Tetrahedron Letters 53 (2012) 4775–4778

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Diastereoselective alkylations of oxazolidinone vinylogous glycolates

Jacqueline Jiménez, Rosa L. Meza-León, Fernando Sartillo-Piscil, Francisco J. Meléndez, Estibaliz Sansinenea *, Aurelio Ortiz *

Facultad de Ciencias Químicas, Benemérita Universidad Autónoma de Puebla, Puebla 72570, Mexico

ARTICLE INFO

Article history:
Received 7 June 2012
Revised 26 June 2012
Accepted 28 June 2012
Available online 4 July 2012

Keywords:
Diastereoselective alkylations
Oxazolidinone vinylogous glycolate
Double bond migration

ABSTRACT

A highly *Z*-selective isomerization (double bond migration) was observed when oxazolidinone vinylogous glycolate was exposed to a strong base to give *N*-acyl oxazolidinone, bearing an electron rich olefin. The corresponding enolate was exposed to alkyl halides to provide alkylated compounds on the γ-position with respect to OBn group, with high regioselectivity and moderate diastereoselectivity. However, the nature of the chiral oxazolidinone leads to a significant increase in the reaction diastereoselectivity. A stereospecific formation of *cis*-olefin was also observed in these alkylated compounds.

The metalation reaction of achiral hetero-substituted allylic ethers has been extensively studied.[1] These studies have focused primarily in the regioselectivity of the allylic carbanion reactions with electrophiles, since it is possible to obtain α and γ-products due to the nature of these anions.[2] It has been found that this regioselectivity is insensitive to change in solvent or temperature but is influenced by the ligand R (steric effects), substituent atom, counterion and type of electrophile.

The hetero-substituted allylic anions generally react with alkyl halides at the position while the allylic anions react with carbonyl compounds at the α position, except when using allylic aluminum or boron 'ate' complexes,[3] which direct both carbonyl compounds and alkyl halides to the α position with high regioselectivity.

It is noteworthy that the formation of the *cis*-enol ether stereoisomer on the γ product is highly stereospecific, suggesting that the alkylation reaction of allylic anions is carried out via internally coordinated metallocycle (Fig. 1).[2]

We report herein, a highly regioselective asymmetric alkylation reaction carried out on chiral oxazolidinone vinylogous glycolates with a strong base in the presence of alkyl halides. During this process a highly stereospecific double-bond migration is observed.

The preparation of the chiral oxazolidinone vinylogous glycolates **5a** and **b** began with the synthesis of *E*-4-(benzyloxyl)-*Z*-but-2-enoic acid **4**,[4,5] which was prepared from ethyl-2-but-2-ynoate **1** by a γ-addition reaction of benzyl alcohol with assistance of triphenyl phosphine[6] to afford the ester **2** in 80% yield (Scheme 1). A subsequent basic hydrolysis (LiOH, THF–H_2O) delivered the acid **4** in 90% yield. This acid was treated with triethylamine and pivaloyl chloride in dry THF,[7] followed by addition of the oxazolidinone[8] **3a** or **3b** at 0 °C and after stirring for 18 h at room temperature afforded **5a** as a white solid in 60% yield and **5b** as a colorless liquid in 40% yield,[9] as shown in Scheme 1.

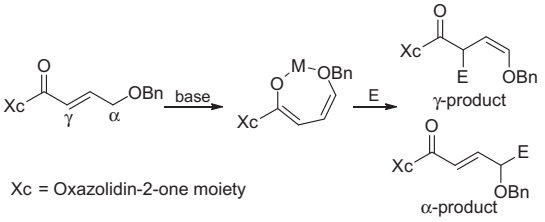
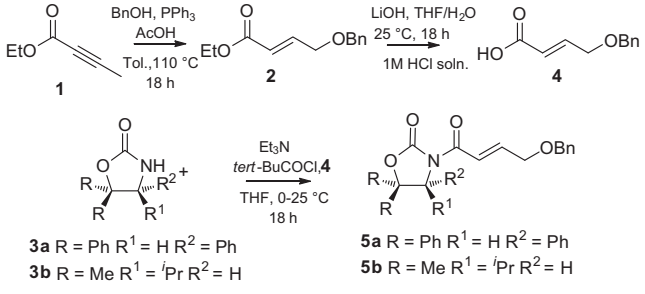


Figure 1. α and γ Alkylation products via metallation.



