A Convenient Synthesis of *N*-Methoxy-*N*-methylamides from Carboxylic Acids Using S,S-Di(2-pyridyl) Dithiocarbonate

Jae In Lee* and Hyun Park

Department of Chemistry, College of Natural Science, Duksung Women's University, Seoul 132-714, Korea
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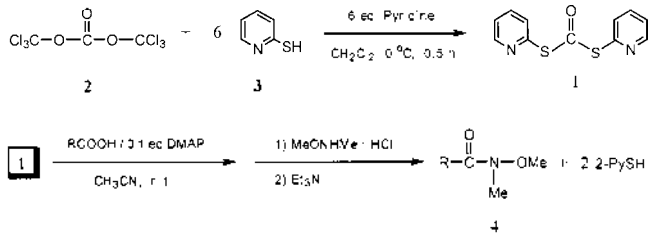
The *N*-methoxy-*N*-methylamides (Weinreb amides) are widely recognized as effective acylating agents since they react with organometallics (RM, M=MgBr, Li) to produce ketones without side products.[1] Preparation of *N*-methoxy-*N*-methylamides is accomplished generally by condensation of carboxylic acids and *N,O*-dimethylhydroxylamine hydrochloride, using coupling reagents. The treatment of carboxylic acids with coupling reagents such as oxalyl chloride,[2] triphenylphosphine/carbon tetrabromide,[3] benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate,[4] 1,1'-carbonyldiimidazole,[5] 1,3-dicyclohexylcarbodiimide/1-hydroxybenzotriazole,[6] 2-halo-1-methylpyridinium salts,[7] and *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate[8] affords the corresponding carboxyl-activated intermediates, which are converted into the corresponding *N*-methoxy-*N*-methylamides by subsequent addition of *N,O*-dimethylhydroxylamine hydrochloride. Some of these methods require relatively expensive coupling reagents or the use of excess additional base. The *N*-methoxy-*N*-methylamides can be also prepared from the mixed anhydride, phosphate, and anhydride intermediates, generated from the treatment of carboxylic acids with isobutyl chloroformate,[9] diethyl phosphorocyanidate,[10] and pivaloyl chloride,[11] respectively, in the presence of base, by nucleophilic displacement with *N,O*-dimethylhydroxylamine hydrochloride. Recently, alternative methods for the preparation of *N*-methoxy-*N*-methylamides from esters,[12] lactones,[13] and *N*-acyl oxazolidinones,[14] using LiN(OMe)Me or Me_3Al-MeONHMe · HCl have been developed, but they require the use of an excess of the corresponding reagents in most cases.

In the present study we report that *N*-methoxy-*N*-methylamides can be conveniently prepared from carboxylic acids and *N,O*-dimethylhydroxylamine hydrochloride, using S,S-di(2-pyridyl) dithiocarbonate **1** in one-pot. The coupling reagent **1** has been prepared by addition of 6 equimolar solutions of 2-mercaptopyridine **3** and pyridine in methylene chloride to a bis(trichloromethyl)carbonate **2** at 0 °C (Scheme 1). **1** was easily separated by aqueous work-up, obtained in 96% yield after a short pathway silica gel column chromatography and was stored in a refrigerator for two months without any decomposition.

Initially, anticipating the direct formation of *N*-methoxy-*N*-methylphenylacetamide **4b** in one step, we added phenylacetic acid and *N,O*-dimethylhydroxylamine hydrochloride



Scheme 1

to a solution of **1** in acetonitrile, followed by the addition of triethylamine and 0.1 equiv of 4-dimethylaminopyridine (DMAP). However, *N*-methoxy-*N*-methyl S-2-pyridyl thiocarbamate was obtained in 95% yield after the solution was stirred for 0.5 h at room temperature. After 24 h, it still was not converted into **4b**. We therefore carried out the preparation of *N*-methoxy-*N*-methylamides **4** by two steps in one-pot method: 1) complete conversion of carboxylic acids into the corresponding S-2-pyridyl thioates, using **1** in the presence of 0.1 equiv of DMAP 2) subsequent addition of an equimolar amount of *N,O*-dimethylhydroxylamine hydrochloride and triethylamine to the mixture. After the reaction to completion, acetonitrile was evaporated under vacuum and the reaction mixture was dissolved in tetrahydrofuran, followed by filtering off triethylamine hydrochloride. The concentration of the mixture and the addition of 15% EtOAc /*n*-hexane afforded **3** as a precipitate, which was recovered by filtration and reused for the preparation of **1**.

