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Synthesis of *cis*-2-aryl-3-pyrrolidine carboxylic esters via diastereoselective cyclization of γ-imino esters using a $TiCl_4/Et_3N$ reagent system

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Abstract—Facile synthesis of *cis*-2-aryl-3-pyrrolidine carboxylates from readily accessible γ-imino esters by intramolecular cyclization mediated by a $TiCl_4/Et_3N$ reagent system is described.

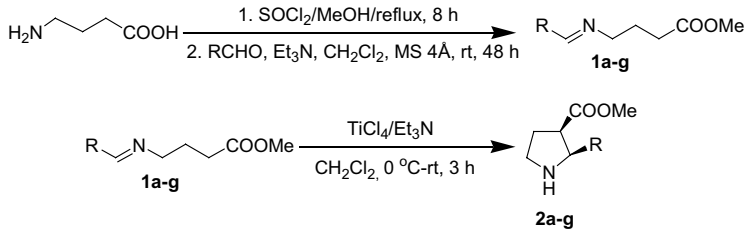
Pyrrolidines are an important class of structural motifs present in many biologically active compounds.[1] For instance, several drug candidates displaying anticancer,[2] antibacterial,[3] anti-HIV,[4] antiviral,[5] antifungal,[6] and analgesic activities[7] contain the pyrrolidine ring system, as do several biologically important alkaloids[8] and amino acids.[9] Further, many chiral ligands containing the pyrrolidine ring system are useful in asymmetric synthesis.[10] Hence, there has been continuing interest in the development of new methods for the construction of the pyrrolidine ring system.[11] We wish to report a novel and facile synthesis of *cis*-2,3-disubstituted pyrrolidines by the intramolecular cyclization of γ-imino esters mediated by $TiCl_4/Et_3N$.

During the course of investigations on the synthetic utility of the $TiCl_4/Et_3N$ reagent system,[12] we examined the reaction of the γ-imino esters, which are readily accessible from the γ-aminobutyric esters. We found that the imino ester **1a** reacted with $TiCl_4/Et_3N$ to give **2a** (Scheme 1).[13]

Interestingly, only one stereoisomer was formed in the reaction. Comparison of the ^1H NMR and ^{13}C NMR spectral data of the product **2a** with the previously reported data for **2a** indicated that the phenyl and ester groupings are *cis*.[14]

The structural assignment was further confirmed by a single crystal X-ray analysis of the oxalic acid salt of the amino ester **2a** (Fig. 1).[15]

We have examined this transformation with various imino esters prepared using substituted aromatic



Scheme 1. Intramolecular coupling of γ-imino esters mediated by the $TiCl_4/Et_3N$ reagent system.

Keywords: Imino esters; Intramolecular cyclization; Pyrrolidines.
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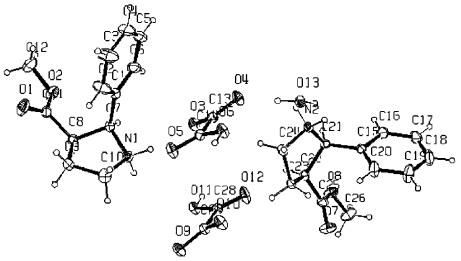

Figure 1. ORTEP representation of the crystal structure of the hydrated complex of **2a** with oxalic acid (thermal ellipsoids are drawn at 25% probability).

Table 1. Reaction of γ-imino esters **1** with $TiCl_4/Et_3N$ to give *cis*-2,3-disubstituted pyrrolidines **2**

Entry	R	Substrate	Product	Yield[b] of **2** (%)
1	C_6H_5[a]	**1a**	**2a**[a]	75
2	*p*-$H_3CC_6H_4$	**1b**	**2b**	64
3	*p*-$H_3COC_6H_4$	**1c**	**2c**	76
4	*p*-ClC_6H_4	**1d**	**2d**	71
5	*p*-$O_2NC_6H_4$	**1e**	**2e**	69
6	1-Naphthyl	**1f**	**2f**	66
7	$(CH_3)_2CH$	**1g**	**2g**	32

[a] Compound **2a** was confirmed by spectral data (IR, ^1H NMR, ^{13}C NMR) and X-ray analysis and by comparison with reported data.[14] Compounds **2b–g** were identified by the comparison of their spectral data with **2a**.

[b] Yields are for isolated products.

aldehydes. The products were obtained in 64–76% yields (Table 1). The product obtained using the imino ester prepared from *iso*-butyraldehyde was formed only in poor yield (32%). Comparison of the ^1H NMR spectral data obtained for the substituted derivatives **2b–g** with those obtained for **2a** indicated that **2b–g** all had the *cis* stereochemistry.

The high level of stereoselectivity observed in this transformation can be tentatively explained by postulating the formation of a pseudo six-membered chair-like transition state **A** (Fig. 2), assuming that the geometry of the titanium enolate is *Z*[16]and that the imine has an *E* configuration.[17] The chelated six-membered titanocycle **A** would then undergo ring closure leading to the 2,3-*cis* configuration in the newly constructed pyrrolidine ring (Fig. 2).

Though several methods have been reported for the selective synthesis of *trans*-2,3-disubstituted pyrrolidines,[18] the selective formation of *cis*-2,3-disubstituted pyrrolidines is not common.[19] Accordingly, the method described here for the highly diastereoselective synthesis of *cis*-2,3-disubstituted pyrrolidine derivatives has good synthetic potential.

