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LEWIS ACID-PROMOTED DIRECT SUBSTITUTION OF 4-METHOXY- AND 4-PHENYLTHIO-2-OXAZOLIDINONES BY ALKYL CUPRATES. FACILE PREPARATION OF (*3S,4S*)-STATINE AND (*3S,4S*)-CYCLOHEXYLSTATINE.

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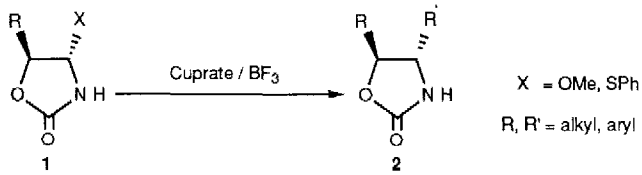
Summary Treatment of 4-methoxy- and 4-phenylthio-2-oxazolidinones with a combination of cuprates and BF_3 results in smooth formation of 4-alkyl and 4-aryl derivatives in high yield By this method, the titled compounds of biological interest are readily synthesized from (*4S,5S*)-5-allyl-4-methoxy (or 4-phenylthio)-2-oxazolidinones stereoselectively

The 2-aminoalcohol moiety is a structural unit found in a substantial number of bioactive substances such as peptidic enzyme inhibitors,[1a] amino sugar antibiotics [1b] and sympathomimetic amines.[1c] A number of papers have dealt with stereochemically controlled constructions of such functional skeletons,[2] particularly in connection with considerable current interest in renin inhibitors [3]

We recently reported facile routes for the conversion of simple heterocycle, 2-oxazolone, to (*4R,5R*)- and (*4S,5S*)-5-allyl-4-methoxy-2-oxazolidinones,[4] which served well as building blocks for chiral 2-aminoalcohols [5] The versatility of these chiral synthons could be greatly extended by the direct replacement of 4-alkoxy groups for simple alkyls except allyl and methallyl functions.[5] Only few practical methods for such substitution of the *N, O*-acetals have been explored so far [6] This paper describes the promising procedures for smooth introductions of a wide variety of alkyls as well as aryl groups to the 4-position of 2-oxazolidinones, leading to a facile preparation of statine and its analogs.[3]

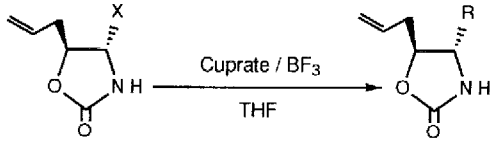
Treatment of 4-methoxy-2-oxazolidinone derivatives (**1** X=OMe) with cuprate reagents in the presence of $BF_3 \cdot Et_2O$ [7] has been found to give an excellent yield of 4-alkyl or 4-aryl-2-oxazolidinones, while reaction with a combination of Grignard reagents and $BF_3 \cdot Et_2O$ [6] resulted in gen-



1 2

erally lower yield.[8] This method is versatile enough to permit the smooth introduction of *prim* - to *tert* -alkyls and aryl groups at the 4-position of 2-oxazolidinone moieties Similar substitution-alkylation reactions proceeded smoothly with 4-phenylthio-2-oxazolidinones(**1** X=SPh), readily available from the corresponding 4-methoxy derivatives,[9] to afford the 4-substituted products, but in slightly lower yield.[10] Thus, *trans*-4-methoxy- and 4-phenylthio-5-allyl-2-oxazolidinones were treated with a mixture of cyclohexylmethylmagnesium bromide (4.0 eq.), CuCN (4.4 eq.) and LiCl (8.8 eq) in the presence of BF_3•Et_2O at -30 °C to give stereoselective formation of *trans* -5-allyl-4-

Table 1. The BF_3-Promoted Substitution of 4-Methoxy- and 4-Phenylthio-2-oxazolidinones by Alkyl and Phenyl Cuprates.[a)]



