Pergamon

Tetrahedron Letters, Vol. 35, No. 48, pp. 8977-8980, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)02021-3

ENANTIORETENTIVE ALKYLATION OF OXAZOLIDINONE ALUMINUM ENOLATES WITH EPOXIDES: PREPARATION OF UNCODED HOMOSERINE ANALOGS

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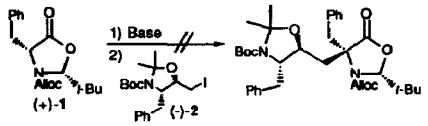
Abstract: The alkylation of Karady/Seebach oxazolidinone enolates with epoxides, promoted by 2.1 equivalents of diethylaluminum chloride, furnishes ring-opened adducts in moderate-to-good yields with high diastereoselectivity. The method provides an effective approach to uncoded homoserine analogs and expands the utility of readily available oxazolidinones in asymmetric synthesis.

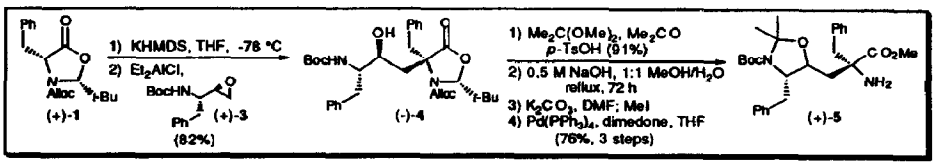
The enantioretentive alkylation of 1,3-oxazolidin-5-ones, introduced by Karady[1] and Seebach,[2] has become a standard method for the synthesis of uncoded α-amino acids, particularly α,α-disubstituted structures.[3] However, we and others[4] have observed that this process is limited to highly electrophilic alkylating agents such as methyl, allyl or benzyl halides, aldehydes, acid chlorides and nitro olefins; unactivated primary or secondary halides react sluggishly or not at all. In connection with our program directed toward the design and synthesis of novel HIV-1 protease inhibitors,[5] we attempted unsuccessfully to alkylate oxazolidinone (+)-1 with the highly functionalized primary iodide (-)-2 under a variety of experimental conditions (Scheme 1). We then decided to explore the coupling of 1 with epoxide (+)-3[6] (Scheme 2), a precursor of 2.

Scheme 1



A literature search provided no precedent for the alkylation of 1,3-oxazolidin-5-one enolates with epoxides, although Seebach and associates had reported a related coupling of an imidazolidinone enolate with ethylene oxide in the presence of BF_3•OEt_2.[7] Accordingly, we began by studying the reaction of the enolate of (+)-1 with 3 and BF_3•OEt_2, isolating alcohol (-)-4 in 30% yield as a 7:1 mixture of diastereomers. After examining several Lewis acids, we discovered

Scheme 2

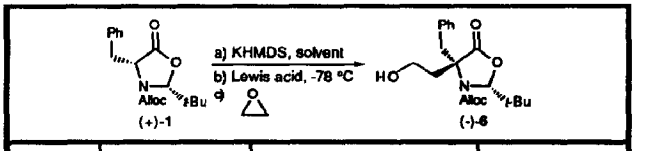


that addition of diethylaluminum chloride (ca. 6 equiv) to a mixture of the potassium enolate and epoxide at -78 °C (Scheme 2) furnished 4 in 82% yield. As anticipated, alkylation occurred anti to the *t*-butyl substituent; ^{1}H NMR analysis revealed only a trace of the minor diastereomer (>97% de). Protection of the hydroxyl and NH groups (dimethoxypropane, *p*-TsOH)

followed in turn by hydrolysis (0.5 M NaOH,1:1 MeOH/H_2O), esterification of the resultant carboxylic acid (MeI, K_2CO_3, DMF), and removal of the Alloc protecting group [$Pd(PPh_3)_4$, dimedone] furnished amino ester (+)-**5** (76% for three steps), as required for the synthesis of our target HIV-1 protease inhibitor.[4]

To define the scope and limitations of the new alkylation protocol, we evaluated several oxazolidinones, epoxides, solvent systems and Lewis acids. Of the five Lewis acids examined (Table 1, entries 1-4 and 6), diethylaluminum chloride gave the highest yields. In general, toluene proved to be a superior solvent (entries 6 and 8), except for coupling of **1** with **3**. The optimal quantity of Et_2AlCl appeared to be 2.1equivalents (entries 5-7).

