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Efficient Method for Preparation of *N*-Methoxy-*N*-methyl Amides by Reaction of Lactones or Esters with Me_2AlCl-MeONHMe·HCl

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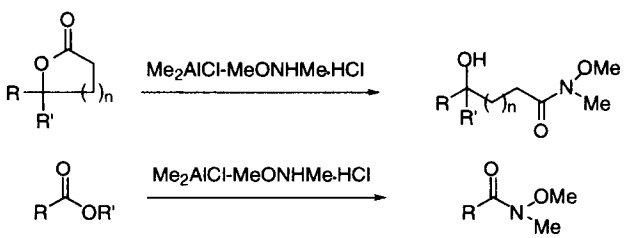
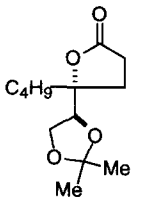
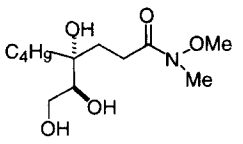
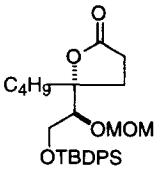
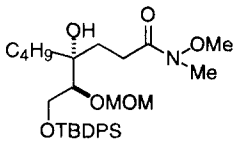
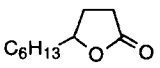
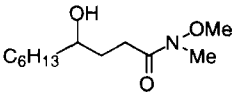
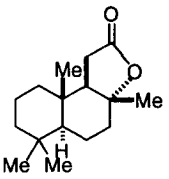
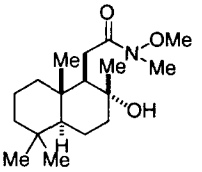
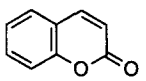
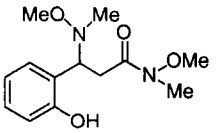
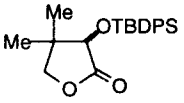
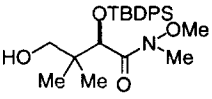
Abstract : The reaction of a lactone or an ester with dimethylaluminum chloride and *N*, *O*-dimethylhydroxylamine hydrochloride provided an efficient method for preparation of *N*-methoxy-*N*-methyl amide. © 1997 Elsevier Science Ltd.

N-Methoxy-*N*-methyl amides (Weinreb amides) are very useful intermediates in organic synthesis since they react efficiently with organometallics and hydrides to produce the ketones and the aldehydes, respectively.[1] The *N*-methoxy-*N*-methyl amides have been generally prepared by condensation of carboxylic acids and *N*, *O*-dimethylhydroxylamine hydrochloride in the presence of a coupling reagent such as DEPC or py·BOP, or by treatment of lactones, esters or *N*-acyl oxazolidone with trimethylaluminum-*N*, *O*-dimethylhydroxylamine hydrochloride (Me_3Al-MeONHMe·HCl).[2] Recently, an alternative method for preparation of *N*-methoxy-*N*-methyl amides from esters using MeONHMe·HCl and an organomagnesium reagent has been reported.[3] In our synthetic studies of natural products,[4] it was found the general method using Me_3Al-MeONHMe·HCl, however, gave unsatisfactory results in the case of sterically hindered lactones. After several attempts to improve the aminolysis, we have found that dimethylaluminum chloride and *N*, *O*-dimethylhydroxylamine hydrochloride (Me_2AlCl-MeONHMe·HCl) smoothly reacted with the lactones to afford the desired *N*-methoxy-*N*-methyl amides in exellent yield. In this paper, we describe an efficient method for preparation of *N*-methoxy-*N*-methyl amides from lactones or esters using Me_2AlCl-MeONHMe·HCl.



