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Regio- and diastereoselective synthesis of cyclic amino esters

Kyung-Ho Park, Thomas M. Kurth, Marilyn M. Olmstead and Mark J. Kurth*

Department of Chemistry, University of California, One Shields Avenue, Davis, CA 95616, USA

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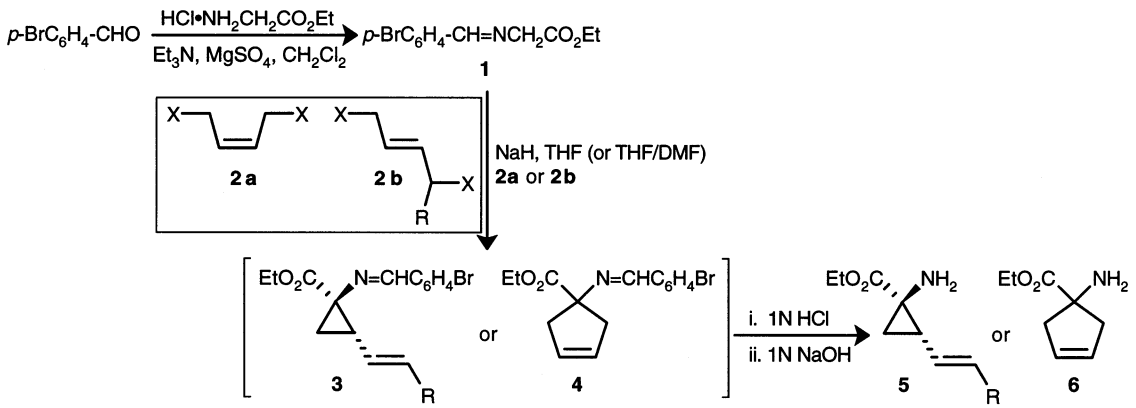
Abstract—Several cyclic amino esters have been prepared regio- and diastereoselectively depending on the electrophile (*cis* or *trans* alkene) and its leaving group. © 2001 Published by Elsevier Science Ltd.

1-Amino cyclopropane (**5**) and 1-amino cyclopentene (**6**) carboxylate ester derivatives are key precursors to 2,3-methanoamino acids[1] and biologically important excitatory amino acids,[2] respectively. Indeed, significant effort has been applied to the synthesis of cyclopropane amino acid derivatives like **5**[3]—both because of their abundance in nature[4] and because of their interesting biological properties.[5] A previous study from our lab required cyclopentene amino acid **6** as starting material and, in that work, we observed that alkylation of **1** with **2a** (X = Cl) gave only **4** with no trace of the potential cyclopropane amino acid side product (**3**, R = H; Table 1, entry 1).[6] We have since found, and report here, that alkylation of **1** with altered bis-electrophile **2** [modifying 'X' (entry 2) and/or the olefin geometry (entries 3–5)] allows for control of which cyclic amino ester (i.e. **3** versus **4**) is produced. In contrast, a related and stepwise palladium(0)-mediated route to the cyano analog of **3** from either *cis*- or *trans*-**2** gives no cyclopentene product (cyano analog of **4**).[3]

Condensation of the hydrochloride salt of glycine ethyl ester with 4-bromobenzaldehyde delivers Schiff base[7] **1** (5 mmol scale, 95%) and activates the methylene moiety of glycine for *C*-alkylation. Base treatment of **1** (excess NaH in THF or THF/DMF 10:1) followed by addition of bis-electrophile **2** results in bis-alkylation to the protected amino esters **3** and/or **4** (3 mmol scale, ≈ 80%). Subsequent hydrolysis of the labile imine with 1N HCl followed by neutralization of the resulting ammonium salt with 1N NaOH delivered cyclic amino esters **5** or **6** with good to excellent regioselectivity (i.e. **5** versus **6**) and, in the case of **5**, excellent diastereoselectivity (Table 1). When *cis*-1,4-dichloro-2-butene (**2a**, X = Cl) is employed as the alkylating agent, only cyclopentene amino ester **6** is obtained (entry 1)—that is, only direct S_N2 displacement of chloride is operative in the ring-closing alkylation step. On the other hand, *cis*-1,4-dimesyl-2-butene[8] (**2a**, X = OMs) delivered cyclopropane **5** (R = H) as the major product together



* Corresponding author.