The effect of solvents was examined for the condensation of phenylacetic acid and *N,O*-dimethylhydroxylamine hydrochloride with **1** in the presence of 0.1 equiv of DMAP. When acetonitrile, methylene chloride, and 1,2-dichloroethane were employed as a solvent, the reaction of the 1st/2nd step went to completion in 2 h/0.3 h, 9 h/0.3 h, and 10 h/0.7 h, respectively, and **4b** was obtained in 90%, 92%, and 82% yield, respectively, at room temperature. For tetrahydrofuran and diethyl ether solvent, the 1st step of the above reaction went to completion in 8 h and 10 h, respectively, but the conversion of the intermediate was very sluggish, yielding **4b** in 55% and 54% yield, respectively, along with the recovery of S-2-pyridyl phenylmethylthioate in 31% and 27% yield, respectively, after 24 h at room temperature.

We next examined the efficiency of some coupling reagents containing 2-pyridyl moiety for the preparation of *N*-meth-

Table 1. Preparation of *N*-methoxy-*N*-methylamides from carboxylic acids and *N,O*-dimethylhydroxylamine hydrochloride using **1**

Entry	RCOOH	Equiv of	Reaction time, h		Isolated
4	R	DMAP	1st step	2nd step	yield, %[a]
a	$CH_3(CH_2)_8$	0.1	3	0.5	98(90)
b	$C_6H_5CH_2$	0.1	2	0.3	90(98)
c	*c*-C_6H_{11}	0.1	3	5.5	94(84)
d	C_6H_5	0.1	9	7	98(91)
e	*p*-CH_3O-C_6H_4	0.1	3	24	85(89)
f	*p*-Cl-C_6H_4	0.1	6	2.5	98(87)
g	2-Furoic	0.2	7	1	93(86)
h	CH_2=$CH(CH_2)_8$	0.1	2	0.5	97(98)
i	*trans*-C_6H_5CH=CH	0.1	2	0.3	73(87) 22[b]
j	$Cl(CH_2)_3$	0.1	3	2	90(98)
k	$C_2H_5OOC(CH_2)_4$	0.1	1.5	0.3	87(97)
l	$C_6H_5CO(CH_2)_2$	0.1	1	12	91(97)

[a]The numbers in parentheses indicate the recovery yield of 2-mercaptopyridine. [b]Isolated yield of *N*-methoxy-*N*-methy-3-phenyl-3-(2-thiopyridyl)propanamide.

oxy-*N*-methylamides. The treatment of phenylacetic acid with **1**, di-2-pyridyl carbonate, and di-2-pyridyl thionocarbonate in acetonitrile in the presence of 0.1 equiv of DMAP afforded S-2-pyridyl phenylmethylthioate intermediate in 2 h, 0.2 h, and 0.3 h, respectively, at room temperature. Sequential addition of an equimolar amount of *N,O*-dimethylhydroxylamine hydrochloride and triethylamine produced **4b** in 90%, 87%, and 51% yield, respectively, after 0.3 h, 6 h, and 3 h, respectively. Thus, the condensation between carboxylic acids and *N,O*-dimethylhydroxylamine hydrochloride proceeded well with **1** in acetonitrile at room temperature.

As shown in Table 1, various *N*-methoxy-*N*-methylamides were conveniently prepared by this method in high yields. The reaction of the most primary/secondary aliphatic carboxylic acids (**4a-4c**) and *N,O*-dimethylhydroxylamine hydrochloride with **1** gave the corresponding **4** with the recovery of **3** in high yields. The condensation of aromatic carboxylic acids (**4d-4f**), including 2-furoic acid (**4g**) proceeded more sluggishly than that of aliphatic carboxylic acids. The conversion of *p*-methoxybenzoic acid having electron-donating group into the S-2-pyridyl *p*-methoxybenzothioate proceeded faster than the conversion of *p*-chlorobenzoic acid having electron-withdrawing group, whereas its transformation into **4e** proceeded slower than the transformation of S-2-pyridyl *p*-chlorobenzothioate. The present method was also effective for the preparation of *N*-methoxy-*N*-methylamides having C=C, chloro, carboethoxy, and benzoyl functional groups. Thus, the reaction of 10-undecenoic acid (**4h**), 4-chlorobutanoic acid (**4j**), 5-(carboethoxy)valeric acid (**4k**), and 3-benzoylpropionic acid (**4l**) with **1** and the subsequent addition of equimolar amounts of *N,O*-dimethylhydroxylamine hydrochloride and triethylamine afforded the corresponding **4** without damage to these functional groups. However, the treatment of α,β-unsaturated acid such as *trans*-cinnamic acid (**4i**) with **1**, followed by the addition of an equimolar amount of *N,O*-dimethylhydroxylamine hydrochloride and triethylamine, gave *N*-methoxy-*N*-methyl *trans*-cinnamide in 73% yield, together with 22% yield of *N*-methoxy-*N*-methy-3-phenyl-3-(2-thiopyridyl) propanamide, which was produced by 1,4-addition of **3** to the product.

