

Stereoselective Alkylations of a Bicyclic Lactam Derived from Pyroglutamic Acid

Rui Zhang, Floyd Brownnewell and Jose S. Madalenoitia*

Department of Chemistry, University of Vermont, Burlington, Vermont 05405

Received 13 November 1998; revised 8 February 1999; accepted 9 February 1999

Abstract: Improvements in the stereoselective alkylation of a bicyclic lactam derived from pyroglutamic acid are described. This methodology is used to synthesize a conformationally constrained homo-glutamic acid analog. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Amino Acids and Derivatives

As part of our program focused on the development of mimics of the poly-L-proline type II secondary structure by the synthesis of peptides composed of proline templated amino acids (PTAAs)¹, we are interested in developing methods for the stereoselective synthesis of 4-substituted proline analogs. An approach to the introduction of a substituent at the 4-position could involve enolization and alkylation of one of the many synthons derived from pyroglutamic acid.² There are advantages and disadvantages to these synthons trading off polyalkylation, reactivity, distereoselectivity, and ease of isolation of product. We seek methodology which will be selective for the synthesis of 2,4-*trans*-substituted PTAAs and will be amenable to the construction of multigram quantities of PTAAs. This paper describes improvements in the alkylation methodology of the Thottahil bicyclic lactam (**1**, Figure 1).

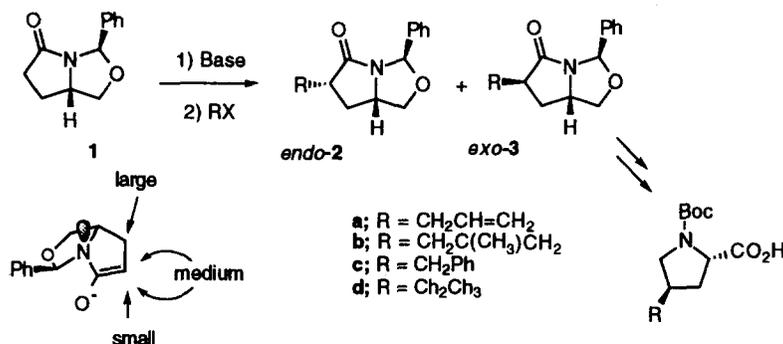


Figure 1

Although it may be expected that alkylation of **1** should proceed selectively from the less hindered *exo* face, alkylation of the lithium enolate of **1** with MeI affords a 5:1 mixture of *endo/exo* isomers, while alkylation

with allyl bromide is unselective affording a 1:1 mixture of isomers and prenyl bromide is moderately *exo*-selective (1:3 *endo/exo*).^{1,2c} This selectivity has been explained in terms of a competing steric and stereoelectronic effect. With small electrophiles (MeI), the nitrogen lone pair directs the alkylation to the sterically more hindered *endo*-face. As the size of the electrophile increases, sterics compete with the stereoelectronic effect with medium-sized electrophiles affording mixtures and large electrophiles alkylating preferentially the less hindered *exo*-face.^{2c,3}

In exploring alternative conditions to effect this transformation, we found that the potassium enoxyborate derived from **1** reacted with allyl bromide to afford the *exolendo* isomers in 81:19 ratio and 49% yield thus improving the selectivity over the lithium enolate (Table 1, entry 1).⁴ Yield and *exo*-selectivity were dramatically improved in the Pd(PPh₃)₄ catalyzed reaction (entry 3) affording a 94:6 ratio of isomers in 82% yield. Furthermore, the reaction could be catalyzed by as little as 0.1 mol% Pd(PPh₃)₄ thus making this reaction attractive for large scale work (entry 4). We have carried out this reaction in up to ~50 g scale in comparable yield and selectivity. This transformation should be applicable to the alkylation of additional allylic systems, for example reaction with CH₂C(CH₃)CH₂Br affords a 95:5 ratio of *exolendo* isomers in 81% yield (entry 5).