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Table 1. Regio- (**5** versus **6**) and stereoselective (**5**: amine and vinyl moieties *trans*) cyclic amino ester synthesis

Entry	Alkylating agent	Product	Yield[a] (%)	Reaction conditions
1	**2a** (X = Cl)	**6**	67	THF, reflux
2	**2a** (X = OMs)	**5** (R = H)/**6** (2:1)	60	THF/DMF, rt
3	**2b** (X = Cl, R = H)	**5**	43	THF/DMF, rt
4	**2b** (X = Cl, R = Me)	**5**	25	THF/DMF, rt
5	**2b** (X = Cl, R = Et)	**5**	20	THF/DMF, rt

[a] Overall yield from Schiff base **1**.

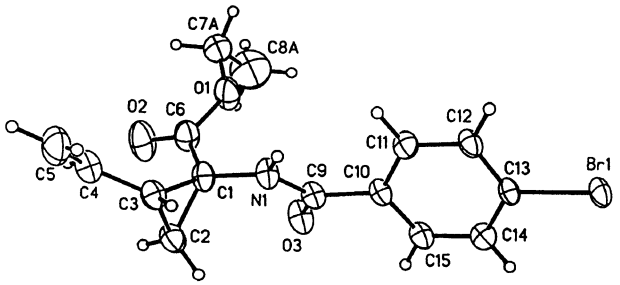

Figure 1. X-Ray crystal structure of **7**.

with cyclopentene **6** [**5** (R = H)/**6** = 2:1; entry 2]. The occurrence of **5** as the major product in this reaction with the *cis*-alkene bis-mesylate electrophile can be explained on the basis of the Hard/Soft-Acid/Base theory.[9]

In an effort to achieve complete regioselectivity in **1**→**5**, we investigated the use of *trans*-1,4-dichloro-2-butene derivatives (**2b**, R = H, Me, Et) as the bis-alkylating agent reasoning that a *trans*-configured alkene would geometrically preclude formation of **6**. As anticipated, cyclopropane amino ester **5** was obtained exclusively with *trans*-**2b** bis-electrophiles (entries 3, 4 and 5). It is interesting to note that only one diastereomer (amine and vinyl moieties are *trans*) is obtained in each of these reactions, implying that a *syn* alkenyl and carboalkoxy relationship is sterically favored in the S'_N cyclization. X-Ray crystallographic analysis of urea **7**, prepared from 4-bromophenylisocyanate and cyclopropane amino ester **5** (R = H), verified the relative stereochemistry in these useful amino cyclopropane carboxylate ester derivatives (Fig. 1).[10]

Typical procedure for the synthesis of **5** (R = H) from Schiff base **1**. Schiff base **1** (0.5 g, 1.85 mmol) was treated with NaH (0.08 g, 3.70 mmol) and *trans*-1,4-dichloro-2-butene (0.23 g, 1.85 mmol) in 5 mL of THF/DMF (10:1) at ambient temperature overnight. Ethyl acetate (20 mL) and ice water (10 mL) were added to the reaction mixture. The organic layer was washed with brine (5 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was roughly purified by short column chromatography (silica-gel, presaturated with 10% Et_3N in hexane) to afford crude compound **3** (R = H), which was treated with aqueous HCl (1N, 2 mL) for 20 min. Ethyl acetate (10 mL) and water (10 mL) were added to the reaction mixture and the separated aqueous layer was neutralized with 1N NaOH (3 mL) and extracted with ethyl acetate. The combined organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give compound **5** (R = H) (0.12 g, 0.79 mmol, 43%) as a liquid. FTIR (thin film) 3381, 3322, 2980, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (ddd, 1H, J = 17.4, 10.3, 10.3 Hz), 5.21 (dd, 1H, J = 17.4, 1.8 Hz), 5.03 (dd, 1H, J = 10.3, 1.8 Hz), 4.21–4.10 (m, 2H), 2.08 (s, 2H), 2.04–1.97 (m, 1H), 1.55 (dd, 1H, J = 7.4, 4.7 Hz), 1.33 (dd, 1H, J = 9.4, 4.7 Hz), 1.27 (t, 3H, 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 135.1, 116.3, 61.1, 42.5, 35.7, 23.1, 14.4.

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