Figure 2. Proposed pathway for the *cis* diastereoselectivity.

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13. *General experimental procedure*: To the imino ester (5 mmol), and triethylamine (5 mmol) in dichloromethane

(40 mL), $TiCl_4$ (10 mmol, 2.2 mL of a 1:1 solution of $TiCl_4$/CH_2Cl_2) in CH_2Cl_2 (15 mL) was added dropwise at 0 °C under N_2 over 15 min. The reaction mixture was stirred at room temperature for 3 h, then quenched with saturated aq K_2CO_3 (15 mL) and filtered through a Büchner funnel. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×25 mL). The combined organic extract was washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified by chromatography on a silica gel column using $CHCl_3$/MeOH (99.5/0.5) as eluent.

Spectral data for products **2a**–**2g**: **2a**: IR (Neat): 3342, 3028, 2949, 1732 cm^{-1}; MS (EI) *m/z*: 205; ^1H NMR (200 MHz, $CDCl_3$): 2.07–2.22 (m, 2H), 2.26 (br, NH), 2.96–3.12 (m, 2H), 3.21 (s, 3H), 3.27–3.43 (m, 1H), 4.36 (d, $J=8$ Hz, 1H), 7.23–7.27 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): 29.6, 46.6, 49.6, 50.9, 66.3, 126.7, 127.2, 128.0, 139.6, 174.3. **2b**: IR (Neat): 3348, 3055, 2954, 1720 cm^{-1}; MS (EI) *m/z*: 219; ^1H NMR (200 MHz, $CDCl_3$): 2.11 (br, NH), 2.18–2.26 (m, 2H), 2.31 (s, 3H), 2.94–3.07 (m, 2H), 3.25 (s, 3H), 3.36–3.46 (m, 1H), 4.33 (d, $J=8$ Hz, 1H), 7.07–7.27 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): 21.0, 29.6, 46.5, 49.5, 50.9, 60.0, 126.5, 128.6, 136.5, 174.2. **2c**: IR (Neat): 3338, 2950, 1732 cm^{-1}; MS (EI) *m/z*: 235; ^1H NMR (200 MHz, $CDCl_3$): 2.06–2.26 (m, 2H), 2.93–3.07 (m, 2H), 3.19 (br, NH), 3.26 (s, 3H), 3.38–3.47 (m, 1H), 3.78 (s, 3H), 4.32 (d, $J=8$ Hz, 1H), 6.83 (d, $J=10$ Hz, 2H), 7.20 (d, $J=10$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 29.5, 46.4, 47.5, 51.1, 55.1, 66.7, 113.4, 127.5, 131.4, 158.7, 174.4. **2d**: IR (Neat): 3332, 2954, 1730 cm^{-1}; MS (EI) *m/z*: 239; ^1H NMR (200 MHz, $CDCl_3$): 1.94–2.00 (m, 2H), 2.08–2.22 (m, 2H), 3.26 (s, 3H), 3.32 (br, NH), 3.36–3.46 (m, 1H), 4.34 (d, $J=8$ Hz, 1H), 7.20–7.30 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): 29.5, 46.5, 49.4, 51.1, 65.4, 128.1, 132.8, 138.4, 174.0. **2e**: IR (Neat): 3419, 2956, 1742 cm^{-1}; MS (EI) *m/z*: 250; ^1H NMR (200 MHz, $CDCl_3$): 1.89 (br, NH), 2.09–2.31 (m, 2H), 3.02–3.25 (m, 1H), 3.27 (s, 3H), 3.34–3.52 (m, 2H), 4.49 (d, $J=8$ Hz, 1H), 7.50 (d, $J=10$ Hz, 2H), 8.17 (d, $J=10$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 29.4, 46.5, 49.4, 51.1, 65.1, 123.0, 127.8, 147.1, 148.1, 173.3. **2f**: IR (Neat): 3336, 3049, 2947, 1732 cm^{-1}; MS (EI) *m/z*: 255; ^1H NMR (200 MHz, $CDCl_3$): 1.88 (br, NH), 2.23–2.34 (m, 2H), 2.87 (s, 3H), 3.08–3.14 (m, 1H), 3.48–3.57 (m, 2H), 5.08 (d, $J=8$ Hz, 1H), 7.27–8.06 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$): 29.7, 46.3, 48.9, 50.7, 62.6, 122.9, 123.1, 125.1, 125.3, 125.9, 127.7, 128.7, 131.4, 133.5, 135.2, 174.2. **2g**: IR (Neat): 2964, 1726 cm^{-1}; MS (EI) *m/z*: 171; ^1H NMR (200 MHz, $CDCl_3$): 0.80–1.32 (m, 6H), 1.37–1.51 (m, 1H), 1.76–2.01 (m, 2H), 2.10–2.22 (m, 1H), 2.27–2.43 (m, 1H), 3.27–3.48 (m, 2H), 3.68 (s, 3H), 3.92 (s, br, NH); ^{13}C NMR (50 MHz, $CDCl_3$): 20.9, 21.6, 30.1, 30.9, 46.1, 46.3, 51.1, 71.7, 175.7.

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