We also explored why the uncatalyzed reaction failed to proceed to completion and returned starting material. We noticed that reaction of the potassium enoxyborate of **1** with 1.2 eq BnBr afforded a 44% yield of products, while reaction of **1** with 4 eq BnBr improved the yield to 65%. Furthermore, if the potassium enoxyborate was allowed to warm to rt and maintained at rt for 1/2 h prior to the addition of 1.2 eq BnBr, the

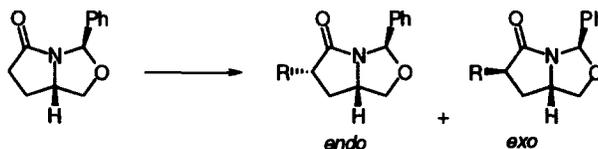


Table 1

| Entry | Conditions | Yield (%) | <i>exolendo</i> |
|-------|---|-----------|-----------------|
| 1 | (i) KHMDS, THF, -78 °C; (ii) Et ₃ B; (iii) 1.2 eq allylBr, -78 °C-rt | 49 | 81:19 |
| 2 | (i) KHMDS, THF, -78 °C; (ii) Et ₃ B; (iii) 1.2 eq allylI, -78 °C-rt | 49 | 89:11 |
| 3 | (i) KHMDS, THF, -78 °C; (ii) Et ₃ B; (iii) 1.2 eq allylBr, 5 mol% Pd(PPh ₃) ₄ , -78 °C-rt | 82% | 94:6 |
| 4 | (i) KHMDS, THF, -78 °C; (ii) Et ₃ B; (iii) 3 eq allylBr, 0.1 mol% Pd(PPh ₃) ₄ , -78 °C-rt | 79% | 94:6 |
| 5 | (i) KHMDS, THF, -78 °C; (ii) Et ₃ B; (iii) 3 eq CH ₂ C(CH ₃)CH ₂ Br, 0.1 mol% Pd(PPh ₃) ₄ , -78 °C-rt | 81% | 95:5 |
| 6 | (i) KHMDS, THF, -78 °C; (ii) Et ₃ B; (iii) 1.2 eq BnBr, -78 °C-rt | 44% | 63:37 |
| 7 | (i) KHMDS, THF, -78 °C; (ii) Et ₃ B; (iii) 4 eq BnBr, -78 °C-rt | 65% | 65:35 |
| 8 | (I) LDA, THF, -78 °C; EtI, -20°C, 4h; (iii) LDA, -78 °C; (iv) H ₂ O quench | 76% | 97:3 |
| 9 | (I) LDA, THF, -78 °C; BnBr, -78 °C, 0.5 h; (iii) LDA, -78 °C; (iv) H ₂ O quench | 60% | >98:2 |

yield of products decreased to 28%. Lower yields were also obtained in the $\text{Pd}(\text{PPh}_3)_4$ catalyzed reaction if the potassium enoxyborate was maintained at rt for 1/2 h prior to the addition of allyl bromide/ $\text{Pd}(\text{PPh}_3)_4$. This information is consistent with the instability of the potassium enoxyborate at higher temperatures. It then follows that conditions that increase the rate of alkylation of the potassium enoxyborate (such as the addition of catalyst or an increase in the concentration of the electrophile) relative to decomposition of the potassium enoxyborate improves the yield of the reaction.

To address the stereoselective alkylation of non-allylic electrophiles, we utilized the *endo*-selective kinetic protonation discovered by Armstrong.^{2c} In a one pot procedure, **1** is enolized with LDA at -78°C and alkylated with EtI at -20°C for 4 h. The reaction mixture is recooled to -78°C , reenolized with LDA, and then quenched with water to afford a 97:3 mixture of *exo/endo* isomers in 76% yield. The analogous reaction with BnBr as the electrophile resulted in a 60% yield of product also in high stereoselectivity.

With the improvements in yield and diastereoselectivity of the alkylation reaction, we have applied this methodology to the synthesis of a homo-glutamic acid analog (**10**, Figure 2). Hydrolysis of the *O,N*-acetal **3a** in 1:4:1 TFA/THF/ H_2O afforded the lactam **4** in 63% yield.⁵ Reduction of the amine with LAH in refluxing THF followed by protection of the resultant amine with Boc_2O in CH_2Cl_2 at 0°C gave the protected prolinol **5** in 89% yield. Jones oxidation of the alcohol was accomplished by the protocol of Thottahil affording the acid **6** (88%). The carboxylic acid was subsequently protected as the trichloroethyl ester with diisopropylcarbodiimide, trichloroethanol and DMAP.⁶ Ozonolysis of the double bond, followed by decomposition of the ozonide with dimethyl sulfide gave the aldehyde **8** (90%). Oxidation of the aldehyde with PDC in DMF gave the carboxylic acid which was protected as the benzyl ester with BnBr, NaI, NaHCO_3 in DMF.^{7,8} Finally, α -carboxy deprotection was accomplished with Zn dust in THF to afford the PTAA suitably protected for Boc solid phase peptide synthesis.⁹

