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Synthesis of Chiral 5-Substituted 2-Pyrrolidinones: An Unusual One-Step Transformation

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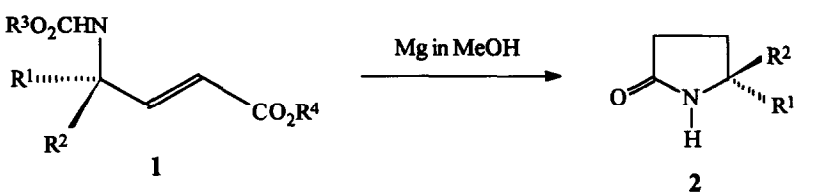
Abstract. An efficient methodology for the enantioselective synthesis of γ-lactams, using a one-pot reaction of chiral N-alkoxycarbonyl γ-amino α,β-unsaturated carboxylates with magnesium in methanol, afforded the target chiral compounds in high chemical yield (87-95%) and optical purity (96-99% ee).

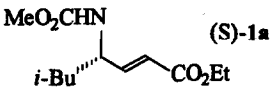
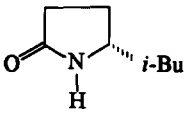
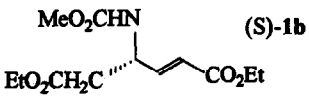
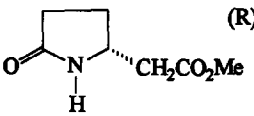
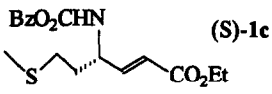
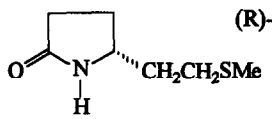
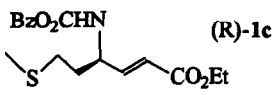
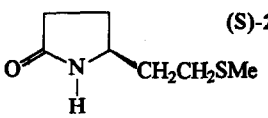
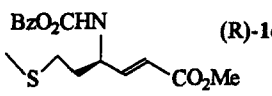
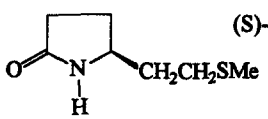
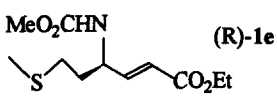
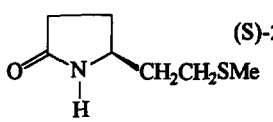
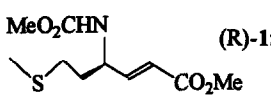
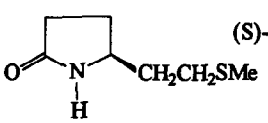
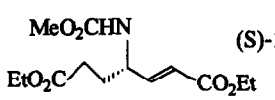
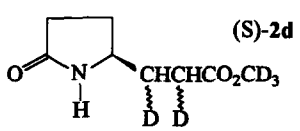
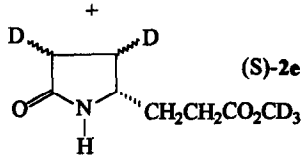
The 2-pyrrolidinone (γ-lactam) ring system is present in many biological active compounds and it is also a versatile intermediate particularly for the syntheses of novel amino acids and pyrrolidine derivatives.[1-4] Thus, it is not surprising that numerous racemic syntheses[5-7] of these heterocycles have been described. Meyers *et al.*[1] recently described an efficient asymmetric synthesis of 5-substituted 2-pyrrolidinones that should find general applicability to a variety of synthetic challenges.

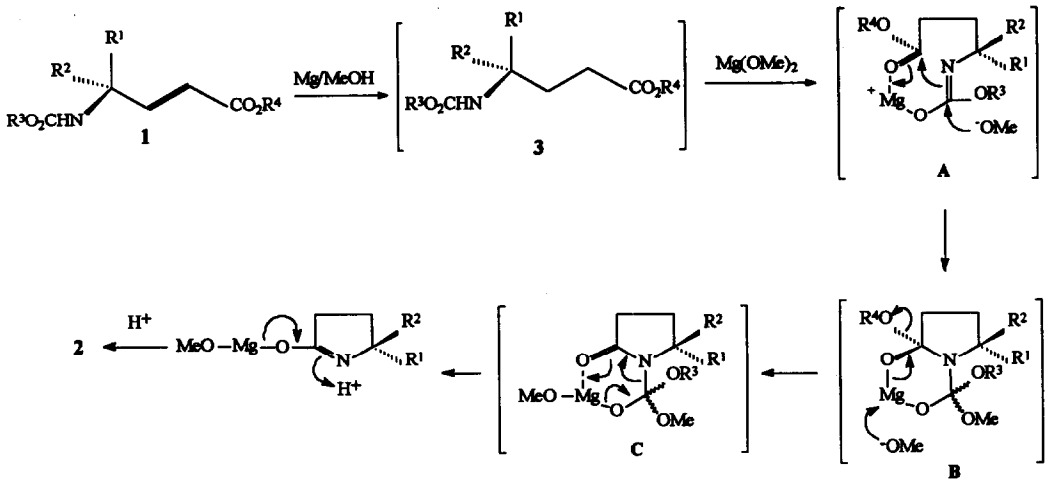


Scheme 1

Magnesium-methanol is a simple, yet selective reagent, for the reduction of α,β-unsaturated esters.[8,9] We have now found that the reaction of N-protected γ-amino-α,β-unsaturated carboxylates (**1**) with magnesium in methanol afforded 5-substituted 2-pyrrolidinones (**2**) in excellent yield (Scheme 1). Some examples that illustrate this reaction are summarized in Table 1. Transesterification occurred in all cases. In a typical procedure, a mixture of the N-protected γ-amino-α,β-unsaturated carboxylate (**1**, 1.0 mmol) and magnesium turnings (0.24 g, 10 mmol) in 10 mL methanol was stirred for 4 hr at 0°C and then for 8 hr at 25°C. After neutralization with hydrochloric acid (2N), the mixture was extracted with chloroform (2 x 40 mL). The combined chloroform extracts were washed with brine (10 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a residue which was purified by silica gel column chromatography to yield the 5-substituted 2-pyrrolidinone (**2**).

