An Efficient Synthesis of *N*-Methoxy-*N*-methylamides from Carboxylic Acids Using *N*-Methoxy-*N*-methylcarbamoyl Chloride

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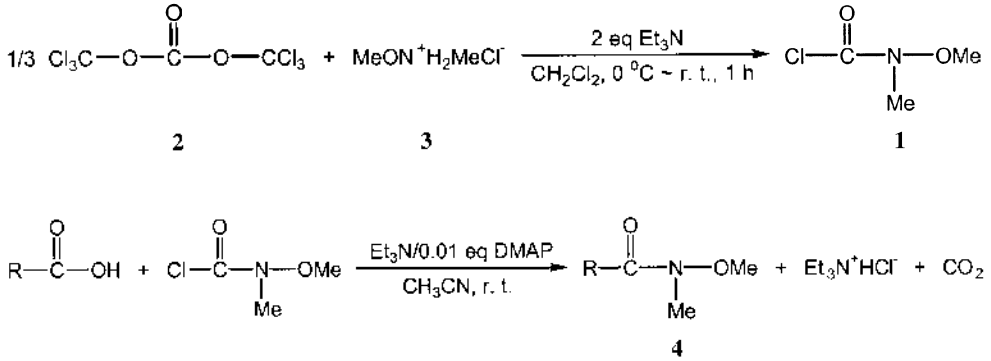
The *N*-methoxy-*N*-methylamides (Weinreb amides) have been widely used as effective carbonyl equivalents since they react with organometallics to provide various carbonyl functional groups through very stable metal-chelated intermediates.[1] Their preparations can be generally accomplished by condensation of carboxylic acids and *N,O*-dimethylhydroxylamine hydrochloride using peptide coupling reagents. Typical coupling reagents for this purpose are dicyclohexylcarbodiimide and/or 1-hydroxybenzotriazole,[2] 1,1'-carbonyldiimidazole,[3] BOP,[4] 2-halo-1-methylpyridinium salts,[5] 2-pyridyl esters,[6] HBTU,[7] and 2-chloro-4,6-dimethoxy-[1,3,5]triazine.[8] These methods are especially useful for the preparation of *N*-methoxy-*N*-methylamides from *N*-protected α-amino acids without any racemization, but some of these require the use of an excess of additional base and coupling reagents such as BOP and HBTU are expensive. The *N*-methoxy-*N*-methylamides can be also prepared from *in situ* mixed anhydrides, anhydride, and phosphonic anhydrides, generated from the treatment of carboxylic acids with alkyl chloroformates (R=Me,[9a] Et,[9b] *i*-Bu),[9] pivaloyl chloride,[10] and diethyl phosphorocyanidate[11] or propylphosphonic acid anhydride,[12] respectively, by subsequent addition of *N,O*-dimethylhydroxylamine hydrochloride in the presence of base. However, the removal of isobutyl alcohol in case of using isobutyl chloroformate from the reaction mixture is often tedious and phosphonic derivatives are expensive coupling reagents.

Recently, the preparation of *N*-methoxy-*N*-methylamides by the palladium-catalyzed coupling reactions[13] between *N*-methoxy-*N*-methylcarbamoyl chloride and organostannanes was reported, however the scope of the reaction is limited to sp and sp^2 hybridized organostannanes. In this paper we report that *N*-methoxy-*N*-methylamides can be efficiently prepared from carboxylic acids and *N*-methoxy-*N*-methylcarbamoyl chloride in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP).

The *N*-methoxy-*N*-methylcarbamoyl chloride **1** was prepared by a modification of a known method,[14] where phosgene is treated with *N,O*-dimethylhydroxylamine hydrochloride in benzene, but yield is moderate. To a mixture solution of one third equivalent of bis(trichloromethyl) carbonate **2** and *N,O*-dimethylhydroxylamine hydrochloride **3** in methylene chloride was added 2 equiv of triethylamine over 20 min at 0 °C (Scheme 1). The reverse addition of **2** in methylene chloride to a mixture solution of **3** and triethylamine in methylene chloride at 0 °C led to competing side reaction and thus **1** was obtained in 84% yield with the formation of *N,N'*-dimethoxy-*N,N'*-dimethyl urea as a by-product in 6% yield. After the reaction methylene chloride was evaporated and the mixture was dissolved in tetrahydrofuran, followed by filtering off triethylamine hydrochloride. The condensed residue was purified by Kugelrohr vacuum distillation to afford **1** in 90% yield as a colorless liquid.

