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# Reaction of Trimethylsilylamines with N-Cbz-L-Serine-β-Lactone: A Convenient Route to Optically Pure β-Amino-L-alanine Derivatives

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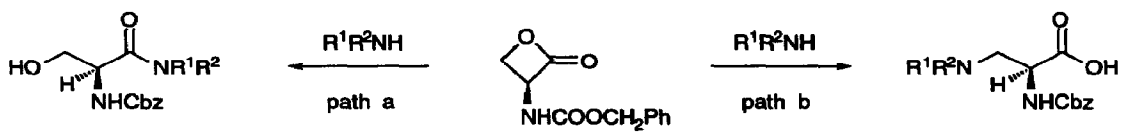
*Abstract:* Trimethylsilylamines, $Me_3Si\text{-}NR_2$, react with N-Cbz-L-serine-β-lactone in acetonitrile primarily by alkyl oxygen cleavage of the lactone ring to give optically pure N-Cbz-β-amino-L-alanine derivatives in good yields. Use of halogenated solvents such as chloroform alters the regiospecificity to give primarily acyl oxygen cleavage and generate amides of N-Cbz-L-serine. The latter are also obtained by reaction of aluminum-amine reagents with the β-lactone.

Derivatives of β-amino-L-alanine ((2S)-2,3-diaminopropanoic acid) occur in nature both as free amino acids and as constituents of peptides with antibiotic or antitumor activity.[1,2] Many such compounds contain heterocyclic rings at the β-carbon, and display neurotoxic effects.[1,3] Synthetic derivatives of β-amino alanine and peptides containing them have also proved useful for enzyme inhibition studies[4] and for construction of metal chelating peptides.[5] Among the methods available for synthesis of such optically pure α-amino acids,[6,7] the ring opening of serine β-lactones with nucleophiles (Scheme 1) is attractive because it avoids the elimination to dehydroalanine derivatives which often plague attempts to displace a leaving group at the β-carbon.[6-8] However, reactions of nitrogen nucleophiles with serine-β-lactones[9,10] or β-propiolactone[11] can generate a mixture of products; namely, the amide arising from acyl-oxygen cleavage (Scheme 1, path a) and the amino acid arising from alkyl-oxygen cleavage (Scheme 1, path b). The mode of ring-opening appears to be very sensitive not only to the particular nucleophile, but also to solvent and reaction conditions, and hence more reliable control over regiochemistry of attack is clearly desirable. The present study describes the ring opening of optically pure N-Cbz-L-serine-β-lactone (**1**) by aluminum-amine reagents and by N-silyl amines to afford good yields of L-serinamides and β-amino-L-alanine derivatives, respectively.

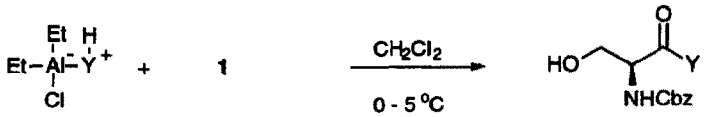
**Scheme 1**




**1**

Since Lewis acid or metal ion catalysis can direct nucleophilic attack on N-protected serine β-lactones,[12] aluminum-amine compounds[13] appeared likely to cleave **1** with high regiospecificity. As seen in Scheme 2, reagents derived from $Et_2AlCl$ and an amine[13] react smoothly at the carbonyl of **1** to afford high isolated yields of the corresponding L-serinamides.[14]

**Scheme 2**

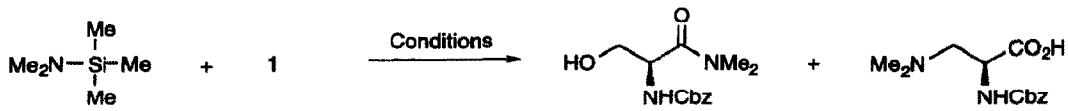



| Y [a] | Yield (%) |
|---|---|
| $NHCH_3$ | 80 |
| $N(CH_3)_2$ | 84 |
| NHPh | 80 (75) [b] |

