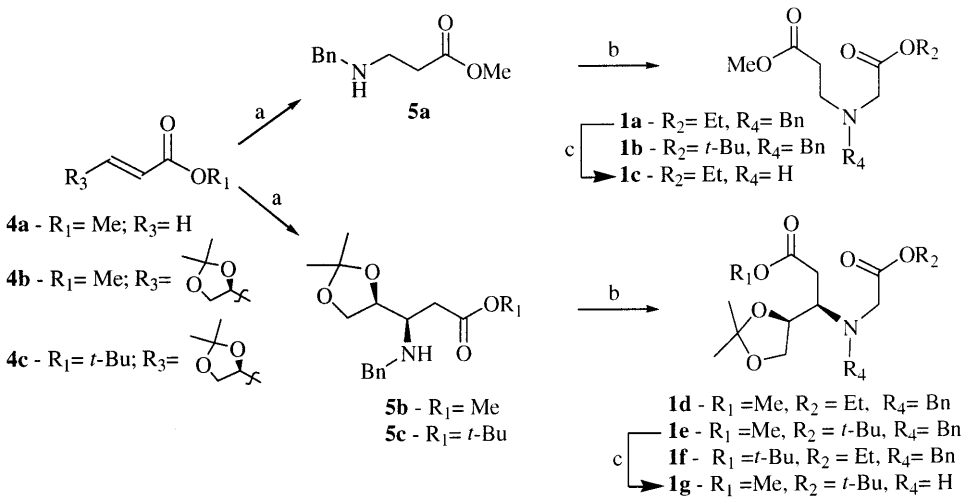


Scheme 1. Preparation of α,β-aminoesters **1a**–**g**. (a) Neat $BnNH_2$, −30°C, 48 h, **5a** (90%), **5b**, (78%), **5c** (67%); (b) $BrCH_2CO_2R$ (*t*-Bu or Et), THF/H_2O, Na_2CO_3, reflux, 14 h, **1a** (86%), **1b** (83%), **1d** (84%), **1e** (81%), **1f** (67%), c-Pd–C (10%), AcOEt, H_2 60 Psi, 4 h, rt, **1c** (95%), **1g** (96%)

The key step for the synthesis of chiral α,β-aminodiesters **1d**–**g** was the *syn*-selective conjugate addition of benzylamine to enantiomerically pure enoates **4b**,**c**, easily prepared from D-(+)-mannitol (Scheme 1). Compound **5b** was obtained in 80% *de* (>95% *de* after chromatographic purification) by reacting **4b** with neat $BnNH_2$, as previously described by Yamada et al.[4] Compound **5c** was also prepared with a high *syn*-selectivity when **4c** was used as acceptor. These adducts were then alkylated with the required α-bromoacetates leading to **1d**–**f**. Hydrogenolysis of **1e** furnished **1g**.

The Dieckmann reaction of **1a**–**g** was investigated in the presence of *t*-BuOK in THF at −78°C (Scheme 2). Under these conditions compound types **2**, **3** or **6** were obtained with different chemoselectivities, depending on the nature of groups R_3 and R_4.[5]

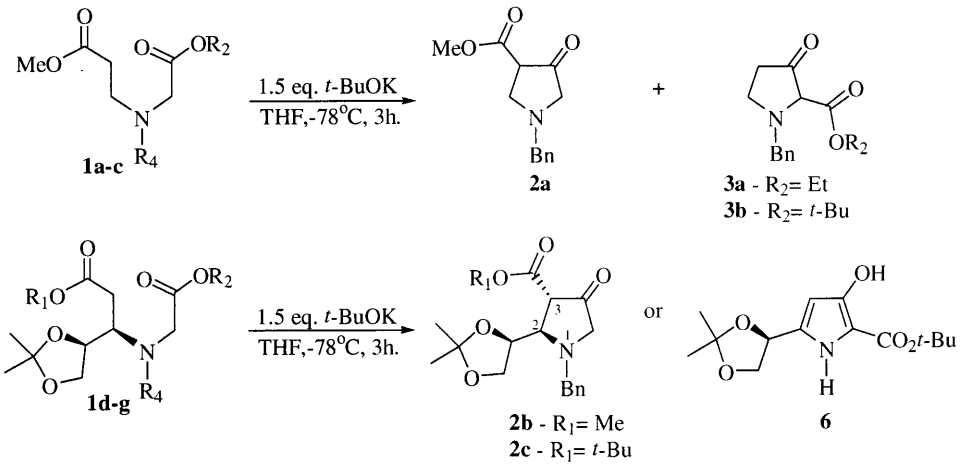
When **1a**,**b** ($R_3 = H$; $R_4 = Bn$) were used as substrates, the chemoselectivity favored **2a** (Scheme 2, entries 1 and 2), despite the nature of the ester group R_2, while from N-debenzylated derivative **1c** (entry 3), a complex mixture of products was formed.