X	Reagent	R'	Yield (%) [b)]
OMe	*n* - BuCu(CN)Li, LiCl [c)]	*n* - Bu	90
SPh	*n* - BuCu(CN)Li [c)]	*n* - Bu	82
OMe	*i* - BuCu(CN)MgBr, LiCl	*i* - Bu	91
SPh	*i* - BuCu(CN)MgBr	*i* - Bu	75
OMe	*c*- $C_6H_{11}CH_2Cu(CN)MgBr$, LiCl	*c*- $C_6H_{11}CH_2$	99
SPh	*c*- $C_6H_{11}CH_2Cu(CN)MgBr$, LiCl	*c*- $C_6H_{11}CH_2$	83
OMe	$PhCH_2Cu(CN)MgBr$, LiCl	$PhCH_2$	73
SPh	$(PhCH_2)_2CuMgBr$ [d)]	$PhCH_2$	62
OMe	*i* - PrCu(CN)MgBr, LiCl	*i* - Pr	94
SPh	*i* - PrCu(CN)MgBr	*i* - Pr	64
OMe	*t* - BuCu(CN)MgBr, LiCl	*t* - Bu	67
OMe	PhCu(CN)MgBr, LiCl	Ph	85
SPh	$(Ph)_2CuMgBr$ [d)]	Ph	60

a) The reaction was performed by using Grignard reagent (4 0 eq), CuCN (4 4 eq) and BF_3•Et_2O (2.0 eq) in the presence or absence of LiCl (8.8 eq) at -30 °C for 1 h, unless otherwise stated

b) Isolated yield of 4-substituted product whose stereochemistry was based on ^{1}H-NMR (400MHz) analysis

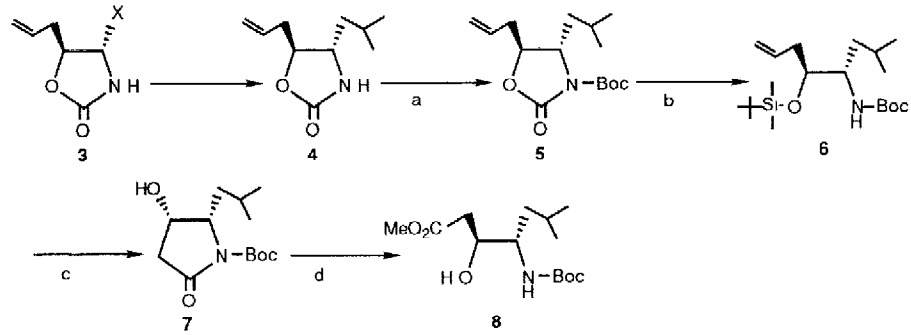
c) BuLi(4.0 eq.) was used

d) Grignard reagent (8 0 eq.) and CuI (4 4 eq.) were used

cyclohexylmethxyl-2-oxazolidinone in 99% and 83% yield, respectively. The results obtained with other cuprate reagents are summarized in Table 1, demonstrating the effective alkylations and arylations associated with the C-O and C-S bond cleavage of the *N,O*- and *N,S*-acetal skeletons The reactions might proceed *via* iminium complexes as might be well recognized in structurally related alkoxy-lactams [11]