To investigate the optimum conditions for the synthesis of *N*-methoxy-*N*-methylamides **4**, we first added phenylacetic acid to a solution of **1** in acetonitrile, and next triethylamine at room temperature. The reaction proceeded slowly to give *N*-methoxy-*N*-methylphenylacetamide **4a** in 89% yield after



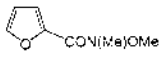
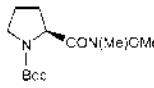
Scheme 1

6 h. However, the use of 0.01 equiv of DMAP accelerated the reaction, and thus **4a** was obtained in 94% yield after only 0.4 h. The effect of solvents was also examined for the condensation of benzoic acid and **1** in the presence of 0.01 equiv of DMAP at room temperature. When methylene chloride and acetonitrile were employed, the reaction went to completion in 2 h and 1 h, respectively, and *N*-methoxy-*N*-methylbenzamide **4c** was obtained in 95% and 94% yield, respectively. For tetrahydrofuran and diethyl ether solvent, the corresponding reaction proceeded slowly and **4c** was obtained in 93% and 95% yield, after 8 h and 9 h, respectively. Thus the direct conversion of carboxylic acids to the corresponding **4** using **1** proceeded well with 0.01 equiv of DMAP in acetonitrile at room temperature.

The condensation between carboxylic acids and **1** seemed to proceed *via* the mixed carboxylic-carbamic anhydride. The treatment of 2-furoic acid with **1** and triethylamine in acetonitrile at room temperature produced the corresponding mixed carboxylic-carbamic anhydride, detected by 300 MHz ^{1}H NMR and FT-IR spectroscopy, in 91% yield. Characteristic aromatic protons of *N*-methoxy-*N*-methyl-2-furamide **4f** appeared in δ 7.60 (s, 1H), 7.15 (d, J = 3.6 Hz, 1H), and 6.52 (d, J = 3.6 Hz, 1H), whereas aromatic protons of the corresponding mixed carboxylic-carbamic anhydride appeared in δ 7.70 (s, 1H), 7.36 (d, J = 3.6 Hz, 1H), and 6.60-6.64 (m, 1H). Furthermore, a characteristic carbonyl stretching of **4f** was observed in 1636 cm^{-1} (one band), whereas carbonyl stretching of the corresponding mixed carboxylic-carbamic anhydride was observed in 1735 and 1781 cm^{-1} (two bands). The molecular ion of the corresponding mixed carboxylic-carbamic anhydride was not observed in the mass spectrum, however the molecular ion due to loss of carbon dioxide appeared at m/z = 155 (21%) along with the base peak (m/z = 95, $C_5H_3O_2^+$). Nucleophilic attack by DMAP on the more electrophilic acyl carbon atom of mixed carboxylic-carbamic anhydride afforded to give *N*-acylpyridinium salt with the evolution of carbon dioxide, which was readily converted to **4** by subsequent nucleophilic acyl displacement with *N*-methoxy-*N*-methyl anion.

As shown in Table 1, various *N*-methoxy-*N*-methylamides were efficiently prepared by this method in high yields. The reaction of primary/secondary aliphatic carboxylic acids (**4a**, **4b**) and **1** gave the corresponding **4** in high yields within 1 h. The condensation of aromatic carboxylic acids (**4c-4f**) proceeded slightly slower than that of aliphatic carboxylic acids. Especially, the conversion of *p*-methoxybenzoic acid into 4-methoxy-*N*-methoxy-*N*-methylbenzamide **4d** proceeded sluggishly, reflecting on the decreased electrophilicity of *p*-methoxybenzoyl carbon atom in mixed carboxylic carbamic anhydride intermediate because of electron-donating effect by *p*-methoxy group. The present method was also effective for the preparation of **4** having benzoyl, C=C, bromo, carboethoxy, and carbamate functional groups. Thus, the reaction of benzoylformic acid (**4g**), *trans*-cinnamic acid (**4h**), 10-undecenoic acid (**4i**), 6-bromohexanoic acid (**4j**), 5-(carboethoxy)valeric acid (**4k**), and *N*-carbobenzyloxyglycine (**4l**) with **1** afforded the corresponding **4** without damage to these functional groups. *N*-(*tert*-Butoxycarbonyl)-L-proline (**4m**) was also converted to *N*-methoxy-*N*-methylamide without racemization of the chiral center.

Table 1. Preparation of *N*-methoxy-*N*-methylamides from carboxylic acids using *N*-methoxy-*N*-methylcarbamoyl chloride[a]