In the chiral series, aminoesters **1d**–**f** (R_3 = 1,2-dihydroxyethyldimethylacetal group, $R_4 = Bn$) led exclusively to type **2** pyrrolidines (**2b** and **2c**, respectively), despite the nature of R_1 and R_2 (entries 4–6), although the chemical yield was lower from **1f** (entry 6), even when a more prolonged reaction time was used. The chemoselectivity could be reversed when N-debenzylated derivative **1g** was used as substrate, but in this case the expected β-ketoester was not isolated, being transformed into **6** in the reaction medium, probably through enolization followed by aromatization.[6,7]

The configuration at C_3 in **2b**,**c** was determined by NOE experiments (Fig. 1) once irradiation at H_3 led to an increase in the absorption of one of the hydrogen atoms of the dimethylacetal moiety (Hc or Hc′) and Hb, while no effect was observed on H_2. The NOE experiments also suggest that in the main conformers of **2b**,**c** the benzyl group at the nitrogen is α-oriented, once irradiation of H_2 led to an increase in the absorption of H_a, $H_{a'}$ and $H_{5\alpha}$.

In Scheme 3 we propose a mechanistic rationale to explain the observed results. Due to the electronic effect of the nitrogen atom, the kinetic deprotonation of **1** led preferentially to

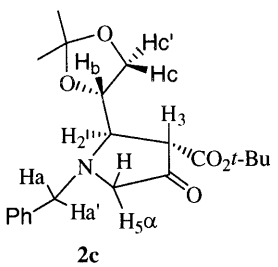
enolates type **E-2**, but once potassium enolates equilibrate, even at −78°C,[8] the enolate distribution is thermodynamically controlled, allowing the formation of enolates type **E-1**, required to explain the formation of products type **2**. On the other hand, the cyclization step is kinetically controlled once the product distribution did not change when the experiments were interrupted at different reaction times. Since the cyclization of **1a** led preferentially to **2a**, one can conclude that $\mathbf{TS_{1a}}$ was favored over $\mathbf{TS_{2a}}$ (R_3 = H, R_4 = Bn). A possible explanation is that in the first case CO_2R_1 and Bn (R_4) groups are assuming a 1,3-relationship, while in the second a stronger 1,2-steric interaction between these groups would be observed (Scheme 3). On the other hand, when R_3 is the dimethylacetal group and R_4 = Bn, the three substituents in both transition states $\mathbf{TS_{1b}}$ and $\mathbf{TS_{2b}}$ are expected to be assuming a *trans-trans* orientation. However, while in $\mathbf{TS_{1b}}$ CO_2R_1 and Bn groups are 1,3-*cis* oriented, the same relationship occurs in $\mathbf{TS_{2b}}$



Entry	Aminodiester	2 (%)	3 (%)	6 (%)
1	**1a**	**2a**(74)	**3a**(13)	0
2	**1b**	**2a**(69)	**3b**(9)	0
3*	**1c**	--	--	--
4	**1d**	**2b**(82)	0	0
5	**1e**	**2b**(76)	0	0
6	**1f**	**2c**(30)	0	0
7	**1g**	0	0	(29)

* Complex mixture of products obtained in low yield.

Scheme 2. Dieckmann reaction of aminodiesters **1a–g**



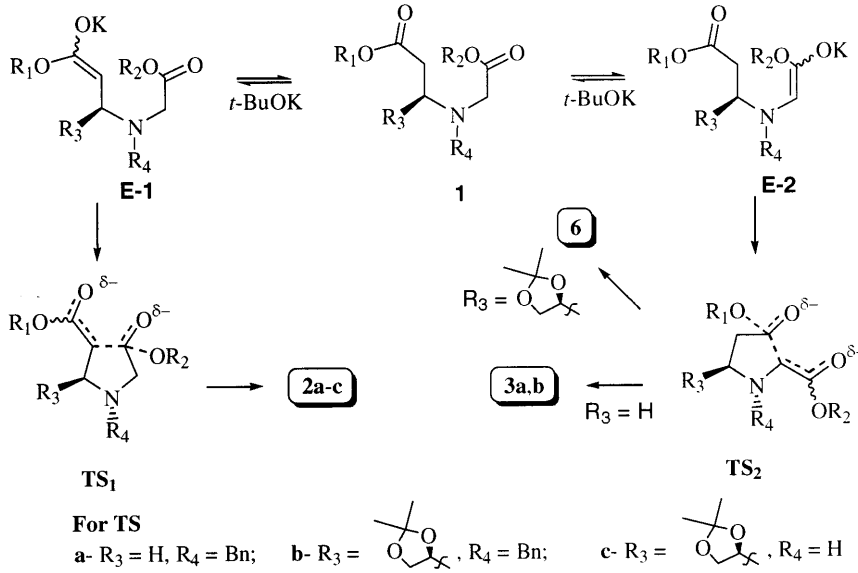
JH_2,H_3 = 9.0Hz

Irradiation of H_3
3.7% nOe at Hc or Hc'
3.1% nOe at Hb

Irradiation of H_2
6.6% nOe at Ha or Ha'
3.1% nOe at Ha or Ha'
3.3% nOe at $H_5\alpha$