The present method provides an efficient conversion of carboxylic acids to the *N*-methoxy-*N*-methylamides by one-pot. It has the advantage of high yield synthesis, recovery/renewability of **3**, and the stability of **1** and, therefore, can be utilized in many synthetic applications.

Experimental Section

^{1}H NMR spectra were recorded with a Bruker AVANCE 300 (300 MHz) or 500 (500 MHz), using $CDCl_3$ as a solvent. FT-IR spectra were recorded with a Bruker vector 22. Low-resolution mass spectra were measured with VG-TRIO 2 GC/MS. Thin layer chromatography analyses were performed on Merck silica gel 60F-254, and silica gel (silica gel 60, E. Merck, 0.063-0.200 mm) was used for column chromatography.

Preparation of S,S-di(2-pyridyl) dithiocarbonate 1. To a bis(trichloromethyl)carbonate (1.2464 g, 4.2 mmol) in methylene chloride (30 mL) was slowly added a mixture solution of 2-mercaptopyridine (2.8016 g, 25.2 mmol) and pyridine (2.04 mL, 25.2 mmol) in methylene chloride (35 mL) at 0 °C. After being stirred for 30 min, the reaction mixture was extracted with methylene chloride (3 × 30 mL) and washed with brine (45 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The crude product was purified by short pathway silica gel column chromatography using 50% EtOAc/*n*-hexane as an eluant to give **1** (3.0039 g, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60-8.61 (m, 2H), 7.70-7.73 (m, 2H), 7.66 (d, J = 7.9 Hz, 2H), 7.28-7.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.5, 150.4, 150.2, 137.3, 130.3, 124.0; FT-IR (film) 3030, 2938, 1660 (C=O), 1496, 1455, 1383, 1174, 1007, 730, 698 cm^{-1}; Ms *m/z* (%) 249 (M^++1, 4), 248 (M^-, 11), 220 (50), 187 (27), 156 (15), 138 (49), 78 (100).

Preparation of *N*-methoxy-*N*-methylphenylacetamide 4b. (General procedure) To a phenylacetic acid (272.3 mg, 2.0 mmol) in acetonitrile (5 mL) was added **1** (496.7 mg, 2.0 mmol), followed by the addition of DMAP (24.4 mg, 0.2 mmol) at room temperature. The stirring was continued for 2 h and then was added *N,O*-dimethylhydroxylamine hydrochloride (195.1 mg, 2.0 mmol) and triethylamine (279 μL, 2.0 mmol). After being stirred for 0.3 h, acetonitrile was evaporated *in vacuo* and the reaction mixture was dissolved in anhydrous tetrahydrofuran (3 × 5 mL), followed by filtering off triethylamine hydrochloride. Tetrahydrofuran was evaporated *in vacuo* and the mixture was dissolved in 15% EtOAc/*n*-hexane (3 × 5 mL), followed by recovering of 2-mercaptopyridine (435.7 mg, 98%). The concentrated residue was subjected to short pathway silica gel column chromatography using 30% EtOAc/*n*-hexane as an eluant to afford **4b** (322.6 mg, 90%) as a colorless oil. ^{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) 3031, 2938, 1660 (C=O), 1496, 1455, 1383, 1007, 731, 698 cm^{-1}.

***N*-Methoxy-*N*-methyloctanamide (4a)**. ^1H NMR (300 MHz, $CDCl_3$) δ 3.69 (s, 3H), 3.18 (s, 3H), 2.42 (t, J = 7.5 Hz, 2H), 1.60-1.68 (m, 2H), 1.25-1.38 (m, 8H), 0.88 (t, J = 7.5 Hz, 3H); FT-IR (film) 2928, 2855, 1669 (C=O), 1464, 1384, 997 cm^{-1}.