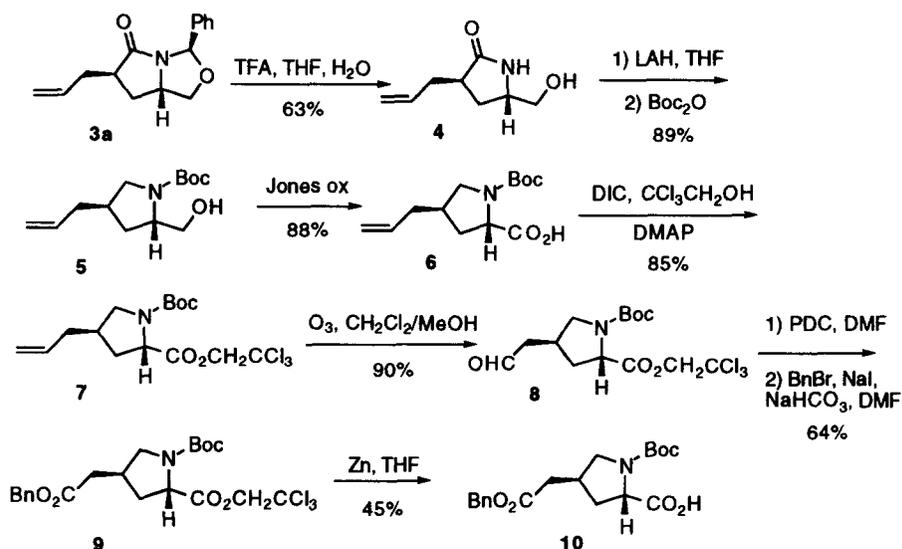


Figure 2

Representative experimental procedure for the allylation of 1: A solution of **1** (56.2 g, 0.277 mol) in THF (250 mL) was cooled to -78 °C and KHMDS (608 mL, 0.304 mol) was added as a 0.5 M solution in toluene with good stirring. The suspension was maintained at -78 °C for 15 min and Et₃B (416 mL, 0.416 mol) was added as 1 M solution in THF. The solution was maintained at -78 °C for an additional 15 min and Pd(PPh₃)₄ (3.20 g, 0.0027 mol) was added as a solution in THF (150 mL) followed by allyl bromide (100 g, 0.827 mmol). The reaction mixture was allowed to warm to rt. After 1.5 h, brine (200 mL) was added and the layers were separated. The aqueous layer was washed with EtOAc (3 × 200 mL) and the combined organic fractions were dried (Na₂SO₄) and concentrated to afford 93.9 g of an orange oil. Purification of the residue on silica gel afforded 52.4 g (77%) of **3a** as a colorless oil.

Acknowledgment. This work was supported by the University of Vermont, NSF Vermont EPSCoR OSR9350540 and CA75009 from the NIH.

References and Notes

1. (a) Zhang, R.; Brownell, F.; Madalengoitia, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 3894. (b) Zhang, R.; Madalengoitia, J. S. *Tetrahedron Lett.* **1996**, *37*, 6235.
2. (a) Thottahil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. *J. Org. Chem.* **1986**, *51*, 3140. (b) Langlois, N.; Rojas, A. *Tetrahedron Lett.* **1993**, *34*, 2477. (c) Armstrong, R. W.; DeMattei, J. A. *Tetrahedron Lett.* **1991**, *32*, 5749. (d) Baldwin, J. E.; Moloney, M. G.; Shim, S. B. *Tetrahedron Lett.* **1991**, *32*, 1379. (e) Ezquerra, J.; Pedregal, C.; Rubio, A.; Yruretagoyena, B.; Escribano, A.; Sanchez-Ferrando, F. *Tetrahedron* **1993**, *49*, 8665. (f) Hon, Y.-S.; Chang, Y.-C.; Gong, M.-L. *Heterocycles* **1990**, *31*, 191.
3. For discussions on the origin of the stereoelectronic effect see: (a) Durkin, K. A.; Liotta, D. *J. Am. Chem. Soc.* **1990**, *112*, 8162. (b) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 4565.
4. For alkylations of potassium enoxyborates see: Negishi, E.; Matsushita, H.; Chatterjee, S.; John, R. A. **1982**, *47*, 3188.
5. Griffart-Brunet, D.; Langlois, N. *Tetrahedron Lett.* **1994**, *35*, 119.
6. Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranaganathan, H.; Vorbruggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852.
7. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399.
8. Bocchi, V.; Casnati, G.; Dossena, A.; Marchelli, R. *Synthesis* **1979**, 961.
9. Just, G.; Grozinger, K. *Synthesis* **1976**, 457.