Scheme 1.

* Corresponding authors. Tel.: +52 222 2295500x7518; fax: +52 222 2295584.
E-mail addresses: estisan@yahoo.com (E. Sansinenea), aurelioom@yahoo.com (A. Ortiz).

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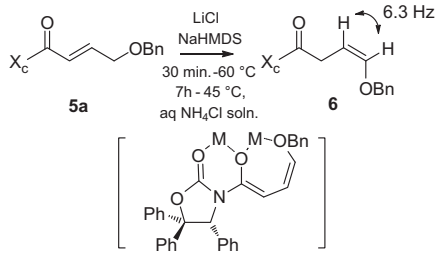
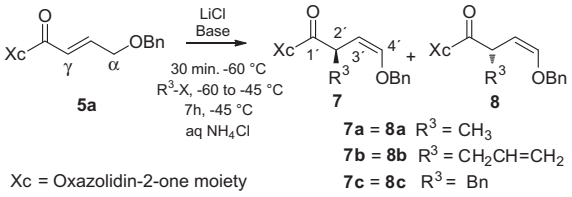
http://dx.doi.org/10.1016/j.tetlet.2012.06.133



Scheme 2. Double bond migration in *N*-enoyl oxazolidinone.

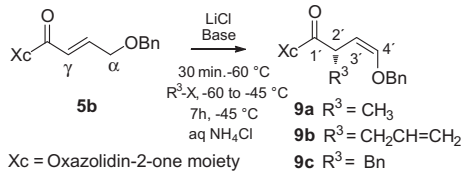
Table 1
Alkylation of oxazolidinone vinylogous glycolate **5a**



Entry	Base	R^3-X	Yield[a] (%)	d.r.[b] **7/8**
1	NaHMDS	CH_3I	74	85/15
2	KHMDS	CH_3I	80	87/13
3	LiHMDS	CH_3I	50	83/17
4	KHMDS	AllylBr	85	72/28
5	KHMDS	BnBr	85	76/24
6	KHMDS	EtI	0	0

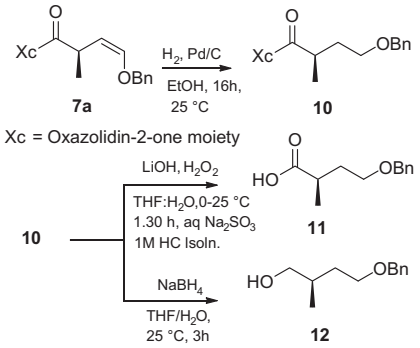
[a] Yield corresponding to purified mixture of diastereomers.
[b] Diastereomeric ratios were determined by NMR of crude reaction mixture.

Table 2
Alkylation of oxazolidinone vinylogous glycolate **5b**



Entry	Base	R^3-X	Yield (%)[a]	d.r.[b]
1	KHMDS	CH_3I	60	98/2
2	KHMDS	AllylBr	52	98/2
3	KHMDS	BnBr	50	98/2

[a] Yield corresponding to purified diastereomer.
[b] Diastereomeric ratios were determined by NMR of crude reaction mixture.



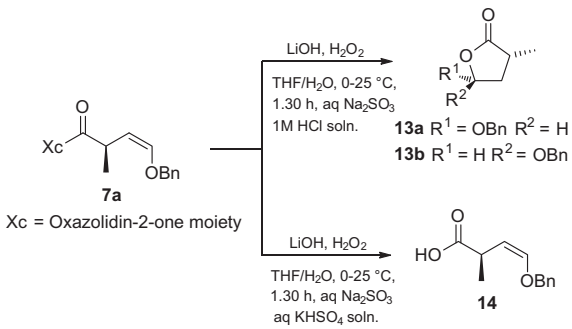
Scheme 3.

