A Novel Synthesis of *N*-Methoxy-*N*-methylamides from 4,6-Pyrimidyl Urethane and Grignard Reagents

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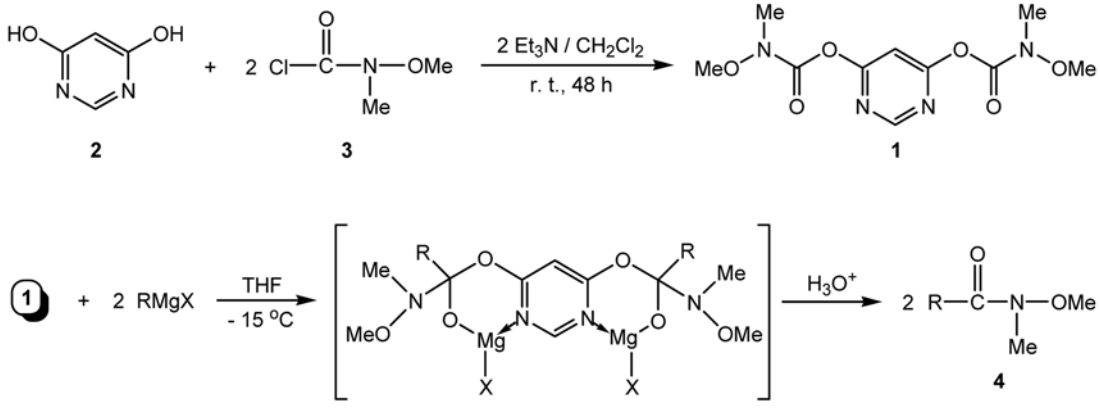
The *N*-methoxy-*N*-methylamides (Weinreb amides) have enjoyed tremendous popularity because they react with organometallics (RM, M=Li, MgX) to provide various ketones through stable metal-chelated intermediates without side products.[1] Among the various methods for the preparation of *N*-methoxy-*N*-methylamides, the condensation of carboxylic acids and *N*,*O*-dimethylhydroxylamine hydrochloride ($MeONH_2MeCl$) using peptide coupling reagents has been frequently employed. The treatment of carboxylic acids with Ph_3P/CBr_4,[2] Bu_3P/(2-pyridine-*N*-oxide)disulfide,[3] 1,1'-carbonyldiimidazole (CDI),[4] S,S-di(2-pyridyl)dithiocarbonate,[5] DCC/HOBT,[6] 2-halo-1-methylpyridinium iodide,[7] BOP,[8] HBTU,[9] and 2-chloro-4,6-dimethoxy[1.3.5]triazine (CDMT)[10] in the presence of base gives the activated ester intermediates, which are converted to the corresponding *N*-methoxy-*N*-methylamides by nucleophilic acyl substitution with MeONHMe. Although most of these methods are especially useful for the preparation of *N*-methoxy-*N*-methylamides of *N*-protected α-amino acids without any racemization, some of them require the use of an excess of base and coupling reagents such as BOP and HBTU are expensive.

The conversion of carboxylic acids to the corresponding *N*-methoxy-*N*-methylamides can also be carried out *via* anhydride intermediates. The treatment of carboxylic acids with trimethylacetyl chloride,[11] alkyl chloroformates,[12] and phosphonate reagents (DEPC and PPA)[13] affords *in situ* anhydrides, mixed anhydrides, and phosphonic anhydrides, respectively, in the presence of base, which are converted to the corresponding *N*-methoxy-*N*-methylamides by nucleophilic displacement with MeONHMe. However, the removal of isobutyl alcohol is often tedious in case of using isobutyl chloroformate and phosphonate reagents are expensive. The recent method *via* acyl mesylates,[14] generated from carboxylic acids and methanesulfonyl chloride, is especially useful for the preparation of sterically hindered *N*-methoxy-*N*-methylamides, but it can be complicated by the formation of *N*-methoxy-*N*-methylmethanesulfonamides as by-products.

Alternatively the preparation of *N*-methoxy-*N*-methylamides has been accomplished by the reaction of carboxylic acid derivatives and $MeONH_2MeCl$. The treatment of acid chlorides,[15] carboxylic esters,[16] and oxazolidinones/thiazolidinones[17] with $MeONH_2MeCl$/pyridine, MeONMeM (M = Li, MgCl), $AlMe_3/MeONH_2MeCl$, respectively, affords the corresponding *N*-methoxy-*N*-methylamides, but these methods proceed in two steps from carboxylic acids. Although various methods for the preparation of *N*-methoxy-*N*-methylamides have been reported, they only afford 1 equiv of *N*-methoxy-*N*-methylamides from carboxylic acids or their derivatives. As part of our continuing study on the preparation of *N*-methoxy-*N*-methylamides[18] we report that *N*-methoxy-*N*-methylamides can be novely prepared from 4,6-pyrimidyl urethane and Grignard reagents in high yields.