Aminolysis of the sterically hindered lactone **1** by the general method using 5 equiv of Me_3Al-MeONHMe·HCl in CH_2Cl_2 afforded the *N*-methoxy-*N*-methyl amide **3** in only 50% yield after 3 h and in 55% yield after 24 h at room temperature along with the recovered **1** (Table 1, entry 1). On the other hand,

Table 1. Preparation of *N*-Methoxy-*N*-Methyl Amides from Lactones by Aminolysis with Me_2AlCl-MeONHMe·HCl and Me_3Al-MeONHMe·HCl[a]

Entry	Lactone	Aluminum Reagent (equiv)	Reaction Time	Amide	Yield (%)	Recovered Lactone (%)
1	 **1**	Me_2AlCl (5)	1.5 h	 **3**	94	0
		Me_3Al (5)	3 h		50	43
		Me_3Al (5)	24 h		55	39
2	 **2**	Me_2AlCl (5)	1.5 h	 **4**	87 (8)[b]	2
		Me_3Al (5)	1.5 h		40 (8)[b]	36
		Me_3Al (5)	24 h		31 (27)[b]	16
3	 **5**	Me_2AlCl (2)	0.5 h	 **9**	91	0
		Me_3Al (2)	1 h		84	0
4	 **6**	Me_2AlCl (3)	2.5 h	 **10**	84	0
		Me_3Al (3)	2.5 h		86	0
5	 **7**	Me_2AlCl (4)	24 h	 **11**	21	60
		Me_3Al (4)	24 h		0	94
6	 **8**	Me_2AlCl (3)	1 h	 **12**	94[c]	0
		Me_3Al (3)	1 h		42	53
		Me_3Al (3)	24 h		86	0

a) All reactions were carried out in CH_2Cl_2 at room temperature.

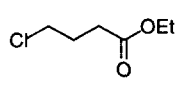
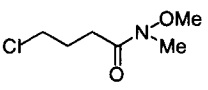
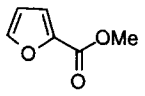
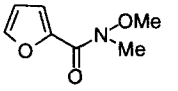
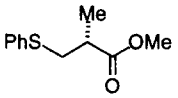
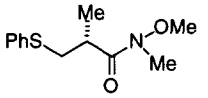
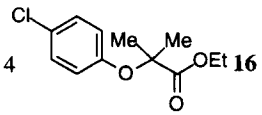
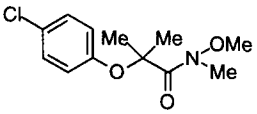
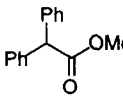
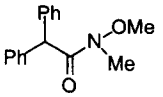
b) The yield of the de-MOM derivative is indicated in parentheses.

c) The enantiomeric excess is > 99% based on the ^{1}H-NMR spectra of the corresponding MTPA esters.

Me_2AlCl-MeONHMe·HCl smoothly reacted with **1** in CH_2Cl_2 at room temperature to give **3** in 94% yield in just 1.5 h. The lactone **2** showed similar reactivity to that of the lactone **1**. Treatment of **2** with Me_2AlCl-MeONHMe·HCl afforded the amide **4** in 87% yield along with 8% of a de-MOM derivative and 2% of **2** after

1.5 h, while the yield of **4** by the reaction of **2** with Me_3Al-MeONHMe·HCl was 40% after 1.5 h and 31% after 24 h, respectively. Then, in order to explore the generality and scope of this new reagent, Me_2AlCl-MeONHMe·HCl, we applied it to the aminolysis of other lactones **5**-**8**. The less hindered lactones **5** and **6** smoothly reacted with both reagents under the same conditions to afford the amides **9** and **10** in good yields, respectively. The lactone **7** did not react with Me_3Al-MeONHMe·HCl. However, Me_2AlCl-MeONHMe·HCl reacted with **7** to give the β-(*N*-methoxy-*N*-methylamino)amide **11** in 21% yield. Treatment of the sterically hindered lactone **8** with Me_2AlCl-MeONHMe·HCl afforded the amide **12** in 94% yield after 1 h. No epimerization occurred during the reaction, which was proved by the ^{1}H-NMR spectra of the corresponding MTPA esters. On the other hand, reaction of **8** with Me_3Al-MeONHMe·HCl produced **12** in only 42% yield after 1 h, although the yield of **12** was 86% after 24 h.