The double bond in oxazolidinone vinylogous glycolate **5a** was isomerized to the unconjugated *cis* double bond **6** (Scheme 2). Therefore, the oxazolidinone vinylogous glycolate **5a** was treated with NaHMDS or KHMDS (1.5 equiv) in the presence of LiCl (1 equiv) in dry THF at −60 °C. After 30 min the temperature was increased at −45 °C and the reaction was stirred for 7 h. After the reaction was quenched by the addition of a saturated solution of NH_4Cl to provide vinyl ether **6** in 95% yield.[10] The isomer **6** was achieved via a double bond migration,[11] with a high *Z*-selectivity (*Z*/*E* 99:1). The *cis* alkene geometry was established based on the measurement of coupling constants of vinyl protons in the NMR spectrum ($J_{H3'-H4'}$ = 6.3 Hz). The high selectivity implies that the coordination of OBn group to the metal plays an important role in the transition state, as shown in the Scheme 2.

The oxazolidinone vinylogous glycolate **5a** was treated under the reaction conditions described above to form the corresponding enolate, followed by addition of excess alkyl halide (3 equiv) and warming the reaction mixture to −45 °C (Table 1). After stirring for 7 h at this temperature the alkylated compounds **7a–c** and **8a–c**,[12] where alkylation took place on the γ-position with respect to OBn group, were achieved with high regioselectivity, moderate diastereoselectivity (72/28-87/13), and moderate yields (50–85%). In all cases, the compounds **7a–c** always were predominant. Stereospecific formation of *cis*-alkenes in all compounds **7a–c** and **8a–c** was also observed. No changes in regioselectivity, diastereoselectivity nor yield were observed when different metals were used in metalation reaction, as shown in Table 1. The use of KHMDS as base in the alkylation reaction of compound **5a** provided the best results (entry 2). Furthermore, lithium chloride (1 equiv) plays an important role in the success of the alkylation because its absence leads to a fast deacylation of the auxiliary even at −78 °C. The alkylation proceeded well with some representative alkyl halides (entries 2, 4–5), however, when ethyl iodide was employed as the electrophile, no alkylation product was observed (entry 6), as shown in Table 1.

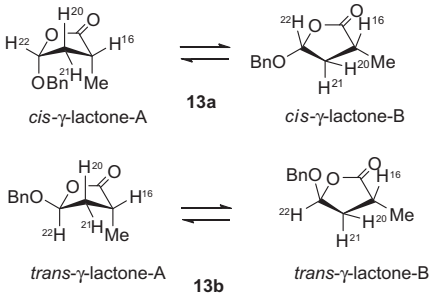
Nevertheless, the nature of the chiral oxazolidinone leads to a significant change in the reaction diastereoselectivity. When the compound **5b** was exposed to the same alkylation reaction condition above described, furnished the compounds **9a–c** in moderate yield (50–60%) and with a high diastereoselectivity (98:2), as shown in Table 2.

To determine the absolute configuration and relative stereochemistry of the alkylation product, compound **7a** was transformed into known carboxylic acid **11**, via a sequence of reactions (Scheme 3). Hydrogenation of **7a** with Pd-C in EtOH provided compound **10** in quantitative yield, removal of the chiral auxiliary with LiOH, H_2O_2, delivered carboxylic acid **11** in 80%



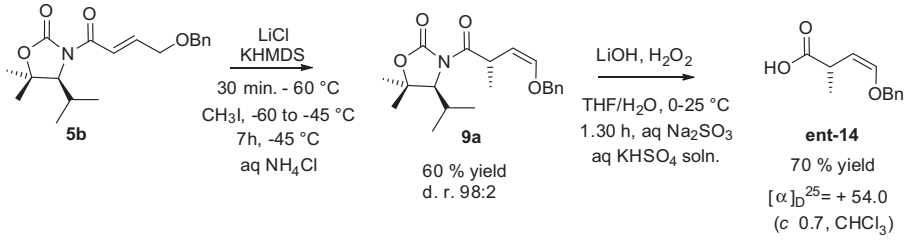
Scheme 4.

