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Reaction of *N*-Acyl-α-methoxyamines with Organozinc Reagents. A Convenient Method for the Synthesis of Homoallylamines and β-Amino Esters.

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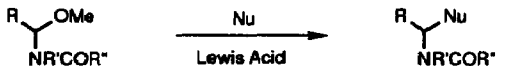
Abstract: The reaction of *N*-acyl-α-methoxyamines with allyl-, propargyl-, and benzylzinc bromides and Reformatsky reagents proceeds in THF at room temperature. Homoallyl- and homopropargylamines and β-amino esters are synthesized in good yields.

Acid catalyzed alkylation of *N*-acyl-α-alkoxyamines with a variety of nucleophiles has extensively studied in our and other laboratories and well demonstrated to be an excellent alternative method to alkylation of imines (eq 1).[1-3] On the other hands, we have already reported that *N*-acyl-α-methoxyamines derived from primary



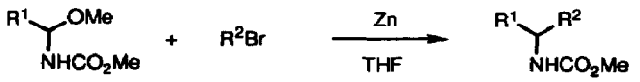
(1)

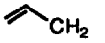
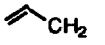
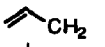
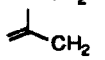
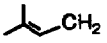
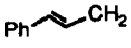
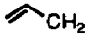
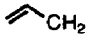
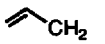
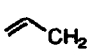
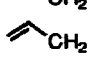
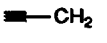
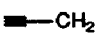
amines (R'=H in eq 1) also react with enolate anions under basic conditions.[4] We wish report here the alkylation of *N*-acyl-α-methoxyamines with organozinc reagents such as allyl-, propargyl-, and benzylzinc bromides and Reformatsky reagents without using any catalyst. This type of reaction provides a convenient method for the synthesis of homoallyl- and homopropargyl amines and β-amino esters.

N-Methoxycarbonyl-α-methoxyamines were prepared from methyl carbamates of primary amines[5] or α-amino acids[6] by anodic oxidation in methanol. The results of the alkylation of *N*-methoxycarbonyl-α-methoxyamines with allyl-, propargyl-, and benzylzinc bromides are summarized in Table 1. A bromide and a *N*-methoxycarbonyl-α-methoxyamine were added simultaneously (method A) or successively (method B) to a suspension of Zn powder in THF at room temperature. The corresponding methyl carbamates of homoallyl amines (runs 1~11), homopropargyl amines (runs 12 and 13), and homobenzyl amines (runs 14 and 15) were obtained in good or moderate yields. It is noted that *N*-methoxycarbonyl-α-methoxyamine which is a equivalent to highly enolaizable imine of phenylacetoaldehyde (R=$PhCH_2$) afforded the adduct in a high yield (run 8). Cyclic α-methoxy lactams also reacted with allylzinc bromide to give the corresponding allyl substituted lactams in good yields (eq 2).

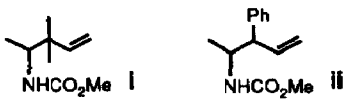
The results of the reaction of *N*-methoxycarbonyl-α-methoxyamines with Reformatsky reagents formed from α-bromoacetates are shown in Table 2. Although prolonged reaction time was needed (12~24 hr), the corresponding methyl carbamates of β-amino esters were obtained in satisfactory yields. Other Reformatsky reagents derived from methyl α-bromo butyrate and γ-bromo crotonate reacted with *N*-methoxycarbonyl-α-methoxyamines (eqs 3 and 4).