4,6-Pyrimidyl urethane **1** was prepared by the addition of 2 equiv of *N*-methoxy-*N*-methylcarbamoyl chloride[19] **3**, prepared from one third equiv of bis(trichloromethyl)-carbonate and $MeONH_2MeCl$, to a mixture solution of 1 equiv of 4,6-dihydroxypyrimidine **2** and 2 equiv of triethyl-



Scheme 1

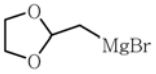
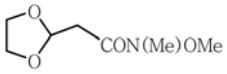
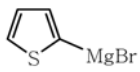
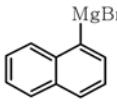
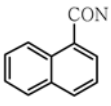
amine in methylene chloride at room temperature (Scheme 1). The nucleophilic acyl substitution of **3** proceeded slowly because **2** was slightly soluble in methylene chloride. After being stirred for 48 h, the resulting homogeneous mixture was separated by aqueous work-up and **1** was obtained in 89% yield after a short pathway silica gel chromatography using EtOAc. The reagent **1** could be stored in a refrigerator for one month without any decomposition.

The successful synthesis of *N*-methoxy-*N*-methylamides **4** using **1** depends largely on the selective substitution of 4,6-pyrimidyl group without concomitant substitution of *N*-methoxy-*N*-methylamino group. We anticipated that 4,6-pyrimidyl group capable of forming 6-membered chelate would be more reactive than *N*-methoxy-*N*-methylamino group toward Grignard reagent. The initial reaction of **1** with 2 equiv of *p*-methoxyphenylmagnesium bromide at 0 °C gave *N*-methoxy-*N*-methyl *p*-methoxybenzamide **4i** in 83% yield along with *p*-methoxybenzophenone (8%). However, the dropwise addition of *p*-methoxyphenylmagnesium bromide to a diluted solution (~0.05 M) of **1** in THF at −15 °C over 15 min gave **4i** in 89% yield without appreciable side products. The preferential formation of **4** seems to result from the formation of 6-membered chelate between magnesium atom of Grignard reagent and carbonyl oxygen/ring nitrogen atom of **1**, which dissociates to give **4** after acidic hydrolysis.

As shown in Table 1, various *N*-methoxy-*N*-methylamides were efficiently synthesized in good to excellent yields by this method. In general the reaction worked well with both aliphatic (**4a**-**4e**) and aromatic Grignard reagents (**4f**-**4l**). The kind of electron donating (**4h**, **4i**) and electron withdrawing group (**4j**) in *p*-substituted phenylmagnesium bromide didn't influence on the selective substitution of 4,6-pyrimidyl group of **1**. Furthermore, the reaction of **1** with less reactive Grignard reagents such as phenylethynylmagnesium chloride (**4d**), *o*-tolylmagnesium chloride (**4g**), and α-naphthylmagnesium bromide (**4l**) proceeded within 20 min at −15 °C to give the corresponding *N*-methoxy-*N*-methylamides in high yields. However, the reaction of **1** with (1,3-dioxolan-2-ylmethyl)magnesium bromide was completed in 3 h at room temperature to give *N*-methoxy-*N*-methyl 1,3-dioxolan-2-ylethanamide **4c** in 73% yield, reflecting the decreased nucleophilicity.

In conclusion the present method provides a novel synthesis of *N*-methoxy-*N*-methylamides from **1** and Grignard reagents in one step. It has the advantages of (i) the stability of **1**, (ii) convenience of one step operation, (iii) economical method by the synthesis of 2 equiv of **4** from 1 equiv of **1** in high yields and, therefore, may be utilized in many synthetic applications.

Table 1. Preparation of *N*-methoxy-*N*-methylamides from 4,6-pyrimidyl urethane and Grignard reagents[a]