Table 3
Calculated vicinal coupling constants (Hz) for the individual conformations A and B of the compounds **13a** and **13b**, as well as their comparison with experimental vicinal coupling constants



γ-Lactone	Energy (u.a)	Dihedral angle	$^3J_{H-H}$ calcd	$^3J_{H-H}$ [b] Karplus	$^3J_{H-H}$ Expl
cis-A	−691.4164	H_{16}–H_{20} 19°	9.4	9.2	10.8
13a		H_{16}–H_{21} 104°	0.4	1.7	8.6
		H_{22}–H_{20} 23°	6.0	7.6	5.6
		H_{22}–H_{21} 96°	−0.4	1.6	0.0
		H_{16}–H_{20} 19°	9.4	9.2	10.8
cis-A[a]	−691.4256	H_{16}–H_{20} 19°	0.4	1.7	8.6
13a		H_{22}–H_{20} 21°	6.2	7.8	5.6
		H_{22}–H_{21} 98°	−0.3	1.7	0.0
		H_{16}–H_{20} 35°	8.5	7.0	10.8
cis-B	−691.4162	H_{16}–H_{21} 157°	10.5	10.6	8.6
13a		H_{22}–H_{20} 31°	5.2	6.6	5.6
		H_{22}–H_{21} 150°	6.1	8.6	0.0
trans-A	−691.4095	H_{16}–H_{20} 23°	9.1	8.8	9.5
13b		H_{16}–H_{21} 99°	0.2	1.3	6.5
		H_{22}–H_{20} 151°	7.0	8.5	5.6
		H_{22}–H_{21} 32°	5.7	6.4	4.3
trans-B	−691.4118	H_{16}–H_{20} 36°	7.5	6.8	9.5
13b					
		H_{16}–H_{21} 159°	9.4	10.8	6.5
		H_{22}–H_{20} 90°	−0.4	1.2	5.6
		H_{22}–H_{21} 30°	4.6	6.6	4.3

[a] The calculation was realized in solution ($CHCl_3$).
[b] Vicinal coupling constants have been calculated with a software which works using a generalized Karplus type equation.[20]



Scheme 5.

yield. By comparison with literature optical data,[13] the absolute stereochemistry of **7a** was established as *R*. On the other hand, when the compound **10** was treated with $NaBH_4$ in THF/H_2O[14] provided the known alcohol[15] **12** in 83% yield as a colorless liquid, as shown in Scheme 3.

Removal of the chiral auxiliary under Evans' hydrolysis procedure[16] in the compound **7a**, led to direct cyclization to lactones **13a–b** as a mixture of diastereomers in 80% yield and with d.r. of 70:30, being **13a** the major diastereomer. During this procedure a 1 M HCl solution was used to adjust the acid pH, so under these reaction conditions, the electron-rich alkene **7a** underwent removal of the chiral auxiliary and intramolecular cyclization reaction to provide the γ-lactones **13a–b**. Carboxylic acid **14**[17] was achieved in 80% yield, when the aqueous 1 M HCl solution was replaced with an aqueous solution of $KHSO_4$ as shown in Scheme 4. It is important to note that carboxylic acid **14** can be transformed to the corresponding γ-lactones **13a–b** after its storage by several days.