Table 1. Evaluation of Lewis acids and solvents.



Entry	Solvent	Lewis acid (equiv)	Yield 6 (%)
1	Toluene	$TiCl_4$ (3.3)	0
2	Toluene	Bu_2BOTf (2.2)	0
3	Toluene	$BF_3{\cdot}OEt_2$ (2.2)	29
4	Toluene	Me_3Al (2.1)	46
5	Toluene	Et_2AlCl (1.1)	36
6	*Toluene*	*Et_2AlCl (2.1)*	*69*
7	Toluene	Et_2AlCl (3.1)	69
8	THF	Et_2AlCl (2.1)	32

In the couplings of various epoxides and oxazolidinones, diastereoselectivities typically exceeded 95% (Table 2). Monosubstituted epoxides alkylated exclusively at the less hindered position (entries 6 and 7; also see Scheme 1), whereas epoxycyclohexane (entry 8) did not react. Entry 6 illustrates the utility of the enantiomerically enriched epoxides available via Sharpless asymmetric epoxidation. Interestingly, coupling of racemic propene oxide (two equiv) occurred with modest kinetic resolution, leading to a 3:1 mixture of diastereomeric alcohols (entry 7). Only two of the four possible products were detected, again suggesting excellent facial selectivity.

The results described above seem likely to derive from the alkylation of aluminum enolates[8] via open transition structures. Closed (i.e., six-membered-ring) transition states appear unlikely; models indicate that the latter arrangement would not permit the correct trajectory for S_N2 attack. The reactions presumably involve two equivalents of diethylaluminum chloride, one for generation of the aluminum enolate and a second for activation of the epoxide oxygen. This hypothesis is in accord with the observation that two equivalents of Lewis acid are required for optimal yields *(vide supra)*. For the reaction of (-)-**1** with racemic propene oxide, models revealed that coupling with the *S* epoxide should be impeded (Figure 1) by steric interactions with the bulky enolate; this expectation was borne out by X-ray analysis of the major diastereomer (+)-**14a** (Figure 2).

Figure 1. Proposed transition structures for the reactions of the aluminum enolate of (+)-**1** with the enantiomers of propene oxide.

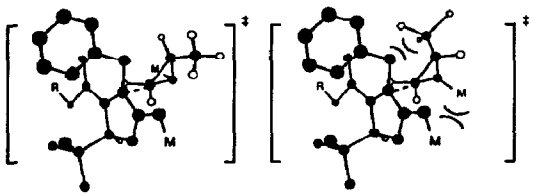


Table 2. Variation of oxazolidinone and epoxide reactants.

