A New Electrophilic Alaninol Synthon. A General Route to Oxazolidinones of D or (*R*)-2-Amino Alcohols from L-Serine

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A new electrophilic alaninol synthon, (*S*)-4-(4'-tolylsulfonyloxymethyl)oxazolidin-2-one, derived from serine, undergoes nucleophilic displacements with Gilman cuprates and/or Grignard/CuX reagents in high yield to provide (*R*)-4-substituted oxazolidinones.

The 1,2-amino alcohol moiety is present in a wide variety of natural products.[1] Additionally, these amino alcohols are useful precursors to amino acids[2] and chiral auxiliaries.[3] A convenient method to introduce the amino alcohol unit is through the use of an alaninol or alanine synthon (Fig. 1). Consequently, the chemistry of electrophilic and nucleophilic alaninol or alanine equivalents is an area of intense interest.[4]

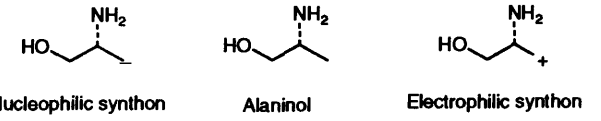


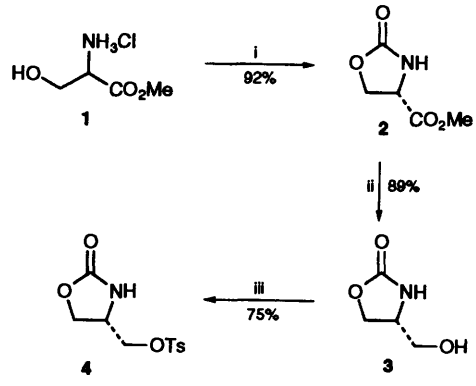
Fig. 1

Carbon–carbon bond constructions using derivatives of serine as electrophilic alanine (alaninol) synthons have been carried out by Viallefont,[5] Baldwin,[6] Vederas[7] and others.[8] In many instances, these reactions proceeded in only moderate to good yields and gave elimination products which resulted in the loss of chirality.

Our efforts in this area have focused on the preparation of both electrophilic and nucleophilic alaninol synthons from common intermediates available from serine. We have recently shown that a nucleophilic alaninol synthon derived from serine provided β,γ-unsaturated amino alcohols in high chemical and optical yields.[9] We have further demonstrated the utility of this nucleophilic alaninol synthon in the total synthesis of the indolizidine alkaloid slaframine.[10] We herein report the chemistry of a new electrophilic alaninol synthon.

The electrophilic alaninol synthon **4** was prepared in 61% yield over three steps starting from L-serine methyl ester hydrochloride and required no chromatographic purification (Scheme 1). After attempting nucleophilic displacements on **4** with simple organometallics (PhLi and PhMgBr) without success (Table 1, entries 1 and 2), we explored the reactivity of **4** with respect to carbon–carbon bond formations using copper-derived reagents. The optimization parameters evaluated in this study were the nature of the copper reagent, yields of the product, racemization of the chiral centre, and by-products from elimination and reduction.

Table 1 lists the data from reactions of **4** with both Gilman cuprates and Grignard/CuX reagents. Several trends are apparent from this data: (1) carbon–carbon bond formation proceeded with both Gilman cuprates and Grignard/CuX reagents with the former reagent being more versatile with respect to stoichiometry,† (2) aliphatic Grignard/CuX reagents gave higher yields as compared to aliphatic Gilman cuprates,



Scheme 1 *Reagents and conditions:* i, $COCl_2$, $KHCO_3$ 92%; ii, $NaBH_4$ 89%; iii, TsCl, pyridine 75%

(3) no racemization occurred during nucleophilic displacements and (4) no elimination products were observed with either reagent.

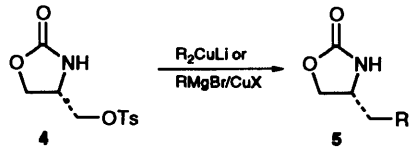
The minimum amount of Gilman reagent required for effective conversion of **4** into **5** was also examined. In the case of diphenylcuprate, use of a slight molar excess of the reagent provided the highest yield of the corresponding oxazolidinone **5a**. Using Gilman reagents derived from BuLi and EtLi, we observed the formation of reduction products. These observations are consistent with previously reported copper-mediated reductions.[11] However, reactions involving nucleophilic displacements with alkyl Grignard/CuX reagents gave no reduction products.

