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A NEW NUCLEOPHILIC ALANINOL SYNTHON FROM SERINE

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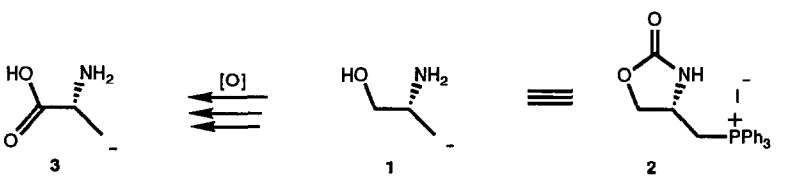
Summary: A new nucleophilic alaninol synthon derived from serine is reported. The utility of this reagent in the stereoselective synthesis of β,γ-unsaturated amino alcohols is described.

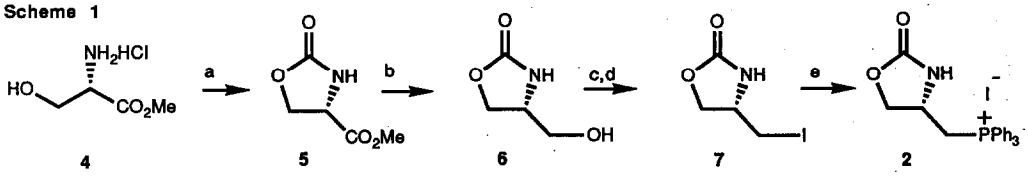
Development of new methodologies for the syntheses of non-protenogenic amino acids is important because of the wide range of biological activities exhibited by these molecules.[2] In particular, β,γ-unsaturated amino acids have attracted considerable interest because of their potential as suicide enzyme inhibitors[3] and synthetic intermediates.[4] The chemistry of nucleophilic and electrophilic alanine or alaninol equivalents is largely unexplored.[5] Sasaki et al.[5f,g] have prepared very useful synthons from L- and D-serine and evaluated them as nucleophilic alaninol equivalents. Mizutani,[5h] in his synthesis of wybutine, showed that a Wittig reagent derived from serine undergoes olefination with little racemization, albeit in very low yields (5-13%). We were interested in preparing a synthon from serine which could be used for generation of either *E* or *Z* β,γ-unsaturated amino alcohols and amino acids, with good stereocontrol, and in high chemical yields. This letter describes the synthesis and reactions of one such synthon, the Wittig reagent **2**.



3 **1** **2**

At the outset we were concerned about maintaining the optical integrity of the chiral center during deprotonation and formation of the ylide from **2**. Encouraged by the studies of Meyers and others,[6] we reasoned that dideprotonation of **2** should prevent formation of any β-eliminated product, and also that the oxazolidinone should reduce the acidity of the methine at the chiral center, rendering it less prone to deprotonation. To put this idea into practice, our initial task was to establish optimal reaction conditions for the preparation of the phosphonium salt **2** from readily available L-serine methyl ester hydrochloride (Scheme 1). We explored different reagents and reaction conditions for the formation of the oxazolidinone methyl ester **5** and found that phosgene (as a 20% toluene solution) in aqueous potassium carbonate (3 h at 0 °C) gave the best conversion.[7] The next step in the sequence was the reduction of the methyl ester using sodium borohydride which furnished alcohol **6** in excellent yields.[8] The alcohol **6** was then converted to the corresponding iodo compound **7** in a two step sequence. Tosylation of the primary alcohol using TsCl/pyridine, followed by refluxing with sodium iodide in acetone for 16 h gave the iodide **7** (68% for two steps). Stirring the iodo compound with excess triphenylphosphine in DMF at 100 °C for 24 h furnished the phosphonium salt **2** in good yields (5 steps, 36% overall yield).

Scheme 1



Reagents: (a) $COCl_2$, K_2CO_3 , 3 h, 0 °C, 60%; (b) $NaBH_4$, EtOH, 0 °C, 1 h, 97%; (c) TsCl/Pyridine, RT, 24 h, 82%; (d) NaI/Acetone, reflux, 16 h, 83%; (e) PPh_3 / DMF, 100 °C, 24 h, 90%

Treatment of compound **2** with 1.9 equivalents of base (n-BuLi, LiHMDS, NaHMDS) in various solvents and additives at -78 °C resulted in an orange to red colored solution which was stirred at that temperature for 1 h and then quenched with an appropriate aldehyde (Scheme 2).[9] Table 1 lists the results of these experiments with aromatic, heterocyclic, and aliphatic aldehydes. Two general aspects are noteworthy. High yields are obtained with a variety of aldehydes. Also, the stereoselectivity depends on the nature of the aldehyde, additives, and reaction conditions.