***N*-Methoxy-*N*-methylcyclohexanecarboxamide (4c)**. ^1H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.17 (s, 3H), 2.64-2.78 (m, 1H), 1.70-1.81 (m, 5H), 1.21-1.53 (m, 5H); FT-IR (film) 2932, 2855, 1656 (C=O), 1450, 1387, 1177, 995, 734 cm^{-1}.

***N*-Methoxy-*N*-methylbenzamide (4d)**. ^1H NMR (300 MHz, $CDCl_3$) δ 7.62-7.65 (m, 2H), 7.33-7.40 (m, 3H), 3.47 (s, 3H), 3.28 (s, 3H); FT-IR (film) 3054, 2985, 1638 (C=O), 1421, 1382, 1265, 909, 738 cm^{-1}.

4-Methoxy-*N*-methoxy-*N*-methylbenzamide (4e). ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 9.0 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 3.82 (s, 3H), 3.55 (s, 3H), 3.34 (s, 3H); FT-IR (film) 3054, 2936, 1636 (C=O), 1421, 1254, 1173, 1029, 842 cm^{-1}.

4-Chloro-*N*-methoxy-*N*-methylbenzamide (4f). ^1H NMR ($CDCl_3$) δ 7.65 (d, J = 6.0 Hz, 2H), 7.37 (d, J = 6.0 Hz, 2H), 3.52 (s, 3H), 3.34 (s, 3H); FT-IR (film) 3054, 2935, 1642 (C=O), 1418, 1381, 1267, 1092, 840, 737 cm^{-1}.

***N*-Methoxy-*N*-methyl-2-furamide (4g)**. ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.14 (d, J = 4.0 Hz, 1H), 6.52 (d, J = 4.0 Hz, 1H), 3.76 (s, 3H), 3.34 (s, 3H); FT-IR (film) 3118, 2937, 1651 (C=O), 1486, 1178, 980, 763 cm^{-1}.

***N*-Methoxy-*N*-methyl-10-undecenamide (4h)**. ^1H NMR (300 MHz, $CDCl_3$) δ 5.74-5.83 (m, 1H), 4.97 (dd, J_1 = 3.0 Hz, J_2 = 18.0 Hz, 1H), 4.91 (dd, J_1 = 3.0 Hz, J_2 = 12.0 Hz, 1H), 3.67 (s, 3H), 3.16 (s, 3H), 2.41 (t, J = 6.0 Hz, 2H), 2.02-2.06 (m, 2H), 1.59-1.64 (m, 2H), 1.25-1.42 (m, 10H); FT-IR (film) 3076, 2927, 2854, 1665 (C=O), 1463, 1385, 1178, 997, 911, 734 cm^{-1}.

***N*-Methoxy-*N*-methyl *trans*-cinnamide (4i)**. ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 15.0 Hz, 1H), 7.54-7.57 (m, 2H), 7.32-7.38 (m, 3H), 7.04 (d, J = 15.0 Hz, 1H), 3.74 (s, 3H), 3.29 (s, 3H); FT-IR (film) 3060, 2936, 1651 (C=O), 1384, 1179, 1098, 997, 762 cm^{-1}.

4-Chloro-*N*-methoxy-*N*-methylbutanamide (4j). ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.63 (t, J = 6.0 Hz, 2H), 3.18 (s, 3H), 2.62 (t, J = 6.0 Hz, 2H), 2.06-2.15 (m, 2H); FT-IR (film) 2965, 1663 (C=O), 1419, 1388, 1176, 998, 732 cm^{-1}.

5-Carboethoxy-*N*-methoxy-*N*-methylvaleramide (4k). ^1H NMR (300 MHz, $CDCl_3$) δ 4.12 (q, J = 7.1 Hz, 2H), 3.69 (s, 3H), 3.18 (s, 3H), 2.36-2.45 (m, 2H), 2.31- 2.35 (m, 2H), 1.65-1.70 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H); FT-IR (film) 2939, 1732 (**CO**O), 1667 (**CO**N), 1385, 1180, 997, 733 cm^{-1}.

3-Benzoyl-*N*-methoxy-*N*-methylpropionamide (4l). ^1H NMR (300 MHz, $CDCl_3$) δ 7.98-8.01 (m, 2H), 7.51-7.54 (m, 1H), 7.41-7.46 (m, 2H), 3.76 (s, 3H), 3.33 (t, J = 7.5 Hz, 2H), 3.19 (s, 3H), 2.89 (t, J = 7.5 Hz, 2H); FT-IR (film) 3059, 2937, 1685 (C_6H_5**CO**), 1661 (**CO**N), 1448, 1361, 1179, 1001, 736, 691 cm^{-1}.

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