Having established that the displacements were facile, we evaluated the potential of this reaction with a variety of nucleophiles. These results are summarized in Table 2. The displacements proceeded in high chemical and optical yields with the products being protected (*R*)-2-amino alcohols. The hydrolysis of oxazolidinones to amino alcohols and subsequent oxidation to amino acids is well precedented in the literature.[2,12] *Thus, our methodology provides a convenient route for the preparation of unnatural amino alcohols or amino acids from* L-*serine.*[13] Several of the compounds listed in Table 2 have found applications as chiral starting materials. For example, the D-enantiomer of the versatile Evans' chiral auxiliary **5a**,[14] can be synthesized in 56% yield over five steps from an inexpensive starting material. Similarly, the oxazolidinone **5d** is the starting material in the synthesis of azapodophyllotoxin,[15] and the amino aldehyde obtainable from **5h** is a precursor to potent renin inhibitors.[16]

Utilization of the displacement methodology in the synthesis of isodityrosine,[17] pilocarpine analogues,[18] diphthamide,[19] and pseudodistomins[1h,i] is currently underway in our laboratory, and results from these endeavours will be reported.

† An excess (6.0 equiv.) of the Grignard reagent is necessary for efficient conversion. The reaction proceeded in high yield (70–80%) with less (2.5 equiv.), but took substantially longer for completion (**5a**, 1 week; **5i**, 24 h). Optimized conditions will be reported.

Table 1 Comparison of Gilman cuprates with Grignard/CuX reagents

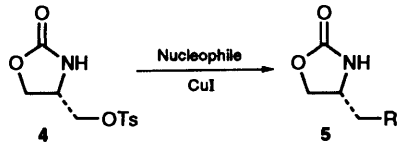


4 5

Entry	R	RM (equiv.)	Reaction conditions	Product	Yield (%)[a]
1	Ph	PhLi (2.5)	−78 °C ⟶ RT (no CuX)	**5a**	0
2	Ph	PhMgBr (7.0)	−78 °C ⟶ RT (no CuX)	**5a**	0
3	Ph	Ph_2CuLi (2.0)	0 °C ⟶ RT/24 h	**5a**	79
4	Ph	Ph_2CuLi (1.5)	0 °C ⟶ RT/2 h	**5a**	80
5	Ph	Ph_2CuLi (1.2)	0 °C ⟶ RT/4 h	**5a**	92
6	Ph	PhMgBr (7.0)	(1.5 equiv. CuI) RT/50 h	**5a**	85
7	Ph	PhMgBr (7.0)	(1.5 equiv. CuBr) RT/50 h	**5a**	79
8	Et	Et_2CuLi (1.2)	−40 °C/6 h ⟶ RT/12 h	**5f**	< 50[b]
9	Et	EtMgBr (6.0)	(1.5 equiv. CuI) RT/8 h	**5f**	85
10	Bu	Bu_2CuLi (1.2)	−40 °C/3 h ⟶ RT/3 h	**5g**	33 (18)[c]
11	Bu	BuMgBr (6.0)	(1.5 equiv. CuI) RT/8 h	**5g**	87

[a] Yields are of column purified materials. [b] Mixture of three inseparable products. [c] Yield of product from reduction reaction **5** (R = H).

Table 2 Preparation of (*R*)-4-substituted 2-oxazolidinones in the presence of CuI



4 5

Compd.	R	Nucleophile (equiv.)	Yield (%)	ee (%)[a,f,g]
5a	Ph	PhLi (1.2)	92	> 99[a,f]
5b	Bn	BnMgBr (6.0)	82	> 99[f]
5c	4-$MeOC_6H_4$	4-$MeOC_6H_4Li$ (1.2)	97	> 99[f]
5d	Piperonyl	4-PiperonylLi (1.2)	97	> 95[b]
5e	Me	MeLi (1.2)	92	> 95[c,d]
5f	Et	EtMgBr (6.0)	85	> 95[d]
5g	Bu	BuMgBr (6.0)	87	> 95[g]
5h	Cyclohexyl	CyclohexylMgBr (6.0)	90	> 95[e]
5i	Dodecyl	DodecylMgBr (6.0)	87	> 95[g]