Fig. 1. Experiments of NOE in **2c**

between CO_2R_2 and dimethylacetal group. This latter interaction should be stronger since both groups are bulky and polar (stereoelectronic interactions), disfavoring $\mathbf{TS_{2b}}$ and, consequently, providing only compounds type **2**. Finally, when R_3 is the dimethylacetal group and $R_4 = H$, a 1,2-steric interaction occurs between CO_2R_1 and the dimethylacetal moiety (R_3) in the $\mathbf{TS_{1c}}$, while in $\mathbf{TS_{2c}}$ the steric interaction is released once these groups are in a 1,3-relationship. Therefore, the chemoselectivity was reversed, with the preferential formation of a β-ketoester type **3**, precursor of aromatic derivative **6**.



Scheme 3. Proposed transition states leading to **2** and **3**

The use of this strategy to prepare enantiomerically pure bioactive pyrrolidine derivatives is underway in our laboratory.

Acknowledgements

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5. The use of LDA as base (non-equilibrating conditions) led to a complex mixture of products from which compounds type **2** were obtained in low yield ($\sim$10%).
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7. Data for β-ketoester **2b**: $[\alpha]_D^{25}=+57.6$ ($c=1.32$, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ (ppm) 1.33 (s, 3H), 1.41 (s, 3H), 2,95 (d, 1H, $J=17.9$ Hz), 3.34 (d, 1H, $J=9.2$ Hz), 3.43 (d, 1H, $J=17.9$ Hz), 3.53 (d, 1H, $J=13.3$ Hz), 3.77 (s, 3H), 3.84 (dd, 1H, $J=9.2$; 5.2 Hz), 3.93 (dd, 1H, $J=8.8$; 6.6 Hz), 4.01 (dd, 1H, $J=8.8$; 6.8 Hz), 4.24 (d, 1H, $J=13.3$ Hz), 4.49 (ddd, 1H, $J=6.8$; 6.6; 5.2 Hz), 7.20–7.40 (m, 5ArH); ^{13}C NMR (50 MHz, $CDCl_3$/TMS) δ (ppm) 24.29, 25.58, 52.52, 56.19, 58.98, 61.86, 64.77, 65.78, 75.53, 109.65, 128.30, 128.40, 137.36, 167.86, 205.24. Data for β-ketoester **2c**: $[\alpha]_D^{25}=+55.85$ ($c=3.76$, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ (ppm) 1.34 (s, 3H), 1.45 (s, 3H), 1.48 (s, 9H), 2.90 (d, 1H, $J=17.7$ Hz), 3.20 (d, 1H, $J=9.0$ Hz), 3.39 (d, 1H, $J=17.7$ Hz), 3.51 (d, 1H, $J=13.3$ Hz), 3.76 (dd, 1H, $J=9.0$; 5.6 Hz), 3.89 (dd, 1H, $J=8.7$; 6.9 Hz), 4.01 (dd, 1H, $J=8.7$; 6.8 Hz), 4.27 (d, 1H, $J=13.3$ Hz), 4.49 (ddd, 1H, $J=6.9$; 6.8; 5.6 Hz), 7.20–7.40 (m, 5ArH); ^{13}C NMR (50 MHz, $CDCl_3$/TMS) δ (ppm) 24.51, 26.04, 27.80, 57.44, 59.10, 61.90, 65.10, 65.82, 76.14, 82.23, 109.70, 127.37, 128.38, 137.55, 166.65, 205.80. Data for pyrrole derivative **6**: $[\alpha]_D^{25}=+1.7$ ($c=1.79$, CH_2Cl_2); mp = 114–115°C; UV $\lambda_{max}=268$ 80 nm, $\lambda_{max}=19$ 586 nm; ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ (ppm) 1.43 (s, 3H), 1.50 (s, 3H), 1.60 (s, 9H), 3.85 (dd, 1H, $J=8.1$; 6.7 Hz), 4.27 (dd, 1H, $J=8.1$; 6.4 Hz), 5.04 (dd, 1H, $J=6.7$; 6.4 Hz), 5.73 (d, 1H, $J=2.8$ Hz).
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