A New Approach for Chiral Allyl Amines *via* a Novel Dichloromethylenation of Oxazolidinones

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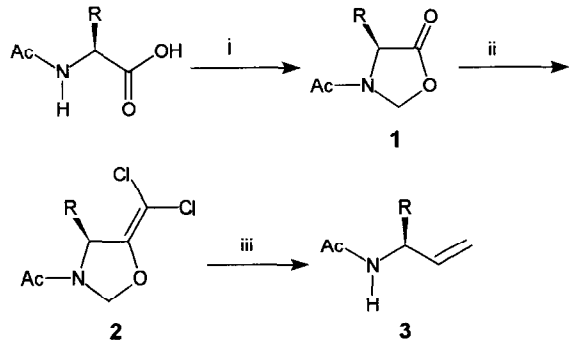
A novel dichloromethylenation of oxazolidinones and their conversion to allyl amines **3a-e**, key precursors for potential HIV protease inhibitors is described.

Optically pure α-substituted allyl amines are versatile building blocks for several biologically active compounds especially to threo α-amino epoxides[1] and threo peptidyl epoxides[2] which can be converted to HIV protease inhibitors.[3-5] These are also useful synthons for β-amino acids.[6] The literature precedents for the preparation of title compounds involves (a) Wittig olefination of N-protected α-amino aldehydes with methylenetriphenylphosphorane,[1,2] (b) reductive deoxygenation of 3-amino-1,2-diols.[6] Though the former one is commonly used method, it suffers from partial racemisation due to the use of configurationally labile N-protected α-amino aldehydes and basic reaction conditions.[7] In view of our interest in the design and synthesis of C_2-symmetric HIV protease inhibitors, we report here an elegant synthesis of allyl amines under neutral conditions starting with readily accessible oxazolidinones **1**[8] by overcoming the earlier drawbacks. The present strategy involves a novel dichloromethylenation of oxazolidinones **1** and their conversion to the title compounds by reductive elimination.

The oxazolidinones **1** were subjected to Wittig reaction by using CCl_4-Ph_3P to give 5-dichloromethyleneoxazolidines **2** in excellent yield. Compounds **2** were fully characterized by spectral data.[9] Important characteristic signals of **2a** : IR(KBr) 1680 cm^{-1} (CO-NH), EIMS : m/z 285 (M^+), 287(M+2), 289 (M+4). The isotopic abundance of M+, M+2, M+4 are in the ratio of 10: 6.5: 1 clearly indicating the presence of two chlorine atoms. In ^1H NMR spectra of **2**, two sets of signals for each proton are appeared due to the existence of two envelope conformers.[9] Similar observation was made with proton nmr of oxazolidinones[10] **1**. Reaction of **2** with metallic sodium in refluxing THF and subsequent quenching with methanol affected the reductive dehalogenation,[11] ring opening and elimination of formaldehyde in a single step to give the desired allyl amines[12] **3** of high optical purity (>99%). Allyl amines **3** obtained are fully characterized by spectral data. Important characteristic signals of **3a** : ^1H NMR : δ 5.05(d, 1H, J = 8.8 Hz), 5.15(d, 1H, J= 14.0 Hz), 5.80(ddd, 1H, J=14.0, 8.8, 6.3 Hz) clearly indicate the terminal olefin functionality. The results obtained with variety of α-amino acids are summarized in Table-1. Optical purities of allyl amines were determined by ^{19}F NMR spectra of the corresponding (R)-Mosher amides[13] and further confirmed by converting **3a** into corresponding N- BOC-derivative. MP 67 °C, $[\alpha]_D^{25}$ = 36.9 (c = 1, $CHCl_3$), (lit. [14] MP 66-67 °C, $[\alpha]_D^{25}$ = 36.7 (c = 0.9, $CHCl_3$).

In summary, we report a novel dichloromethylenation of oxazolidinones and their conversion to allyl amines for the first time. The present methodology involves the use of cheap and readily available reagents, neutral reaction conditions, and enables to synthesise analogous series of compounds avoiding racemisation. Studies are in progress to synthesise C_2-symmetric HIV protease inhibitors using this protocol and will be reported in due course.



Reagents and conditions : i. $(CH_2O)n$, PTSA(Cat), C_6H_6, reflux; ii. PPh_3/CCl_4 , THF, reflux; iii. Na, THF, reflux

Scheme 1.

Table1. Preparation of N-acetyl-5-dichloromethylene oxazolidines and N-acetyl allyl amines

Entry	R	Yield[a] **2**	[b]$[\alpha]_D^{25}$ **2**	Yield[a] **3**	[b]$[\alpha]_D^{25}$ **3**
a	$PhCH_2$	96	-24.9	72	+12.8
b	CH_3	78	-3.5	63	+25.6
c	$(CH_3)_2CH$	75	-2.8	68	+5.7
d	$(CH_3)_2CHCH_2$	81	-8.5	61	+3.7
e	$CH_3CH_2CHCH_3$	80	-20.3	67	+12.5

a: [a]Isolated yield (%). [b]Specific rotations were measured with c *b* : = 1 in methanol.

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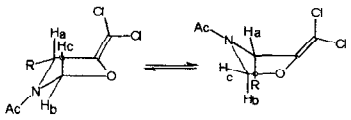
9 Representative Procedure: To a refluxing mixture of **1a** (1.31 g, 6 mmol) and triphenyl phosphine (3.14 g, 12 mmol) in dry THF (24 ml) under N_2 atmosphere was added CCl_4 (4.62 g, 30 mmol) in one portion, with stirring. After completion of the reaction, removal of the solvent and usual work up followed by column chromatography on silica gel gave **2a** (1.64 g).

Spectroscopic (^{1}H NMR, 200 MHz, $CDCl_3$ & EIMS) data of **2a:** δ 1.60, 1.90 (2s, 3H, $\underline{CH_3}CO$), 2.90-3.30 (m, 2H, $\underline{CH_2}Ph$), 4.00, 5.00 , 4.60, 5.60 (4d, 2H, J = 6.1 Hz, H-2), 4.70-4.85, 5.10-5.25 (2m, 1H, H-4), 7.00-7.30 (m, 5H, Ph); m/z 285 (M^+); Anal. Found : C, 54.89; H, 4.81; N, 4.67%. Calcd for $C_{13}H_{13}Cl_2NO_2$: C, 54.54; H, 4.57; N, 4.89%.



Two possible conformers

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12 Representative Procedure: A solution of **2a** (1.14 g, 4 mmol) in THF (12 ml) was treated with sodium (0.55 g, 24 mmol) under reflux. After completion of the reaction, reaction mixture was quenched with methanol. Removal of the solvent and usual work up followed by column chromatography afforded **3a** (0.57 g).

Spectroscopic (^{1}H NMR, 200 MHz,$CDCl_3$ & EIMS) data of **3a:** δ 1.95 (s, 3H, $\underline{CH_3}CO$), 2.85 (d, 2H, J = 13.4 Hz, $\underline{CH_2}Ph$), 4.70-4.88 (m, 1H, $\underline{CH}$-NAc), 5.05 (d, 1H, J = 8.8 Hz, $\underline{CH_2}$=CH), 5.15 (d, 1H, J = 14.0 Hz, $\underline{CH_2}$=CH), 5.35-5.50 (brs, 1H, NH), 5.80 (ddd, 1H, J = 14.0, 8.8, 6.3 Hz, $\underline{CH}$=CH_2), 7.12-7.40 (m, 5H,Ph); m/z 89 (M^+-CH_2Ph); Anal. Found : C, 76.42; H, 8.12; N, 7.46%. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.98; N, 7.40%.

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