To assign the relative configuration of the major diastereomer of γ-lactones **13a** and **13b**, NOESY spectra were obtained; however, in both cases it was not possible to observe any correlation. Therefore, the relative configuration of **13a–b** was assigned in base on comparative analysis between calculated vicinal coupling constants[18] and experimental vicinal coupling constants. Consequently, a geometry optimization for four conformers of γ-lactones **13a–-b** was realized in the gas phase.[19] The results of the calculated and experimental vicinal coupling constants are shown in Table 3. Both conformers of *cis*-γ-lactone **13a** presented similar energy values; however, a comparison between calculated ($^3J_{H22\text{-}H20}$ = 6.0 Hz, $^3J_{H22\text{-}H21}$ = 0.4 Hz) and experimental ($^3J_{H22-}$

$_{H20}$ = 5.6 Hz, $^{3}J_{H22-H21}$ = 0 Hz) vicinal coupling constants, suggests that *cis*-γ-lactone A **13a** conformation is possibly more favored than *cis*-γ-lactone-B **13a** conformation. For *trans*-γ-lactone **13b**, both conformers also presented similar energy values and a comparison between calculated ($^{3}J_{H22-H2}$ = 7.0 Hz, $^{3}J_{H22-H21}$ = 5.7 Hz) and experimental ($^{3}J_{H22-H20}$ = 5.6 Hz, $^{3}J_{H22-H21}$ = 4.3 Hz) vicinal coupling constants, suggests that *trans*-γ-lactone A **13b** conformation is more favored than *trans*-γ-lactone-B **13b** conformation. This analysis of the coupling constants allowed to assign the relative configuration *cis* for γ-lactone **13a** and *trans* for **13b**.

A change of substituent and absolute configuration in the ring of oxazolidinone provides a significant change in the diastereoselectivity of the alkylation of compound **5b** (98:2). Removal of chiral auxiliary under Evans' hydrolysis modified procedure provides **ent-14** in 70% yield as shown in Scheme 5.

In conclusion, we described an unprecedented alkylation of chiral oxazolidinone vinylogous glycolates. The compounds **5a–b** undergo stereo- and regioselective alkylation reactions with concomitant migration of the double bond when exposed to a strong base. The products were found to be alkylated on the γ-position with respect to the OBn group and possess an electron-rich *cis*-alkene. The alkylation reaction was highly regioselective but moderately diastereoselective for the compound **5a**. However, for the compound **5b** this reaction was highly regioselective and diastereoselective. The *cis*-alkene formation was highly stereospecific. Our group is currently working to functionalize the *cis*-alkene as well as to carry out this reaction with other electrophiles.

Acknowledgments

The authors thank VIEP and CONACyT (project 80915).