[a–e] Optical purity determined by comparison of optical rotation to known compounds. [a] L. N. Pridgen, J. Prol, Jr., B. Alexander and L. Gillyard, *J. Org. Chem.*, 1989, **54**, 3231. [b] Ref. 15. [c] K. Rein, M. Goicoechen-Pappas, T. V. Anklekar, G. C. Hart, G. A. Smith and R. E. Gawley, *J. Am. Chem. Soc.*, 1989, **111**, 2211. [d] M. P. Sibi and D. Rutherford, unpublished results. [e] T. Ishizuka, K. Kimura, S. Ishibuchi and T. Kunieda, *Chem. Lett.*, 1992, 991. [f] Determined by HPLC analysis to be > 99% ee using a Chiracel OD column. [g] Converted into amino alcohol and analyzed by Mosher ester.

Experimental

(S)-4-*Methoxycarbonyloxazolidin*-2-*one* **2**. Serine methyl ester hydrochloride **1** (39.50 g, 0.254 mol) and potassium hydrogen carbonate (26.44 g, 0.264 mol) were dissolved in water (350 cm^3) and the solution was stirred at room temperature (RT) for 10 min. Potassium carbonate (37.04 g, 0.268 mol) was added to the solution which was then cooled to 0 °C and treated with a 20% solution of phosgene in toluene (175 cm^3, 0.338 mol) added to it over 10 min. The reaction mixture was stirred for 2 h at 0 °C. The toluene layer was separated and the aqueous layer was lyophilized. The resulting white solid was extracted with methylene dichloride (*ca.* 500 cm^3) and the extract dried ($MgSO_4$) and subjected to rotoevaporation to give a clear oil (33.81 g, 92%). The oil solidified when refrigerated; b.p. 134–137 °C/0.2 mmHg; R_f 0.47 (100% EtOAc); δ_H(400 MHz, $CDCl_3$) 3.82 (s, 3 H), 4.43 (dd, *J* 9.67, 4.83,* 1 H), 4.53 (dd, *J* 9.14, 4.83, 1 H), 4.67 (app. t, *J* 9.68, 9.13, 1 H) and 6.29 (s, 1 H); δ_C(100 MHz, $CDCl_3$) 52.9, 53.7, 66.7, 159.1 and 170.6; ν_{max}($CHCl_3$)/cm^{-1} 3323 and 1767; *m*/*z* (GC/EI) 145 (M^+, 5.4), 87 (5.0), 86 (100) and 58 (11); $[\alpha]_D^{25}$ −18.60† (*c* 4.52, CH_2Cl_2) (Found: C, 41.5; H, 5.1; N, 9.6. Calc. for $C_5H_7NO_4$: C, 41.38; H, 4.86; N, 9.65%).

(R)-4-*Hydroxymethyloxazolidin*-2-*one* **3**.—$NaBH_4$ (1.91 g, 0.050 mol) was added in portions to a solution of the ester **2** (7.00 g, 0.048 mol) in dry EtOH (100 cm^3) at 0 °C. The reaction mixture was allowed to warm to room temperature over 2.5 h, after which it was treated with saturated aqueous NH_4Cl (7.6 cm^3, 0.053 mol) and stirred at RT for 30 min. The white solids were filtered off and the filtrate was concentrated to *ca.* one-third of its volume and refrigerated to induce crystallization. A white solid was obtained (4.08 g, 72%). The filtrate was evaporated to yield a white paste (2.16 g), column chromatography of which using 10:90–20:80 methanol–ethyl acetate yielded additional product (0.95 g, 17%). The alcohol recrystallized readily from methanol: m.p. 96–99 °C; R_f 0.28 (90:10, ethyl acetate–methanol); δ_H(400 MHz, D_2O) 3.61 (app. dd, *J* 12.09, 4.84, 4.30, 1 H), 3.69 (dd, *J* 11.82, 3.76, 1 H), 4.08 (m, 1 H), 4.31

* All *J* values recorded in Hz.

† All [α] values recorded in 10^{-1} deg cm^2 g^{-1}.

