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Stereoselective synthesis of *anti*-2-oxazolidinones by Ph_3P–CCl_4–Et_3N mediated S_N2 cyclization of *N*-Boc-β-amino alcohols☆

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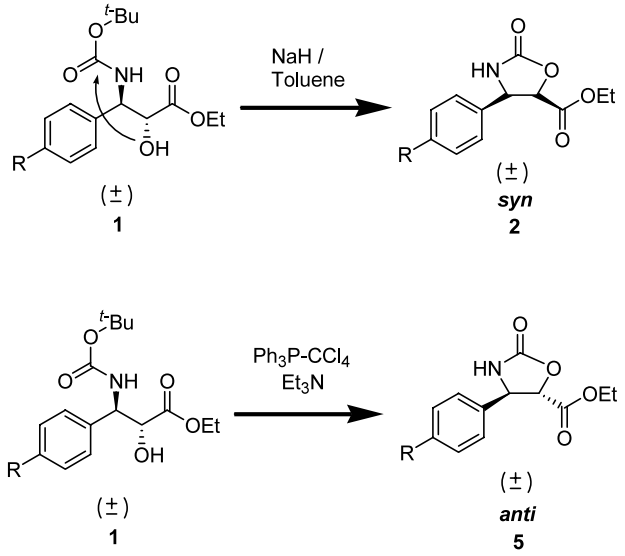
Abstract—Ethyl *anti*-4-substituted phenyl-2-oxo-1,3-oxazolidine-5-carboxylates were synthesized stereoselectively in excellent yields using the Ph_3P–CCl_4–Et_3N system by S_N2 cyclization of *N*-Boc-β-amino alcohols. *syn* to *anti* conversion of ethyl 4-substituted phenyl-2-oxo-1,3-oxazolidine-5-carboxylates using DBU as base is also described.

2-Oxazolidinone moieties are present in many biologically active molecules of pharmaceutical interest. These heterocyclic units are also useful intermediates for the synthesis of polymers and agricultural chemicals. Chiral 2-oxazolidinones are also widely used as a powerful tool in asymmetric synthesis.[1] DUP-721,[2] Linezolid[3] and Cytoxazone[4] are a few examples of drugs that contain the 2-oxazolidinone ring.



Scheme 1.

2-Oxazolidinones can be prepared from a variety of compounds such as other heterocyclic compounds (e.g. epoxides, aziridines, oxetanes, 2-oxazolones), β-difunctional compounds, hydroxy acids or esters and most commonly from amino alcohols.[5,6] Chiral oxazolidine-2-ones have been prepared from β-hydroxy acids using the Curtius rearrangement with intramolecular capture of the intermediate isocyanate.[7] Chiral oxazolidinones have also been prepared from *N*-Boc-β-amino alcohol derivatives by converting the hydroxy group into a tosylate followed by cyclization via an intramolecular S_N2 displacement.[8,9] Zhao et al.[10] reported the preparation of chiral oxazolidinones with good yields by treating *N*-Boc-β-amino alcohol derivatives with *N*,*N*-diethylaminosulfur trifluoride (DAST) under mild conditions. Recently this approach has been used by Benedetti et al.[11] in the preparation of oxazolidinone from mesylate derivatives of *N*-Boc-β-amino alcohols via S_N2 cyclization.

The condensation of carbonyl groups and other nucleophiles with alcohols using Ph_3P–DEAD has become an important technique in the synthesis of many molecules, and is known as the Mitsunobu reaction.[12] The related Ph_3P–CCl_4–Et_3N system was previously utilized for conversion of alcohols to halides,[13] β-

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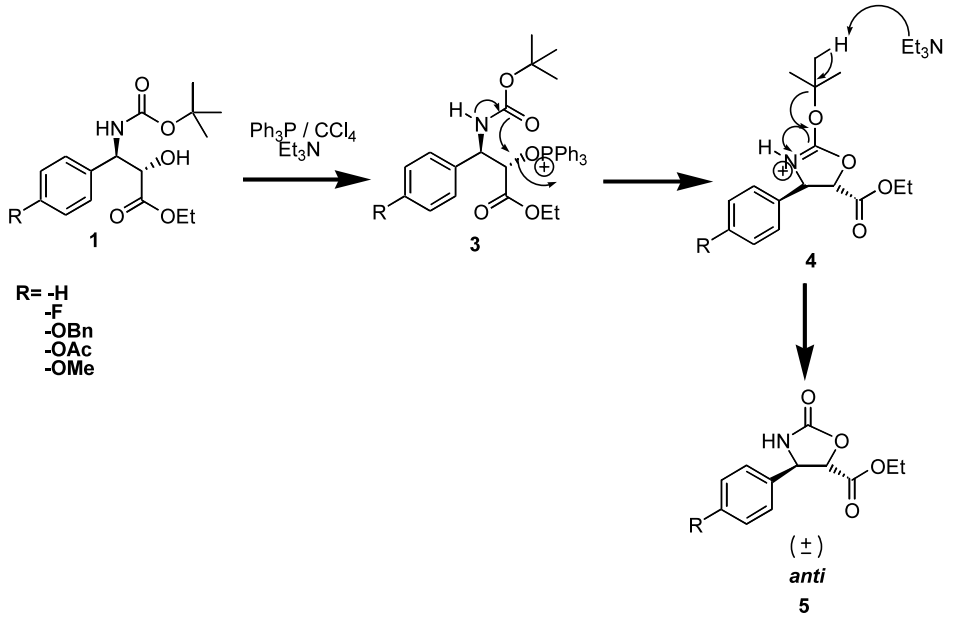
Table 1. Conversion of *N*-Boc-β-amino alcohols **1** to ethyl *anti*-4-substituted phenyl-2-oxo-1,3-oxazolidine-5-carboxylates **5**

Entry	R	Yield (%)	Mp (°C)
1	H	92	84–86
2	F	91	Viscous liquid
3	OBn	88	124–126
4	OAc	87	91–93
5	OMe	90	121–122.5

hydroxy hydroxamic acids to β-lactams,[14] and also for amino alcohols to aziridines[15] with complete inversion.