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9. The compounds **5a–b** were achieved in low yield, however the starting materials were recovered and used again.
10. *Procedure for the isomerization (double bond migration).* To an oven-dried 100 mL round-bottom equipped with a magnetic stir bar was added anhydrous LiCl (0.36 mmol, 15.4 mg) under an argon atmosphere followed of oxazolidinone **5a** (0.3 mmol, 0.15 g). Both solids were dissolved in anhydrous THF (25 mL) and the reaction mixture was stirred for 15 min at −60 °C and then was added NaHMDS (0.61 mmol, 0.61 mL) and the resulting solution was stirred vigorously. After 30 min the temperature was increased at −45 °C and the reaction was stirred for 7 h. After the reaction was quenched by the addition of a saturated solution of NH_4Cl (3 mL), THF was removed under reduced pressure. The organic layer was extracted with CH_2Cl_2 (3 × 30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The oily residue was purified by flash column chromatography eluting with hexane–ethyl acetate (95:5) to give the compound(4R,Z)-N-(4′-benzyloxy-but-3′-enoyl)-4,5,5-triphenyloxazolidin-2-one 6; Yield 95%, $[\alpha]_D^{25}$ +137 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (2H, dt, *J* = 7.0, 1.5 Hz, Ph), 7.44–7.25 (8H, m, Ph), 7.10-6.98 (10H, m, Ph), 6.21 (1H, s, H-4), 6.12 (1H, dt, *J* = 6.3, 1.5 Hz, H-4′), 4.74 (2H, s, CH_2Ph), 4.58 (1H, dt, *J* = 6.6, 6.6 Hz, H-3′), 3.77 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6 (C-1′), 152.6 (C-2), 146.8 (C-4′), 141.7, 138.0, 137.2, 135.7, 128.8, 128.7, 128.4, 128.3, 128.1, 128.0, 127.8, 127.6, 127.4, 127.3, 127.2, 126.1, 125.9 (Ph), 97.5 (C-3′), 89.0 (C-5), 73.6 (CH_2O), 66.0 (C-4′), 31.5 (C-2′). IRυ_{max}: 2923, 1788, 1712, 1496, 1450, 1364, 1347, 997, 845, 759 cm^{-1}; FAB-HRMS: calculated for ($C_{32}H_{28}NO_4$), ([M+H])$^+$ 490.2018; found, 490.2150.
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12. *General Procedure for the alkylation reaction.* To an oven-dried 100 mL round-bottom equipped with a magnetic stir bar was added anhydrous LiCl (0.24 mmol, 10.3 mg) under an argon atmosphere followed of oxazolidinone 5a (0.2 mmol, 0.10 g). Both solids were dissolved in anhydrous THF (25 mL) and the reaction mixture was stirred for 15 min at −60 °C and then was added NaHMDS (0.41 mmol, 0.41 mL) and the resulting solution was stirred vigorously during 30 min. After, was added CH_3I (1.2 mmol, 0.17 g), the temperature was increased at −45 °C and the reaction mixture was stirred for 7 h. After the reaction was quenched by the addition of a saturated solution of NH_4Cl (3 mL), THF was removed under reduced pressure. The organic layer was extracted with CH_2Cl_2 (3 × 30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The oily residue was purified by flash column chromatography eluting with hexane- ethyl acetate (95:5) to give a diastereomeric mixture of the compounds **7a** and **8a**. Their isolation was carried out by preparative thin layer chromatography eluting with hexane CH_2Cl_2 9:1. (2′R,4R,Z)-N-(4′-benzyloxyl-2-methylbut-3′-enoyl)-4,5,5-triphenyloxazolidin-2-one **7a**; $[\alpha]_D^{25}$ +83 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (2H, dd, *J* = 7.0, 1.6 Hz, Ph), 7.38–7.22 (8H, m, Ph), 7.12 –7.00 (10H, m, Ph), 6.20 (1H, s, H-4), 5.90 (1H, dd, *J* = 6.0, 1.2 Hz, H-4′), 4.73 (1H, dq, *J* = 8.4, 7.0 Hz, H-2′), 4.60 (1H, d, *J* = 12.8 Hz, CH_aH_bPh), 4.56 (1H, d, *J* = 12.8 Hz, CH_aH_bPh), 4.53 (1H, dd, J = 8.4, 6.0 Hz, H-3′), 1.21 (3H, d, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.7 (C-1′), 152.2 (C-2), 145.1 (H-4′), 141.8, 138.1, 137.3, 136.0, 128.7, 128.6, 128.3, 128.2, 128.0, 127.7, 127.6, 127.3, 127.1, 126.2, 126.0 (Ph), 105.7 (H-3′), 88.6 (C-5), 73.4 (CH_2Ph), 66.2 (C-4), 34.5 (C-2′), 17.8 (CH_3); IRυ_{max}: 2922, 1782, 1703, 1450, 1329, 989, 696 cm^{-1}; FAB-HRMS: calculated for ($C_{33}H_{29}NO_4$), ([M+H])$^+$ 504.2175; found, 504.2154.
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19. Geometry optimization of the four conformers γ-lactone **13a–b** in gas phase was carried out using DFT calculations with the B3LYP hybrid functional and the 6-31 + G(d) basis set as implemented in the quantum chemical program gaussian09. Harmonic vibration frequency analyses were completed and all vibration frequencies are positive. The computation of the coupling constants, $^3J_{H-H}$, was done employing the NMR (Spin–Spin) keyword at B3LYP/6-31 + G(d) level in gaussian09 package. (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789; (b) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724–728; (C) Gaussian09, revision A.01, Gaussian, Inc. Exploring Chemistry with Electronic Structure Methods Sec Ed., J. B. Foresman and Aleen Frisch.
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