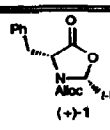
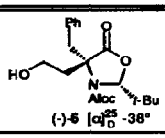
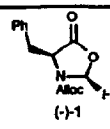
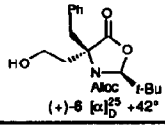
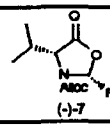
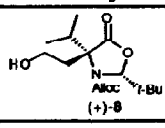
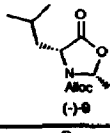
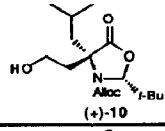
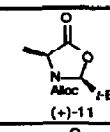
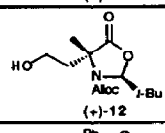
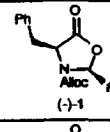
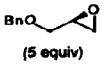
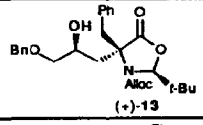
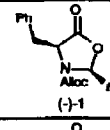
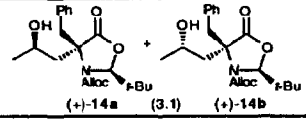
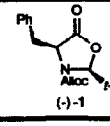
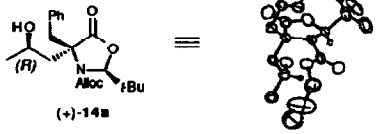
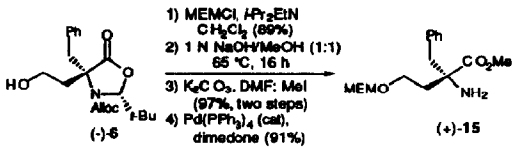
Entry	Oxazolidinone	Epoxide	Product[9]	Yield (%)	Selectivity (de)
1	 (+)-1	 (excess)	 (-)-6 $[\alpha]_D^{25}$ -38°	69	≥95
2	 (-)-1	 (excess)	 (+)-6 $[\alpha]_D^{25}$ +42°	68	≥95
3	 (-)-7	 (excess)	 (+)-8	47	≥95
4	 (-)-9	 (excess)	 (+)-10	54	89
5	 (+)-11	 (excess)	 (+)-12	64	≥95
6	 (-)-1	 (5 equiv)	 (+)-13	40	≥95
7	 (-)-1	 (±; 2 equiv)	 (+)-14a (3.1) (+)-14b	48	≥95 (each isomer)
8	 (-)-1	 (2 equiv)	–	NR	–

Figure 2. Crystal structure of alcohol **14a**, derived from (-)-**1** and *(R)*-epoxypropene.



The alkylated oxazolidinones can be readily converted to the corresponding amino esters via methodology that we have previously described.[10] For example, (-)-**6** was transformed (Scheme 3) to amino ester (+)-**15**[9] by treatment with MEMCl (89%), followed by hydrolysis (1 N NaOH/MeOH, 1:1, 65 °C), esterification (MeI, K_2CO_3, DMF; 97% for two steps), and removal of the Alloc protecting group [$Pd(PPh_3)_4$, dimedone, 91%].

Scheme 3



Representative procedure: A solution of KHMDS in toluene (1.10 mL, 0.5 N, 0.55 mmol) was added to a solution of (-)-**1** (158.2 mg, 0.498 mmol) in dry toluene (5 mL) at -78 °C under argon. After 15 min a solution of diethylaluminum chloride in heptane (1.05 mL, 1.0 N, 1.05 mmol) was introduced dropwise and the resultant mixture stirred for 15 min. Excess gaseous ethylene oxide was then added via a balloon. The reaction mixture was stirred 1.75 h further at -78 °C and then quenched at -78 °C with a mixture of $Na_2SO_4 \cdot 10H_2O$ (ca. 5 g), Na_2CO_3 (ca. 100 mg) and ether (20 mL). The resultant suspension was stirred for 1 h at ambient temperature. Following filtration and concentration *in vacuo*, flash chromatography (hexanes/EtOAc; 6:1 to elute unreacted starting material, then 2:1) afforded (-)-**6** (121.8 mg, 68% yield).

Acknowledgments. This work was supported by the National Institutes of Health (Institute of General Medical Sciences) through grant GM-45611, and by Bachem, Inc. (Torrance, CA), Merck Research Laboratories, and Japan Energy Corporation, the latter by a stipend for A. Y. A. P. is the recipient of an American Cancer Society Postdoctoral Fellowship. The authors also wish to thank Drs. George Furst and Patrick Carroll and Mr. John Dykins for assistance in performing NMR, X-ray and mass spectral analyses, respectively. In addition, the authors thank Drs. Grant Spoors and Paul Sprengeler for helpful discussions.

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9. All synthetic compounds were purified by flash chromatography on silica gel. The structure assigned to each new compound is in accord with its infrared, 500-MHz ^1H NMR and 125-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry. In addition, (-)-**4**, (+)-**5**, (+)-**6**, (-)-**8**, (+)-**11**, (+)-**12**, and (+)-**14a** gave satisfactory C and H combustion analyses.
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(*Received in USA* 22 *September* 1994; *accepted* 7 *October* 1994)