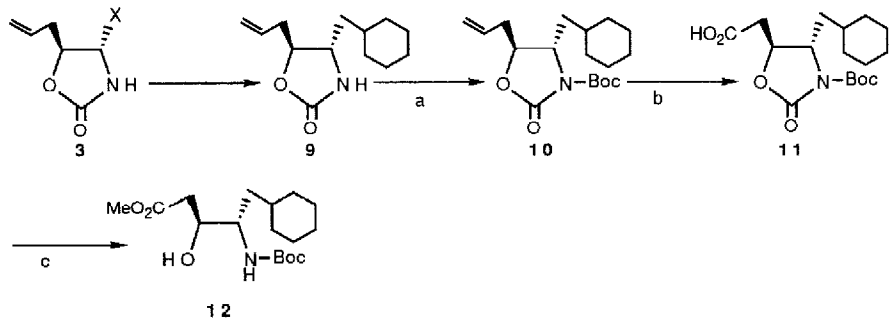
The products thus obtained are all useful precursors for the preparation of 2-aminoalcohols of medicinal interest such as statine and its analogs.[3] Versatility of the methodology was demonstrated by two representative routes for the 3-hydroxy-4-aminocarboxylic acids, as outlined in the following Schemes Thus, (*4S,5S*)-5-allyl-4-methoxy-2-oxazolidinone (**3,** X = OMe) [4] was converted to its 4-isobutyl and 4-cyclohexylmethyl derivatives (**4** and **9**) with full retention of configurations followed by conventional transformations into (*3S,4S*)-statine (**8**) [12] and (*3S,4S*)-cyclohexylstatine (**12**), [13] respectively, in protected forms. As shown in the Scheme 1, ring opening of the cyclic carbamate (**5**) with Cs_2CO_3/MeOH [14] followed by oxidative cleavage of the allyl group resulted in exclusive formation of the lactam (**7**), which was then retreated with Cs_2CO_3/MeOH to give statine methyl ester (**8**) in good yield. In Scheme 2, cyclohexylstatine derivative (**12**) was readily synthesized by an alternative route, which involved oxidative conversion of the allyl group to

Scheme 1



(a) $(Boc)_2O$/BuLi (86%), (b) (1) Cs_2CO_3/MeOH, (2) TBDMSCl/imidazole (57%), (c) (1) O_3/MeOH, (2) $NaBH_4$, (3) PDC/DMF, (4) TBAF (54%), (d) Cs_2CO_3/MeOH (87%)

Scheme 2



(a) $(Boc)_2O$/BuLi (93%), (b) $RuCl_3$-$NaIO_4$/CCl_4-MeCN-H_2O (82%), (c) (1) Cs_2CO_3/MeOH, (2) CH_2N_2 (53%)

the carboxy-methyl (**11**) under the Sharpless conditions [15] followed by the oxazolidinone-ring cleavage under mild conditions.[14] Further synthetic applications of the present methodology are in progress.

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(8) For comparison, 5-allyl-4-methoxy-2-oxazolidinone was treated with *n* - BuMgBr and $PhCH_2MgBr$ (4 0eq) and $BF_3{\cdot}OEt_2$ (2 0 eq) in THF at -30 °C (10 h) to give the 4-substituted products in 65% and 38% yield, respectively

(9) The 4-phenylthio-2-oxazolidinones were obtained nearly quantitatively on mere treatment of 4-methoxy derivatives with thiophenol in trifluoroacetic acid at room temperature

(10) Related displacement reactions using phenylsulfonyl substituent has recently appeared Brown, D S , Charreau, P , Ley, S V *Synlett* **1990**, 749

(11) For review, see Speckamp, W N *Recl Tran Chem. Pays-Bas* **1981**, 100, 345

(12) **8** $[\alpha]_D^{31}$ = - 48.6° (c = 1 0, $CHCl_3$) , mp 57-58 °C , ^{1}H NMR (400MHz, $CDCl_3$) δ 4 73 (d, 1H, J=9 5Hz), 4 06-3 99 (m, 1H), 3.71 (s,3H), 3 66-3 57 (m, 1H), 3 28 (br d, 1H, J=2 9Hz), 2 57-2 50 (m,2H),1 70-1 60 (m,1H), 1 56-1 48 (m, 1H), 1 44 (s, 9H), 1 40-1.30 (m, 1H), 0 93 (d, 6H, J=6 6Hz)

(13) **12** : $[\alpha]_D^{28}$ = -41 6° (c = 0 7, $CHCl_3$) , ^{1}H NMR (400MHz, $CDCl_3$) δ 4 72 (d,1H, J=9.9Hz), 4 05-3.92 (m,1H), 3.71 (s, 3H), 3 75-3 50 (m, 1H), 3.30 (br, 1H), 2.60-2.40 (m, 2H), 1 44 (s, 9H), 1 90-0 80 (m, 13H) , MS (FAB, $CHCl_3$) m/z 330 (M^++1)

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