Entry	4	RCOOH R	Reaction time, h	Product	Isolated yield, %
a		$C_6H_5CH_2$	6[b]	$C_6H_5CH_2CON(Me)OMe$	85
			0.4		94
b		c-C_6H_{11}	1	c-$C_6H_{11}CON(Me)OMe$	97
c		C_6H_5	1	$C_6H_5CON(Me)OMe$	94
d		p-CH_3O-C_6H_4	12	p-CH_3O-$C_6H_4CON(Me)OMe$	91
e		p-O_2N-C_6H_4	1.5	p-O_2N-$C_6H_4CON(Me)OMe$	85
f		2-furoic	1		81
g		C_6H_5CO	1	$C_6H_5COCON(Me)OMe$	76
h		trans-C_6H_5CH=CH	2	trans-C_6H_5CH=$CHCON(Me)OMe$	89
i		CH_2=CH-$(CH_2)_6$	0.5	CH_2=CH-$(CH_2)_8CON(Me)OMe$	93
j		$Br(CH_2)_5$	0.5	$Br(CH_2)_5CON(Me)OMe$	83
k		$C_2H_5OOC(CH_2)_4$	1.5	$C_2H_5OOC(CH_2)_4CON(Me)OMe$	78
l		$C_6H_5CH_2OOCNHCH_2$	1	$C_6H_5CH_2OOCNHCH_2CON(Me)OMe$	75
m		N-(tert-Boc)-L-proline	1		80

[a]The reaction was carried out with 0.01 equiv of DMAP in acetonitrile at room temperature. [b]No DMAP.

In conclusion the present method suggests an efficient conversion of carboxylic acids to the corresponding **4** by one step reaction. It has the advantage of high yield synthesis, convenience/versatility of the reaction, and the stability of **1** and, therefore, many synthetic applications.

Experimental Section

^{1}H NMR spectra were obtained with a Bruker AVANCE 300 (300 MHz) spectrometer on $CDCl_3$ solutions. FT-IR spectra were obtained with a Bruker vector 22. Low-resolution mass spectrum was measured with a VG-TRIO 2 Gc/Ms. Optical rotation was measured with a NOW Polarriz-D polarimeter in a 1 dm tube. Thin layer chromatography analysis was performed on Merck silica gel 60F-254 glass plates and silica gel 60 (E. Merck, 0.063-0.200 mm) was used for column chromatography.

Preparation of *N*-methoxy-*N*-methylcarbamoyl chloride 1. To a mixture solution of *N,O*-dimethylhydroxylamine hydrochloride (1.4388 g, 14.7 mmol) and bis(trichloromethyl) carbonate (1.7508 g, 5.9 mmol) in methylene chloride (74 mL) was added triethylamine (4.32 mL, 31.0 mmol) over 20 min at 0 °C. The reaction mixture was stirred for 1 h between 0 °C and room temperature. Methylene chloride

was evaporated *in vacuo* and the mixture was dissolved in dry tetrahydrofuran, followed by filtering off triethylamine hydrochloride. The condensed filtrate was purified by Kugelrohr vacuum distillation to afford **1** (1.6344 g, 90%) as a colorless liquid. B.p. 68-73 °C/8.0 mm Hg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.33 (s, 3H); FT-IR (film) 2981, 2941, 1747 (C=O), 1460, 1353, 1182, 995, 868, 670 cm^{-1}; Ms *m/z* (%) 125 (M^++1, 12), 123 (M^+, 36), 88 (62), 63 (69), 60 (87), 58 (100).

Preparation of *N*-methoxy-*N*-methylbenzamide 4c. (General procedure) To a *N*-methoxy-*N*-methylcarbamoyl chloride (247.1 mg, 2.0 mmol) in acetonitrile (7 mL) was added benzoic acid (244.2 mg, 2.0 mmol) and triethylamine (293 μL, 2.1 mmol), followed by the addition of DMAP (2.4 mg, 0.02 mmol) at room temperature. After being stirred for 1 h, acetonitrile was evaporated *in vacuo* and the reaction mixture was extracted with methylene chloride (3 × 20 mL), washed with sat. $NaHCO_3$ solution (30 mL). The organic phases were dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness under vacuum. The residue was subjected to short pathway silica gel column chromatography using 30% EtOAc/*n*-hexane as an eluant to afford **4c** (310.5 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.67 (m, 2H), 7.36-7.43 (m, 3H), 3.53 (s, 3H), 3.33 (s, 3H); FT-IR (film) 3054, 2985, 1644 (C=O), 1380, 1265, 909, 738 cm^{-1}.

***N*-Methoxy-*N*-methylphenylacetamide (4a)**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.24 (m, 5H), 3.68 (s, 2H), 3.43 (s, 3H), 3.05 (s, 3H); FT-IR (film) 3030, 2938, 1661 (C=O), 1496, 1455, 1383, 1007, 730, 698 cm^{-1}.

***N*-Methoxy-*N*-methylcyclohexanecarboxamide (4b)**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.17 (s, 3H), 2.65-2.78 (m, 1H), 1.62-1.81 (m, 5H), 1.20-1.62 (m, 5H); FT-IR (film) 2931, 2855, 1660 (C=O), 1449, 1176, 994, 734 cm^{-1}.

4-Methoxy-*N*-methoxy-*N*-methylbenzamide (4d). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 9.0 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 3.81 (s, 3H), 3.55 (s, 3H), 3.33 (s, 3H); FT-IR (film) 3053, 2935, 1635 (C=O), 1610, 1422, 1255, 1174, 910, 734 cm^{-1}.