Entry **4**	RMgX	Products	Isolated yield, %[b]
a	$CH_3(CH_2)_7MgCl$	$CH_3(CH_2)_7CON(Me)OMe$	95
b	$(CH_3)_2CHCH_2MgCl$	$(CH_3)_2CHCH_2CON(Me)OMe$	87
c			73[c]
d	C_6H_5-C≡C-MgCl	C_6H_5-C≡C-CON(Me)OMe	94
e	*c*-$C_6H_{11}MgCl$	*c*-$C_6H_{11}CON(Me)OMe$	87
f	C_6H_5MgBr	$C_6H_5CON(Me)OMe$	88
g	*o*-CH_3-C_6H_4MgCl	*o*-CH_3-$C_6H_4CON(Me)OMe$	91
h	*p*-CH_3-C_6H_4MgBr	*p*-CH_3-$C_6H_4CON(Me)OMe$	90
i	*p*-CH_3O-C_6H_4MgBr	*p*-CH_3O-$C_6H_4CON(Me)OMe$	89
j	*p*-Cl-C_6H_4MgBr	*p*-Cl-$C_6H_4CON(Me)OMe$	91
k			89
l			80

[a]The reaction was carried out at −15 °C for 20 min. [b]Chromatographically pure. [c]The reaction was carried out at room temperature for 3 h.

Experimental Section

Preparation of 4,6-pyrimidyl di(*N*-methoxy-*N*-methyl) urethane 1. To a mixture solution of 4,6-dihydroxypyrimidine (897 mg, 8.0 mmol) and triethylamine (2.34 mL, 16.8 mmol) in methylene chloride (56 mL) was added *N*-methoxy-*N*-methylcarbamoyl chloride (2.08 g, 16.8 mmol) at room temperature. After being stirred for 48 h, the reaction mixture was poured into cold sat. $NaHCO_3$ (50 mL), extracted with methylene chloride, and washed with cold brine (50 mL). The aqueous phase was reextracted twice with methylene chloride (2 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was subjected to a short pathway silica gel column chromatography using EtOAc to afford **1** (2.04 g, 89%) as a viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.15 (s, 1H), 3.81 (s, 3H), 3.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 158.5, 151.6, 102.6, 61.9, 35.4; FT-IR (film) 3099, 2979, 2940, 1740 (C=O), 1583, 1461, 1366, 1146, 1030, 734 cm^{-1}.

Preparation of *N*-methoxy-*N*-methyl nonanamide 4a (General procedure). To a **1** (401 mg, 1.4 mmol) in THF (18 mL) under argon atmosphere was dropwise added octylmagnesium chloride (0.35 M in THF, 8.0 mL, 2.8 mmol) over 15 min at −15 °C. After being stirred for 5 min, the reaction mixture was quenched with sat. NH_4Cl (5 mL). After evaporation of THF, the reaction mixture was poured into sat. NH_4Cl (30 mL) and extracted with methylene chloride (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using 50% EtOAc/*n*-hexane as an eluant to afford **4a** (535 mg, 95%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.18 (s, 3H), 2.41 (t, J = 7.6 Hz, 2H), 1.54-1.68 (m, 2H), 1.22-1.37 (m, 10H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 63.0, 61.2, 32.9, 31.9, 29.5, 29.3, 25.8, 24.7, 22.7, 14.1; FT-IR (film) 2926, 2855, 1666 (C=O), 1464, 1384, 1178, 999 cm^{-1}; Ms *m/z* (%) 141 (77), 103 (18), 71 (74), 61 (100), 55 (42).

***N*-Methoxy-*N*-methyl isovaleramide (4b).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.18 (s, 3H), 2.30 (d, J = 7.0 Hz, 2H), 2.17 (septet, J = 6.6 Hz, 1H), 0.97 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 61.2, 40.7, 36.2, 25.2, 22.7; FT-IR (film) 2958, 2871, 1662 (C=O), 1466, 1380, 1168, 1005 cm^{-1}; Ms *m/z* (%) 145 (M^+, 3), 85 (55), 61 (46), 57 (100).

***N*-Methoxy-*N*-methyl 1,3-dioxolan-2-ylethanamide (4c).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (dd, J_1 = 14.3 Hz, J_2 = 6.8 Hz, 1H), 4.35-4.40 (m, 2H), 4.21 (dd, J_1 = 14.3 Hz, J_2 = 2.2 Hz, 1H), 4.05 (dd, J_1 = 6.8 Hz, J_2 = 2.2 Hz, 1H), 3.90-3.95 (m, 2H), 3.70 (s, 3H), 3.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 87.0, 66.0, 64.2, 62.7, 35.6; FT-IR (film) 2968, 2938, 1707 (C=O), 1460, 1381, 1164, 1053, 827 cm^{-1}; Ms *m/z* (%) 132 (100), 100 (15), 88 (7), 60 (8).

***N*-Methoxy-*N*-methyl phenylpropiolamide (4d).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.60 (m, 2H), 7.37-7.44 (m, 3H), 3.85 (s, 3H), 3.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 133.0, 130.6, 128.9, 120.7, 81.2, 62.5, 60.9, 36.5; FT-IR (film) 3059, 2974, 2935, 2219, 1639 (C=O), 1382, 1101, 758, 690 cm^{-1}; Ms *m/z* (%) 189 (M^+, 2), 130 (16), 129 (100), 101 (9), 75 (16).