Scheme 2

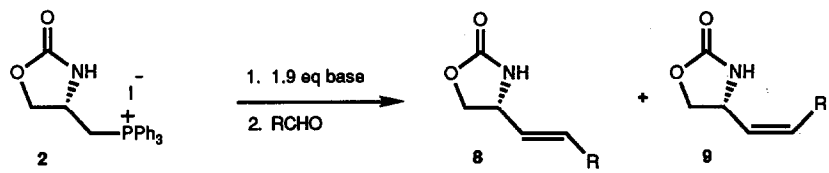


Table 1: Wittig Reactions with compound **2**

Entry	R	Conditions	Yield %[a]	*E* : *Z* (8:9)[b]
1	Ph	n-BuLi, THF, -78 °C to RT	86	>99:1
2		n-BuLi, THF, -78 °C 2.5 h	86	3.6:1
3		n-BuLi, DME, -78 °C to RT	87	>99:1
4		LiHMDS, THF, -78 °C to RT	88	>99:1
5		LiHMDS, THF, -78 °C 2.5 h	62	3.2:1
6		n-BuLi, THF, 20% HMPA, -78 °C to RT	68	1.9:1
7		NaHMDS, THF, -78 °C to RT	62	3.2:1
8		NaHMDS, THF, -78 °C 2.5 h	57	2.5:1
9	3-MeO-Ph	n-BuLi, THF, -78 °C to RT	88	>99:1
10		n-BuLi, THF, -78 °C 2.5 h	88	3.8:1
11	2-Furyl	n-BuLi, THF, -78 °C to RT	88	12:1
12		n-BuLi, THF, -78 °C 2.5 h	72	4.4:1
13	isobutyryl	n-BuLi, THF, -78 °C to RT	82	1:1
14		n-BuLi, THF, -78 °C 2.5 h	59	1:3.1
15	n-Pentanyl	n-BuLi, THF, -78 °C to RT	89	1:2.2
16		n-BuLi, THF, -78 °C 2.5 h	74	1:3.4
17	Methyl	n-BuLi, THF, -78 °C to RT	73	1:1.8
18		n-BuLi, THF, -78 °C 2.5 h	68	1:2.7
19		NaHMDS, THF, -78 °C 2.5 h	60	1:1.3

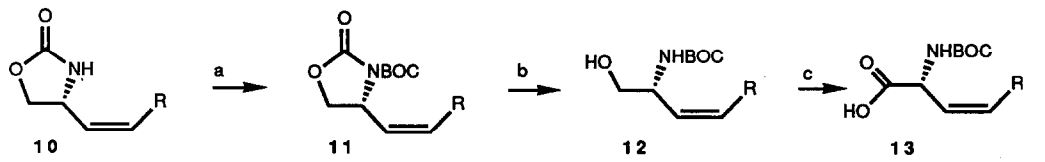
a) Yields after silica gel chromatography. b) Determined by integration of either the vinylic or ring protons.

The olefination process is highly stereoselective. Warming the reaction mixture to room temperature after quenching with aromatic aldehydes furnished the *E* olefin exclusively (*E* : *Z* >99:1, entries 1, 3, and 9).[10] The *E* selectivity observed with this nonstabilized ylide and aromatic aldehyde agrees well with the results of Meyers[6a] and Maryanoff[11] and may be due in part to nucleophilic participation of the β-amino substituent and subsequent equilibration of the betaine intermediate, and partly due to salt effects (compare entries 7 and 8 with 1, 2 and 4). Alternatively, maintaining the reaction temperature at -78 °C after aromatic aldehyde quench gave more of the *Z* isomer (~ 3:1 of *E* : *Z*, entries 2, 10). Addition of HMPA increased the *Z* selectivity of the reaction providing nearly equal amounts of *E* : *Z* mixture (entry 6).

The olefination can be extended readily to a variety of aldehydes (vide supra), but with variations in selectivity. Heterocyclic aldehydes showed lower *E* selectivity than aromatic aldehydes (entry 11). On the other hand, aliphatic aldehydes underwent Wittig reactions with **2** with the normal higher *Z* selectivity (entries 13-19). These results are in good agreement with similar selectivities observed by Meyers.[6a] This selectivity with aliphatic aldehydes decreases using NaHMDS as the base (compare entries 18 and 19). To verify that there was no racemization during the Wittig reaction, we have established the optical purity (>93-95%) of olefinic products by NMR[12] and by conversion to compounds of known rotation (vide infra).

The utility of the olefination procedure is further demonstrated by the ready conversion of the oxazolidinones to the corresponding N-protected β,γ-unsaturated amino alcohols by a two step sequence (Scheme 3). Treatment of **10** with $(BOC)_2O$ in the presence of triethylamine and DMAP in THF furnished the N-BOC oxazolidinone **11** in 95% yield. Cleavage of the oxazolidinone to the amino alcohol **12** proceeds smoothly with either lithium hydroxide or cesium carbonate in methanol/water[13] at room temperature. Sasaki[5g] and Beaulieu[5m] have carried out oxidations of compounds structurally similar to **12** and converted them to the corresponding amino acids **13** in moderate chemical and good optical yields.