In continuation of our earlier work,[16] we have developed a novel method for the preparation of *anti* oxazolidinones from *syn*-*N*-Boc-β-amino alcohols using Ph_3P–CCl_4–Et_3N, in which *O*-substitution is not required. Racemic *N*-Boc-β-amino alcohols **1** were prepared by reductive Boc protection of the corresponding azido alcohols,[17] which were obtained from the corresponding benzaldehydes by Darzen's condensation with ethyl chloroacetate followed by regioselective opening of the epoxides with NaN_3. Compound **1** on treatment with NaH in toluene gave the coresponding *syn*-2-oxazolidinones **2** due to attack of the hydroxyl nucleophile on the carbamide carbonyl group (Scheme 1). We conducted the same reaction using the Ph_3P–CCl_4–Et_3N system[18] and found that different compounds were obtained. These were later confirmed to be *anti*-2-oxazolidinones **5** (Table 1). This can be explained by an S_N2 process, in which nucleophilic attack of the carbonate on the activated hydroxyl bearing center results in cyclization and formation of the inverted product **5**[14,19,20] (Scheme 2). This is a versatile and efficient method for the stereoselective preparation of *anti*-oxazolidinones from the corresponding *N*-Boc-β-amino alcohols.

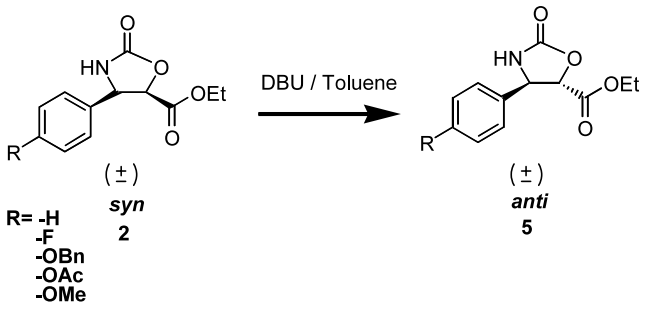
The Ph_3P–CCl_4–Et_3N system has two advantages when compared to that reported[16] earlier in which the *O*-tosyl derivatives of *N*-Boc β-amino alcohols are used; it gives superior yields and also avoids the conversion of the hydroxy group to the tosylate. The formation of *anti*-oxazolidinones was not observed when the reaction was carried out with ethyl carbonates or any other carbonates. This indicates that the tertiary butyl group is a prerequisite for the formation of the corresponding *anti*-oxazolidinones.



Scheme 2.

Table 2. ^1H NMR data of **2** (*syn*) and **5** (*anti*) in $CDCl_3$

Entry	R	*syn* isomer **2**			*anti* isomer **5**		
		H^4 (δ)	H^5 (δ)	J_{4-5} (Hz)	H^4 (δ)	H^5 (δ)	J_{4-5} (Hz)
1	H	5.25	5.25	–	5.0	4.7	5.1
2	F	5.25	5.25	–	5.0	4.7	5.1
3	OBn	5.25	5.2	–	4.9	4.7	5.1
4	OAc	5.1	5.1	–	5.0	4.7	5.3
5	OMe	5.2	5.2	–	4.9	4.7	5.3



Scheme 3.

In their ^{1}H NMR spectra, chemical shift values for the vicinal protons 4H and 5H in compounds **2** and **5** were found to be at $\delta \sim 5.2$ ppm and δ 4.7–5.0 ppm, respectively (Table 2). This is in accordance with reported trends[21] and was further supported by correlation of the dihedral angle calculated by energy minimization of structures **2** and **5** using Chem Draw software (Chem3D Pro Version 3.5.1) and the Karplus curve. According to the Karplus curve, the coupling constant J should be ~ 5.0 Hz for the *anti*-configuration as observed for **5** ($J = \sim 5.0$ Hz). Similarly **2** is assigned the *syn*-configuration.

All *syn* oxazolidinones **2** were converted to their *anti* epimers **5** by epimerisation of the hydroxy center with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[22] in toluene at room temperature (Scheme 3). Energy minimization data[23] further support the formation of *anti* over *syn* products (for *syn*-oxazolidinones **2** ~ 29.4 kcal/mol and for *anti* oxazolidinones **5** ~ 25.2 kcal/mol).

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18. To a solution of compound 1 (2 g) in acetonitrile (20 mL) was added Ph_3P (1.2 equiv.), CCl_4 (2.5 equiv.), Et_3N (2.5 equiv.). The resulting mixture was stirred at room temperature overnight. The reaction mass was concentrated under reduced pressure to give a residue. This residue was purified by flash chromatography on 230–400 mesh silica gel (ethyl acetate–petroleum ether 4:6) to afford the oxazolidinone **5**.
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23. All calculations were carried out on Silicon Graphics Octane 2 workstation. Oxazolidinones **2** and **5** were optimized by using MMFF94 force field and charges. A distance dependent dielectric constant of 1 was used for the calculations.