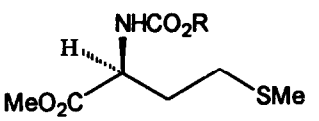
Table 1. Synthesis of Chiral 5-Substituted 2-Pyrrolidinones[10]

Entry	1	2	Yield, %	(ee, %)
1	 (S)-1a	 (R)-2a	91	(> 99)[11]
2	 (S)-1b	 (R)-2b	87	(> 99)[12]
3	 (S)-1c	 (R)-2c	89	(96)
4	 (R)-1c	 (S)-2c	94	(> 97)
5	 (R)-1d	 (S)-2c	92	(> 97)
6	 (R)-1e	 (S)-2c	95	(98)
7	 (R)-1f	 (S)-2c	92	(> 96)
8	 (S)-1g	 (S)-2d +  (S)-2e	94	



Scheme 2

The mechanism of this one-pot reaction may involve the formation of an intermediate N-protected γ-amino carboxylate (**3**), since treatment of the (S)-N-protected γ-amino-α,β-unsaturated carboxylate (**1g**) with magnesium in CD_3OD afforded an approximately 1:1 mixture of the 5-substituted 2-pyrrolidinones **2d** and **2e** (Entry 8). It is plausible that cleavage of the carbamate and ester moieties and cyclization, take place during the formation of the 5-substituted γ-lactams (**2**) from the intermediate **3**, via the transition states **A**, **B** and **C** (see Scheme 2). This explanation is based on the following observations. The carbamates **4a** and **4b** were not cleaved using the same reaction conditions. Secondly, reaction of the N-protected (S)-glutamic acid diethyl ester (**5**) with magnesium in methanol gave the pyroglutamic acid methyl ester (**6**, Equation 1). Finally, using the same reaction conditions, treatment of the N-diprotected γ-amino-α,β-unsaturated carboxylates (S)-**1h** and (S)-**1i** afforded the N-diprotected-γ-amino carboxylates **7a** and **7b** resulting from normal reduction of the α,β-unsaturated olefinic bond.[8] In these latter reactions, neither carbamate-cleavage, or γ-lactam, products were detected (Equations 2 and 3).



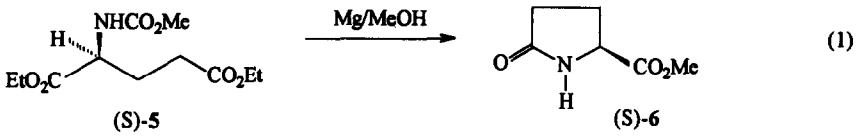
4a, R = Me

4b, R = $PhCH_2$

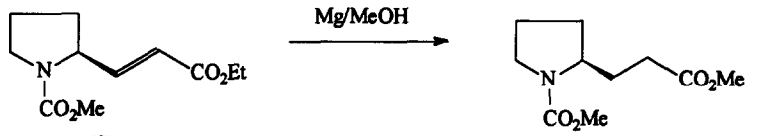
The optical purity of the γ-lactams (R)-**2a**, (R)-**2b**, (R)-**2c** and (S)-**2c** was determined by ^1H nmr analysis of the respective diastereomeric ureide prepared by reaction with (R)-1-phenylethyl isocyanate.[13] The ^1H nmr spectrum of the (R)-**2c** and (S)-**2c** ureide derivatives showed ^1H resonances for *Me*S- as a singlet at δ 2.130 and 2.073, respectively. The ureide derivative of (R)-**2a** and (R)-**2b** existed as a single diastereomer since the ^1H nmr spectrum, upon CH-*Me* irradiation, showed that the benzylic methine proton appeared as a doublet (J_{vic}=8 Hz) at δ 5.014 and 5.012, respectively.

The conversion of N-protected γ-amino-α,β-unsaturated carboxylates (**1**) to their corresponding 5-substituted 2-pyrrolidinones (**2**) normally requires four reactions which include reduction of the C=C double bond, cleavage of the N-protected and ester moieties, and cyclization of the γ-amino acid. The one-pot

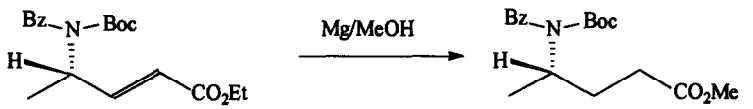
transformation described provides an efficient procedure for the synthesis of chiral 5-substituted 2-pyrrolidinones (2) since the N-protected γ-amino-α,β-unsaturated carboxylates (1) are readily prepared from naturally occuring α-amino acids.



(S)-5 (S)-6 (1)



(S)-1h (S)-7a (2)



(S)-1i (S)-7b (3)

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10. The structures assigned to products **2** are in agreement with their ^{1}H and ^{13}C nmr spectral data, microanalysis (C,H,N) for (R)-**2a-c** and (S)-**2c**, and the high resolution mass spectrum for (S)-**2d-e**.
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