***N*-Methoxy-*N*-methyl cyclohexanecarboxamide (4e).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.17 (s, 3H), 2.64-2.72 (m, 1H), 1.69-1.82 (m, 5H), 1.46-1.50 (m, 2H), 1.25-1.33 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 61.5, 61.3, 40.0, 29.0, 25.8 (overlapped); FT-IR (film) 2931, 2855, 1654 (C=O), 1449, 1386, 1176, 994 cm^{-1}; Ms *m/z* (%) 171 (M^+, 2), 111 (30), 83 (100), 55 (59).

***N*-Methoxy-*N*-methyl benzamide (4f).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.68 (m, 2H), 7.37-7.43 (m, 3H), 3.55 (s, 3H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 134.1, 130.5, 128.1, 128.0, 61.0, 33.8; FT-IR (film) 3059, 2970, 2935, 1644 (C=O), 1447, 1379, 1214, 978, 788, 706 cm^{-1}; Ms *m/z* (%) 165 (M^+, 2), 106 (8), 105 (100), 77 (54).

***N*-Methoxy-*N*-methyl *o*-toluamide (4g).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.31 (m, 4H), 3.53 (s, 3H), 3.35 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 135.6, 135.2, 130.5, 129.6, 126.6, 125.8, 61.4, 36.0, 19.5; FT-IR (film) 3063, 2968, 2934, 1650 (C=O), 1603, 1460, 1379, 1115, 985, 738 cm^{-1}; Ms *m/z* (%) 179 (M^+, 2), 120 (10), 119 (100), 91 (59), 65 (16).

***N*-Methoxy-*N*-methyl *p*-toluamide (4h).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 3.55 (s, 3H), 3.34 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 141.3, 131.5, 129.0, 128.7, 61.3, 34.2, 21.8; FT-IR (film) 3029, 2969, 2934, 1642 (C=O), 1459, 1377, 1182, 978, 830 cm^{-1}; Ms *m/z* (%) 179 (M^+, 2), 120 (10), 119 (100), 91 (44), 65 (14).

***N*-Methoxy-*N*-methyl *p*-methoxybenzamide (4i).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 9.0 Hz, 2H), 3.84 (s, 3H), 3.56 (s, 3H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 161.9, 130.9, 126.4, 113.6, 61.2, 55.7, 34.3; FT-IR (film) 3073, 2966, 2935, 1638 (C=O), 1574, 1460, 1375, 1216, 1029, 842 cm^{-1}; Ms *m/z* (%) 195 (M^+, 2), 136 (10), 135 (100), 107 (10), 77 (15).

***N*-Methoxy-*N*-methyl *p*-chlorobenzamide (4j).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 3.53 (s, 3H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 136.7, 132.3, 129.9, 128.3, 61.1, 33.5; FT-IR (film) 3067, 2970, 2935, 1642 (C=O), 1594, 1460, 1380, 1213, 1091, 840, 746 cm^{-1}; Ms *m/z* (%) 199 (M^+, 2), 141 (33), 139 (100), 113 (11), 111 (34), 75 (16).

***N*-Methoxy-*N*-methyl 2-thiophenecarboxamide (4k).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, J_1 = 3.8 Hz, J_2 = 1.1 Hz, 1H), 7.55 (dd, J_1 = 5.0 Hz, J_2 = 1.1 Hz, 1H), 7.10 (dd, J_1 = 5.0 Hz, J_2 = 3.8 Hz, 1H), 3.78 (s, 3H), 3.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 134.8, 133.6, 132.6, 127.2, 61.9, 33.4; FT-IR (film) 3095, 2973, 2935, 1617 (C=O), 1420, 1382, 1207, 1061, 978, 726 cm^{-1}; Ms *m/z* (%) 171 (M^+, 10), 112 (9), 111 (100), 83 (9).

***N*-Methoxy-*N*-methyl α-naphthamide (4l).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.91 (m, 3H), 7.26-7.53 (m, 4H), 3.50 (s, 3H), 3.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 133.4, 133.2, 129.8, 129.6, 128.3, 126.9, 126.3, 124.9, 124.8, 124.3, 61.3, 34.1; FT-IR (film) 3056, 2971, 2934, 1651 (C=O), 1592, 1508, 1373, 1182, 1102, 974, 801, 779 cm^{-1}; Ms *m/z* (%) 215 (M^+, 5), 156 (13), 155 (100), 128 (9), 127 (68).

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