Scheme 3



10 **11** **12** **13**

Reagents: R = Ph or CH_3 ; for R = Ph (a) $(BOC)_2O$, Et_3N, DMAP, THF, 95%; (b) LiOH or Cs_2CO_3, $MeOH/H_2O$, 90%; (c) ref. 5g

In summary, we have shown that a new nucleophilic alaninol synthon is easily prepared from serine and that it undergoes condensations with aldehydes smoothly and with high stereoselectivity. We are currently using this synthon in the enantioselective syntheses of indolizidine alkaloids castanospermine, slaframine, and *sphingolipids* in our laboratory.

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7. All stable new compounds were characterized spectroscopically and the elemental composition was determined by combustion analysis. Preparation of **5**: A solution of **4** (0.3 mol) and K_2CO_3 (0.48 mol) in 300 mL water was cooled to 0 ^{0}C and treated with phosgene(300 mL, 20% solution in toluene, 0.32 mol) and stirred for 3 h. The water layer was separated and concentrated to dryness. The solid residue was extracted with warm ethyl acetate and removal of ethyl acetate produced a clear oil.: b.p. 134-137°/0.2 mm Hg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 4.43 (dd, J=9.67, 4.83 Hz, 1H), 4.53 (dd, J=9.14, 4.83 Hz, 1H), 4.67 (app.t, J=9.68, 9.13 Hz, 1H), 6.29 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 52.9, 53.7, 66.7, 159.1, 170.6; IR ($CHCl_3$) 3323, 1767 cm^{-1}; MS (GC-MS) *m/e* 145 (M^+, 5.4), 87 (5.0), 86 (100), 58 (11); $[\alpha]_D^{26}$ -18.89° (c=0.972, CH_2Cl_2); Analysis calc'd for $C_5H_7NO_4$: C, 41.38; H, 4.86; N, 9.65; found: C, 41.11; H, 4.88; N, 9.95.
Preparation of **2**: A solution of **7** (0.25 mol) and triphenylphosphine (2.5 mol) in 500 ml of dry DMF was stirred at 100 ^{0}C for 24 h. Then DMF was removed. The resulting residue was triturated with ether to remove excess triphenyl phosphine followed by washing with dry THF to afford a white solid. This solid was further dried in an Abderhalden at 110 ^{0}C and stored in a desiccator. : m.p. 214-218° (decomp); ^{1}H NMR (400 MHz, D_2O) δ 3.79 (m, 1H), 3.96 (m, 1H), 4.04 (app.dd, J=9.14, 4.83 Hz, 1H), 4.38 (app.dt, J=8.87, 1.62 Hz, 1H), 4.54 (m, 1H), 7.85 (m, 15H); ^{13}C NMR (400 MHz, D_2O) δ 28.3 (d), 47.6, 69.2, 116.9 (d), 130.6 (d), 133.7 (d), 135.4, 157.8; IR ($CHCl_3$) 3228, 3174, 1771 cm^{-1}; $[\alpha]_D^{27}$ +25.5° (c=2.11, EtOH); Analysis calc'd for $C_{22}H_{21}INO_2P$: C, 54.00; H, 4.32; N, 2.86; P, 6.33; found: C, 53.48; H, 4.27; N, 2.63.
Rotation values for **6**: $[\alpha]_D^{27}$ + 32.2° (c=1.04, MeOH); **7**: $[\alpha]_D^{27}$ - 28.5° (c=1.66 ,CH_2Cl_2)

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9. A typical Wittig Reaction: In a flame dried flask with an argon inlet, a suspension of **2** (1 mmol) in 10 ml of dry THF was cooled to -78 ^{0}C and was treated with 1.9 mmol of n-BuLi in hexane resulting in a orange to red dianion. This solution was stirred at -78 ^{0}C for 1 h and quenched with an appropriate aldehyde (0.9 mmol). The reaction was allowed to proceed as specified in Table 1 and then treated with aqueous NH_4Cl soln. Normal work up consisted of removal of THF followed by extraction of the aqueous layer with ethyl acetate. The olefinic products were purified by column chromatography.

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12. Analysis of the Mosher esters prepared by a three step process: protection of the NH as its BOC compound followed by LiOH hydrolysis and esterification of the primary alcohol with Mosher acid. (cf. Svatos, A.; Valterova, I.; Saman, D.; Vrkoc, J. *Czech. Chem. Commun.* **1989**, *55*, 485). Optical rotations for some selected olefinic compounds: **8**: R = Ph $[\alpha]_D^{27}$ -6.5° (c=2.42, EtOH); **9**: R = Ph $[\alpha]_D^{27}$ +54.63° (c=2.09, EtOH).

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