[a]prepared *in situ*. [b]yield with $(CH_3)_3Al{\cdot}NH_2Ph$

Itoh *et al.* reported that trimethylsilyl dialkyl amines react with β-propiolactone preferentially with alkyl-oxygen cleavage to give trimethylsilyl esters of β-aminopropionates.[15] However, the mode of condensation of N-Cbz-L-serine-β-lactone (**1**) with *N,N*-dimethyl-*N*-(trimethylsilyl)amine is solvent dependent (Table 1), and in

**Table 1.** Solvent Effects on Reaction of *N,N*-Dimethyl-*N*-(trimethylsilyl)amine with β-Lactone **1**.



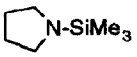
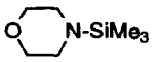
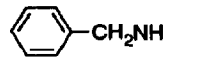
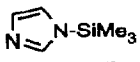

| | | Product ratio | | |
|---|---|---|---|---|
| Entry | Conditions | Amide | Amino Acid | Yield (%) |
| 1 | $CHCl_3$, 20 °C, 3 h | 80 | 20 | 88 |
| 2 | $CH_2Cl_2$, 20 °C, 1 h | 65 | 35 | 85 |
| 3 | $(CH_2)_2Cl_2$, 20 °C, 1 h | 35 | 65 | 90 |
| 4 | THF, 20 °C, 8 h | 20 | 80 | 92 |
| 5 | $CH_3CN$, 20 °C, 4 h | 5 | 95 | 95 |

1,2-dichloroethane (the solvent used by Itoh for the ring opening of β-propiolactone[15a]) selectivity is poor and a mixture of of both amino acid and amide is obtained after aqueous treatment of the reaction mixture (entry 3, Table 1). Use of acetonitrile gives the best selectivity for amino acid formation via alkyl-oxygen cleavage and also affords an excellent overall yield (entry 5, Table 1). The cause of these solvent effects is presently unknown, but it may be due to enhanced stabilization of charge separation in the transition state by a more polar aprotic medium such as acetonitrile.

A variety of other *N*-trimethylsilyl amines[15a,16] react analogously with the β-lactone **1** in acetonitrile to give good yields of the corresponding β-amino-L-alanine derivatives (Table 2).[17] The reaction conditions are

mild and organic extraction of the aqueous layer during workup allows facile isolation of the optically pure amino acid uncontaminated by any minor amounts of amide which may be formed. Medium pressure liquid chromatography (MPLC) of the crude product on a reverse phase (C-8) column rapidly gives analytically pure

**Table 2.** Ring opening of L-serine β-lactone **1** by N-silylamines.


| Silylamine[a] | Conditions | X | Yield (%) |
|---|---|---|---|
| $Me_3Si$-NH-$SiMe_3$ | 50 °C , 22 h | $H_2N$ | 40[b] |
| $H_2N$-$SiEt_3$ | 50 °C , 18 h | $H_2N$ | 45[b] |
| $CH_3NH$-$SiMe_3$ | 20 °C , 1 h | $CH_3NH$ | 70 |
| $(CH_3)_2NH$-$SiMe_3$ | 20 °C , 2 h | $(CH_3)_2N$ | 88 |
| $(C_2H_5)_2NH$-$SiMe_3$ | 20 °C , 9 h | $(C_2H_5)_2N$ | 78 |
|  | 20 °C , 1 h |  | 74 (45)[c] |
|  | 20 °C , 2 h |  | 78 (36)[c] |
|  | 20 °C , 12 h |  | 85 (60)[c] |
|  | 20 °C , 28 h |  | 60 (43)[c,d] |

[a] Purchased or prepared from amine (2 equiv.) and TMSCl; see ref 16. [b] Polymerized material was also obtained. For direct reaction of $NH_3$ see refs. 9 and 10. [c] Yield of amino acid from direct reaction of parent amine with **1**; amide is also generated. [d] See ref. 8.