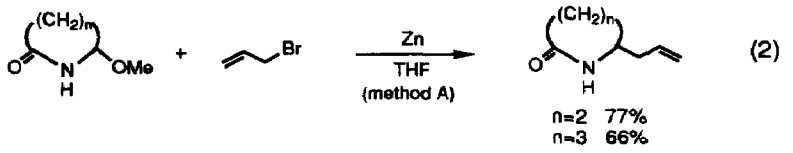
Table 1. Reaction of *N*-Methoxycarbonyl-α-methoxyamines with Allyl-, Propargyl- and Benzylzinc Bromides



Run	R^1	R^2	Method[a]	Yield(%)[b]
1	H		B	83
2	Me		A	68
3	Me		B	90
4	Me		A	89
5	Me		A	66[c]
6	Me		A	90[d]
7	i-Pr		B	98
8	$PhCH_2$		B	96
9	Ph		A	79
10	Ph		B	90
11	$TBDMSOCH_2CH_2$		B	73
12	Me		A	80
13	Me		B	80
14	Me	$PhCH_2$	B	64
15	i-Pr	$PhCH_2$	B	42

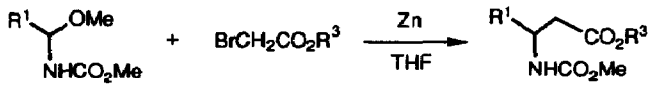
a. Method A: To a suspension of Zn powder (0.375 g, 5 mmol) in THF (10 ml) was added a solution of R^2Br (4.4 mmol) and *N*-methoxycarbonyl-α-methoxyamine (2 mmol) in THF (5 ml) dropwise at room temperature. The mixture was stirred for 2 hr, and then quenched by 1N HCl. The product was isolated by distillation or column chromatography on silica gel. Method B: To a suspension of Zn powder (0.375 g, 5 mmol) in THF (10 ml) was added a solution of R^2Br (4.4 mmol) in THF (2.5 ml) dropwise at room temperature and the mixture was stirred for 1 hr. To the mixture was added a solution of *N*-methoxycarbonyl-α-methoxyamine (2 mmol) in THF (2.5 ml). After stirring for 2 hr, the product was isolated by the same way as method A. b. Isolated yields. c. Rearranged product **i** was obtained. d. Rearranged product **ii** was obtained (diastereomeric ratio = >9/1).





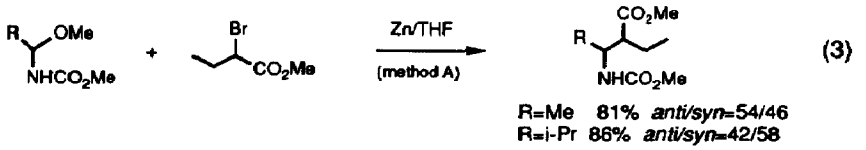
(2)

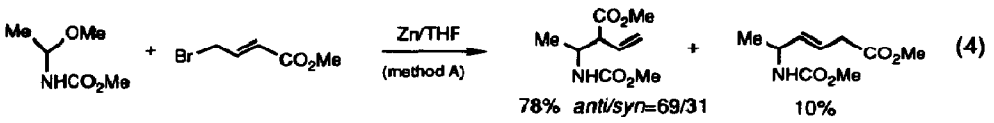
Table 2. Reaction of *N*-Methoxycarbonyl-α-methoxyamines with Reformatsky Reagents



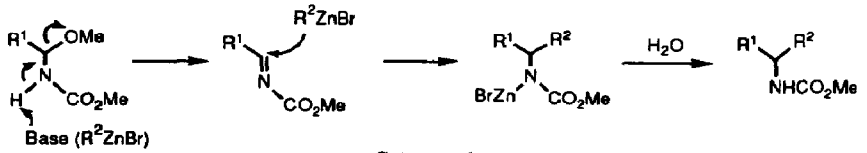
Run	R^1	R^3	Method[a]	Yield(%)[b]
1	Me	Me	A	85
2	Me	t-Bu	B	45
3	i-Pr	Me	A	58
4	i-Pr	t-Bu	B	65
5	t-Bu	Me	A	62
6	$PhCH_2$	t-Bu	B	53
7	Ph	t-Bu	B	67
8	$TBDMSOCH_2CH_2$	t-Bu	B	80

a. See Table 1. b. Isolated yields.