4-Nitro-*N*-methoxy-*N*-methylbenzamide (4e). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 9.0 Hz, 1H), 3.57 (s, 3H), 3.41 (s, 3H); FT-IR (film) 3054, 2937, 1644 (C=O), 1601, 1352, 911, 740 cm^{-1}.

***N*-Methoxy-*N*-methyl-2-furamide (4f)**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.15 (d, J = 3.6 Hz, 1H), 6.52 (d, J = 3.6 Hz, 1H), 3.76 (s, 3H), 3.35 (s, 3H); FT-IR (film) 3143, 2939, 1636 (C=O), 1479, 1179, 980, 765 cm^{-1}.

***N*-Methoxy-*N*-methylbenzoylformamide (4g)**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 5.3 Hz, 2H), 7.60-7.65 (m, 1H), 7.48-7.53 (m, 2H), 3.63 (s, 3H), 3.35 (s, 3H); FT-IR (film) 2981, 2940, 1662 (slightly broad, C=O), 1597, 1450, 1391, 1256, 959, 732 cm^{-1}.

***N*-Methoxy-*N*-methyl-*trans*-cinnamide (4h)**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 15.8 Hz, 1H), 7.54-7.57 (m, 2H), 7.32-7.38 (m, 3H), 7.01 (d, J = 15.8 Hz, 1H), 3.73 (s, 3H), 3.28 (s, 3H); FT-IR (film) 3061, 2968, 2937, 1652 (C=O), 1617, 1450, 1382, 1179, 997, 911, 733 cm^{-1}.

***N*-Methoxy-*N*-methyl-10-undecenamide (4i)**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75-5.84 (m, 1H), 4.98 (dd, J_1 = 3.0 Hz, J_2 = 18.0 Hz, 1H), 4.92 (dd, J_1 = 3.0 Hz, J_2 = 12.0 Hz, 1H), 3.68 (s, 3H), 3.17 (s, 3H), 2.41 (t, J = 7.5 Hz, 2H), 2.02-2.07 (m, 2H), 1.58-1.65 (m, 2H), 1.31-1.39 (m, 10H); FT-IR (film) 3076, 2925, 2854, 1668 (C=O), 1464, 1384, 1178, 997, 910 cm^{-1}.

***N*-Methoxy-*N*-methyl-6-bromohexanamide (4j)**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.69 (s, 3H), 3.42 (t, J = 6.6 Hz, 2H), 3.18 (s, 3H), 2.44 (t, J = 7.2 Hz, 2H), 1.87-1.92 (m, 2H), 1.61-1.69 (m, 2H), 1.46-1.52 (m, 2H); FT-IR (film) 2939, 1652 (C=O), 1462, 1387, 1179, 910, 734 cm^{-1}.

***N*-Methoxy-*N*-methyl-5-carboethoxyvaleramide (4k)**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (q, J = 7.2 Hz, 2H), 3.69 (s, 3H), 3.18 (s, 3H), 2.45-2.47 (m, 2H), 2.31-2.36 (m, 2H), 1.65-1.70 (m, 4H), 1.25 (t, J = 7.2 Hz, 3H); FT-IR (film) 2940, 1733 (**CO**O), 1660 (**CO**N), 1463, 1386, 1181, 733 cm^{-1}.

***N*-Methoxy-*N*-methyl-α-(benzyloxycarbonylamino) glycineamide (4l)**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.37 (m, 5H), 5.68 (br s, 1H), 5.11 (s, 2H), 4.13 (d, J = 5.1 Hz, 2H), 3.69 (s, 3H), 3.18 (s, 3H); FT-IR (film) 2940, 1719 (**OCO**N), 1671 (**CO**N), 1455, 1249, 1167, 910, 733 cm^{-1}.

***N*-Methoxy-*N*-methyl-α-(*t*-butoxycarbonylamino)-L-prolineamide (4m)**. ^{1}H NMR (300 MHz, $CDCl_3$) δ (mixture of two conformers) 4.73 (d, J = 3.4 Hz, 0.5 H), 4.60 (d, J = 3.4 Hz, 0.5H), 3.79 (s, 1.5H), 3.74 (s, 1.5H), 3.52-3.59 (m, 1H), 3.43-3.52 (m, 1H), 3.20 (s, 3H), 2.08-2.25 (m, 1H), 1.84-2.08 (m, 3H), 1.46 (s, 4.5H), 1.42 (s, 4.5H); FT-IR (film) 2975, 2879, 1689 (slightly broad, C=O), 1402, 1166, 1000, 733 cm^{-1}; $[\alpha]_D^{25}$ -38.5° (c=1, MeOH); lit.[5] $[\alpha]_D^{26}$ -37.6° (c=1, MeOH).

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