material. The method is applicable to trialkylsilyl derivatives of ammonia as well as of primary, secondary, and heterocyclic amines. Parent (unsilylated) tertiary amines (e.g. trimethylamine) have previously been shown to react exclusively at the β-position of **1** to give the 3-substituted amino acids (e.g. N-Cbz-β-(trimethylammonio)-L-alanine) as internal salts.[9] Thus use of aluminum and silyl amine reagents allows effective control of the mode of attack on β-lactone **1** and permits specific generation of either L-serinamides or the chiral derivatives of β-amino-L-alanine. Studies on the application of this methodology to the synthesis of some biologically important heterocyclic β-substituted alanines are in progress.

**Acknowledgements**

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14. Procedure: aniline (186 mg, 2 mmol) in dry $CH_2Cl_2$ (5 mL) was treated with $Et_2AlCl$ (1.00 mL, 2 mmol, 2 M in hexane) at 5 °C. The mixture was warmed to 20 °C for 20 min, cooled to 0 °C, and **1** (221 mg, 1 mmol) in $CH_2Cl_2$ (4 mL) was added. This was stirred at 20 °C for 3 h, cooled to 0 °C, and cold 0.2 M HCl (15 mL) was added below 5 °C. The suspension was stirred at 20 °C for 30 min. The layers were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 15 mL). The organic phase was washed with $H_2O$ (50 mL), dried ($Na_2SO_4$), and concentrated to give pure amide (252 mg, 80 %) ($R_f$ = 0.38, EtOAc:hexane, 6:4) which crystallized from EtOAc-hexane: mp 160-161 °C; IR (KBr) 1698, 1686, 1662, 1600 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_3OD$) δ 7.55 (m, 2H), 7.0-7.4 (m, 7H), 7.10 (m, 1H), 5.15 (s, 2H), 4.33 (br t, 1H, $J$ = 5 Hz), 3.83 (d, 2H, $J$ = 5 Hz); $^{13}C$ NMR (100 MHz, $(CD_3)_2CO$) δ 174.0, 159.8, 139.8, 138.0, 129.5, 129.2, 128.7, 124.5, 67.0, 63.3; EI MS 314.1257 (314.1266 calcd). Anal Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 65.30; H, 5.79; N, 8.98.
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17. Procedure: 1-(trimethylsilyl)pyrrolidine (93.2 mg, 0.65 mmol) in dry MeCN (3 mL) was treated with **1** (111 mg, 0.5 mmol) in dry MeCN (2 mL) under Ar. The mixture was stirred 1 h, cooled in ice, and cold 0.1 M HCl (10 mL) was added. The mixture was brought to 20 °C and stirred for 30 min. Extraction with $CH_2Cl_2$ (3 x 10 mL) and evaporation of the aqueous phase gave 144 mg of a white foam. A portion (69 mg) was purified by MPLC (RP C-8 30 % MeOH:$H_2O$) to give 52 mg of (2*S*)-3-(pyrrolidin-1-yl)-2-aminopropanoic acid (74 %): mp 158-160 °C (dec); IR ($CH_2Cl_2$ cast) 3600-2100, 1713, 1621 $cm^{-1}$; $^1H$ NMR (360 MHz, $D_2O$) δ 7.45 (s, 5H), 5.15 (s, 2H), 4.35 (br t, 1H, $J$ = 7 Hz), 3.56 (dd, 1H, $J$ = 13, 4 Hz), 3.50-3.20 (br m, 5H), 1.9-2.10 (m, 4H); $^{13}C$ NMR (100.6 MHz, $CD_3OD$) δ 174.5, 158.5, 138.0, 129.5, 129.1, 129.0, 67.9, 58.3, 55.6, 53.5, 24.0; EI MS 292.1424 (292.1423 calcd). Anal Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.26; H, 6.98; N, 9.40.


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