Table 2. Preparation of *N*-Methoxy-*N*-Methyl Amides from Esters by Aminolysis with Me_2AlCl-MeONHMe·HCl and Me_3Al-MeONHMe·HCl[a]

Entry	Ester		Aluminum Reagent (equiv)	Reaction Time	Amide		Yield (%)	Recovered Ester (%)
1		**13**	Me_2AlCl (3)	0.5 h		**18**	96	0
			Me_3Al (3)	0.5 h			24	65
			Me_3Al (3)	24 h			99	0
2		**14**	Me_2AlCl (3)	0.5 h		**19**	99	0
			Me_3Al (3)	0.5 h			19	79
			Me_3Al (3)	24 h			97	0
3		**15**	Me_2AlCl (5)	2 h		**20**	97[b]	0
			Me_3Al (5)	2 h			18	81
			Me_3Al (5)	24 h			84[c]	15
4		**16**	Me_2AlCl (5)	2 h		**21**	97	0
			Me_3Al (5)	2 h			7	91
			Me_3Al (5)	24 h			76	18
5		**17**	Me_2AlCl (5)	5.5 h		**22**	99	0
			Me_3Al (5)	5.5 h			18	80
			Me_3Al (5)	24 h			30	69

a) All reactions were carried out in CH_2Cl_2 at room temperature.

b) $[\alpha]_D^{28}$ +39.2 (c 2.5, $CHCl_3$).

c) $[\alpha]_D^{27}$ +35.5 (c 1.0, $CHCl_3$).

Next, we examined the aminolysis of esters using Me_2AlCl-MeONHMe·HCl in comparison with the reaction with Me_3Al-MeONHMe·HCl. The results are shown in Table 2. All of the esters **13-17** examined were smoothly converted into the *N*-methoxy-*N*-methyl amides **18-22** in excellent yields, respectively, by the reaction with Me_2AlCl-MeONHMe·HCl. On the other hand, the amination of the esters **13-17** with Me_3Al-MeONHMe·HCl proceeded slowly. The amides **18-22** were obtained in 24, 19, 18, 7 and 18% yields, respectively, in the same reaction time as the corresponding reactions with Me_2AlCl-MeONHMe·HCl were completed. The sterically hindered amide **22** was obtained in only 30% yield even after 24 h.

The real reaction species in the present aminolysis was proved to be $Cl_2AlNMe(OMe)$ prepared *in situ* from Me_2AlCl-MeONHMe·HCl (1:1) based on the ^1H-NMR data {δ 3.02 (s, 3H; NMe), 3.83 (s, 3H; OMe)} in CD_2Cl_2. The evolution of 2 mol equiv of methane gas was also observed.

The following is a representative procedure for preparation of the *N*-methoxy-*N*-methyl amide by the reaction of a lactone or an ester with Me_2AlCl-MeONHMe·HCl. A solution of Me_2AlCl (1.01 M hexane solution, 2-5 equiv) was added over a 5-min period to a stirred suspension of MeONHMe·HCl (the same equiv as that of Me_2AlCl) in CH_2Cl_2 (20 ml) under nitrogen at 0 °C, and the mixture was stirred for 1 h allowing the temperature to rise to room temperature. Then, a solution of lactone or ester (1 mmol) in CH_2Cl_2 (10 ml) was added dropwise. After the reaction completed, a solution of a phosphate buffer (pH 8.0) (3 ml per 1 mmol of Me_2AlCl) was added and the stirring was continued for 10 min. The mixture was diluted with $CHCl_3$, filtrated through a Celite pad and washed thoroughly with $CHCl_3$. The aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel flash column chromatography to give the amide.

In summary, we have developed an efficient method for preparation of *N*-methoxy-*N*-methyl amides by the reaction of lactones or esters with Me_2AlCl-MeONHMe·HCl. The present method proceeded faster than that with Me_3Al-MeONHMe·HCl to afford the amides in exellent yields. Application of this method to natural product synthesis is being further investigated in these laboratories.

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