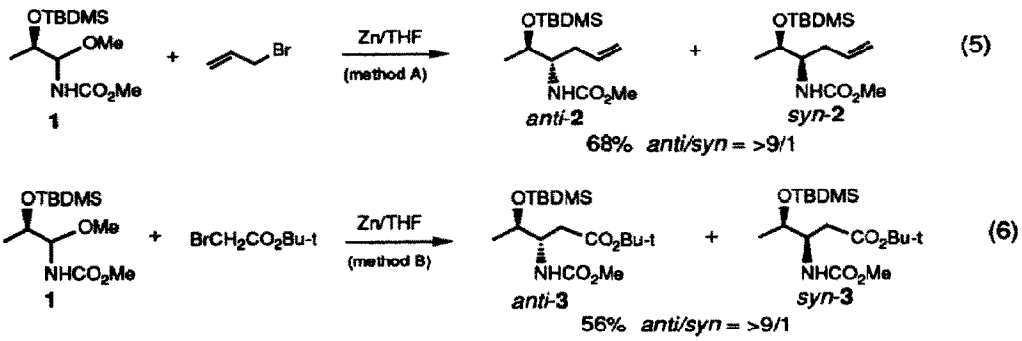


The mechanism of this reaction is the elimination of methanol from *N*-methoxycarbonyl-α-methoxyamines followed by the addition of alkylzinc reagent to the resulting *N*-methoxycarbonylimine (Scheme 1). Consequently, two equivalents of alkylzinc reagents are necessary to complete the reaction.



Scheme 1

The reactions of *N*-methoxycarbonyl-α-methoxyamine **1**[2a] prepared from L-threonine with allylzinc bromide and Reformatsky reagent gave *anti*-adducts preferentially (eqs 5 and 6).[7] The *anti*-selectivity in these reactions can be explained by a non-chelation control[9] in the addition of allylzinc reagent to *N*-methoxycarbonylimine. This result is contrast to the *syn*-selectivity in the $TiCl_4$ catalyzed reaction of **1** with allylsilane (*syn*/*anti* = 4 : 1).[2a]



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3. Recently, diastereoselective acid catalyzed alkylation of α-acetoxy lactams with chiral tin enolates has been reported: (a) Y. Nagao, W. Dai, M. Ochiai, S. Tsukaguchi, E. Fujita, *J. Org. Chem.*, **1990**, *55*, 1148. (b) Y. Nagao, M. Ochiai, M. Shiro, *Tetrahedron*, **1990**, *46*, 6361, and references therein.
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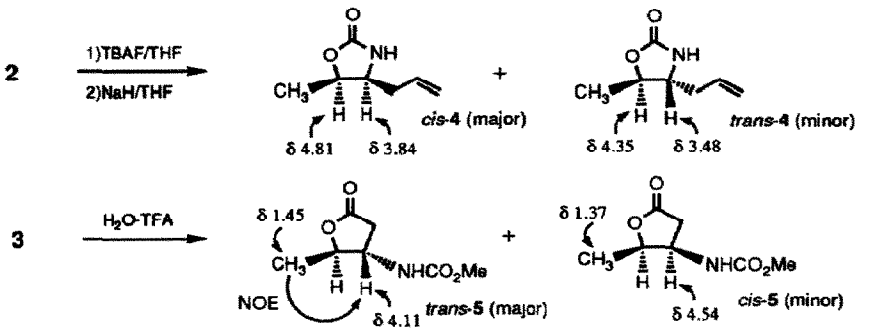
7. The diastereomeric ratio of **2** was determined by ^{1}H NMR spectra (200 MHz, $CDCl_3$). The chemical shifts (δ value) of methyl protons were as follows: *anti*-**2** 1.14; *syn*-**2** 1.13. The stereoconfiguration of **2** was confirmed by the transformation to cyclic carbamates **4** and their ^{1}H NMR analysis.[8] The diastereomeric ratio of **3** and the assignment of the stereoconfiguration were based on the ^{1}H NMR analysis of lactone **5**.



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