(app. dd, J 8.87, 5.37, 4.84, 1 H) and 4.57 (t, J 9.13, 1 H); δ_C(100 MHz, D_2O) 56.3, 65.2, 70.6 and 164.9; $\nu_{max}(CHCl_3)/cm^{-1}$ 3370; m/z (GC-MS) 117 (M^+, 0.6), 87 (15), 86 (100), 85 (16) and 58 (11); $[\alpha]_D^{25}$ +32.25 (c 1.044, MeOH) (Found: C, 40.8; H, 6.0; N, 11.8. Calc. for $C_4H_7NO_3$: C, 41.02, H, 6.02; N, 11.96%).

(S)-4-(4'-*Tolylsulfonyloxymethyloxazolidin-2-one* **4**. Pure TsCl (85.98 g, 0.451 mol) was added at 0 °C to a solution of the alcohol **3** (34.34 g, 0.293 mol) in dry pyridine (110 cm^3). The reaction mixture was stirred at RT for 6 h after which pyridine was removed on a vacuum pump. The gel-like residue was dissolved in methylene dichloride (500 cm^3) and the solution washed with HCl (2 mol dm^{-3}; 6 × 100 cm^3). The HCl layer was twice back-extracted with methylene dichloride. The combined organic phase and extracts were dried ($MgSO_4$) and subjected to rotoevaporation. The resulting solid was washed with hot pentane to remove excess of TsCl and recrystallized from methylene dichloride to give a fluffy white solid (59.73 g, 75%) the optical purity of which was determined to be >99% ee by HPLC analysis (R_t/min 40.5 (R), 48.1 (S); Chiracel OD; 80:20 hexane–propan-2-ol/0.1% triethylamine; flow 1 cm^3 min^{-1}); m.p. 131–132 °C; R_f 0.50 (100% EtOAc); δ_H(400 MHz, $CDCl_3$) 2.48 (s, 3 H), 4.08 (m, 4 H), 4.49 (t, 1 H), 5.52 (s, 1 H), 7.39 (d, J 8.06, 2 H), 7.80 (d, J 8.10, 2 H); δ_C(100 MHz, $CDCl_3$) 21.7, 50.9, 66.3, 69.7, 127.9, 130.2, 132.2, 145.6 and 158.8; $\nu_{max}(CHCl_3)/cm^{-1}$ 3449, 3266 and 1768; m/z (GC-MS) 271 (M^+, 5), 241 (4), 155 (5), 92 (21), 91 (34), 86 (100) and 65 (18); $[\alpha]_D^{25}$ + 11.61 (c 2.35, CH_2Cl_2) (Found: C, 49.0; H, 4.8; N, 5.3. Calc. for $C_{11}H_{13}NO_5S$: C, 48.70; H, 4.83; N, 5.16%).

General Procedure for Nucleophilic Displacement using Grignard Reagents.—Compound **4** (1.6 mmol) and CuI (2.3 mmol) were added to a flame dried, round-bottom flask which was then flushed with nitrogen and charged with freshly distilled THF (15 cm^3). The grey suspension was cooled to −78 °C and the Grignard reagent (10 mmol) was added to it over 5 min; during this, the suspension changed from grey to yellow. The supension was stirred at −78 °C for 30 min and then at RT for 7.5 h. Saturated aqueous NH_4Cl (~10 cm^3) was added carefully to the dark green reaction mixture which was then stirred at RT for 30 min; after this it was subjected to rotoevaporation. The resulting blue solution was extracted with ethyl acetate (3 × 50 cm^3), and the combined extracts were dried ($MgSO_4$), filtered and evaporated and the resulting residue subjected to column chromatography (ethyl acetate–hexanes, 75:25) to afford the 4-substituted oxazolidinone.

General Procedure for Nucleophilic Displacement using Cuprates.—A solution of compound **4** (1.5 mmol) in freshly distilled THF (10 cm^3) was syringed into a pre-formed solution of the cuprate (1.8 mmol) in diethyl ether at −78 °C. This mixture was stirred for 10 min at −78 °C and then at RT for 4 h. Saturated aqueous NH_4Cl (~10 cm^3) was added carefully to the dark green reaction and the mixture stirred at RT for 30 min; the organic solvents were removed by rotoevaporation. The resulting blue solution was extracted with ethyl acetate (3 × 50 cm^3), and the combined extracts were dried ($MgSO_4$), filtered and evaporated. Column chromatography of the resulting residue using 75:25 ethyl acetate–hexanes afforded the 4-substituted oxazolidinone.

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