A New Synthesis of N-Methoxy-N-methylamides from S-2-Pyridyl Thiocarbamate and Grignard Reagents

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The N-methoxy-N-methylamides ( Weinreb amides ) have been widely utilized as effective acylating agents since they react with Grignard or organolithium reagents to produce ketones without side products. Among the various methods for the preparation of N-methoxy-N-methylamides, the condensation of carboxylic acids and N,O-dimethylhydroxylamine hydrochloride (MeONH₂MeCl) using coupling reagents is the most common. The treatment of carboxylic acids and MeONH₂MeCl with coupling reagents such as Ph₃P/CBr₄, CDI, HOBt/DCC, 2-halo-1-methylpyridinium iodide, BOP-Ph₃P, HBTU, and 2-chloro-4,6-dimethoxy[1,3,5]triazine (CDMT) in the presence of base affords the corresponding activated esters, which are transformed into the corresponding N-methoxy-N-methylamides by subsequent addition of MeONH₂MeCl and base. Although these methods are the most convenient and 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 CDI, BOP-Ph₃P, HBTU, and CDMT are expensive. The treatment of carboxylic acids with pivaloyl chloride, alkyl chloroformate (R=Me, Et, i-Bu), and phosphonate reagents also affords the anhydride, mixed anhydride, and phosphonic anhydride intermediates, respectively, in the presence of base, which are transformed into the corresponding N-methoxy-N-methylamides by nucleophilic substitution with MeONH₂MeCl. However, the removal of isobutyl alcohol is often tedious and phosphonate reagents are generally expensive.

It has been recently reported that N-methoxy-N-methylamides are prepared by the reaction of carboxylic acids and methanesulfonyl chloride following by the addition of MeONH₂MeCl. This procedure via acyl mesylate intermediates is especially useful for the preparation of sterically hindered N-methoxy-N-methylamides. Alternatively N-methoxy-N-methylamides are also prepared from carboxylic acid derivatives such as acid chlorides, esters, lactones, and oxazolidinone carboxamides using MeONH₂MeCl/pyridine, MeONMeM (M=Li, MgCl), MeAlClMeONH₂MeCl, and MeAl(NO)Me₃, respectively, but these reactions proceed in two steps from carboxylic acids and furthermore require the use of an excess of the reagent in case of tran-
However, there are no reports on the preparation of N-methoxy-N-methylamides from Grignard reagents in one step. As part of our continuing studies for the preparation of N-methoxy-N-methylamides, we wish to report that N-methoxy-N-methylamides can be newly prepared by the reaction of S-2-pyridyl thiocarbamate and Grignard reagents under mild conditions.

**EXPERIMENTAL**

**Preparation of S-2-pyridyl thiocarbamate (1)**

To a solution of S,S-di(2-pyridyl)dithiocarbamate (1.24 g, 5.0 mmol) in dichloromethane (20 mL) was added N,N-dimethylhydroxylamine hydrochloride (487.8 mg, 5.0 mmol) and triethylamine (697 µL, 5.0 mmol) at -10 °C. After being stirred for 1 h, the mixture was poured into brine (40 mL) and extracted with dichloromethane (3×25 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography using 30% EtOAc/n-hexane as an eluant to give 4g (351.4 mg, 90%) as a colorless liquid. ¹H NMR (300 MHz, CDCl₃) δ 7.73 (d, J=8.7 Hz, 2H), 6.90 (d, J=8.7 Hz, 2H), 3.83 (s, 3H), 3.56 (s, 3H), 3.35 (s, 3H); FT-IR (film) 3055, 2966, 2935, 1637 (C=O), 1607, 1374, 1254, 1029, 842 cm⁻¹; Ms m/z 195 (M⁺, 1), 136 (10), 135 (p-CH₃-C₆H₄CO⁻, 100), 92 (12), 77 (14).

**N-Methoxy-N-methylnonamide (4a)**: ¹H NMR (300 MHz, CDCl₃) δ 3.68 (s, 3H), 3.18 (s, 3H), 2.41 (t, J=7.6 Hz, 2H), 1.56-1.68 (m, 2H), 1.19-1.38 (m, 10H), 0.88 (t, J=6.7 Hz, 3H); FT-IR (film) 2928, 2855, 1668 (C=O), 1465, 1385, 1179, 1121 cm⁻¹; Ms m/z (%) 141 [CH₂CH₂CO⁺, 100].

**N-Methoxy-N-methylcyclohexanecarboxamide (4b)**: ¹H NMR (300 MHz, CDCl₃) δ 3.70 (s, 3H), 2.64-2.72 (m, 1H), 1.73-1.81 (m, 5H), 1.46-1.50 (m, 2H), 1.25-1.28 (m, 3H); FT-IR (film) 2931, 2855, 1658 (C=O), 1449, 1177, 1116, 994 cm⁻¹; Ms m/z (%) 171 (M⁺, 2), 111 (G9), 83 (c-C₆H₄N⁺, 100), 55 (44).

**N-Methoxy-N-methylphenylpropiolamide (4c)**: M.p. 37 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.56-7.64 (m, 2H), 7.34-7.44 (m, 3H), 3.85 (s, 3H), 3.30 (s, 3H); FT-IR (KBr) 3063, 2974, 2936, 2219, 1642 (C=O), 1382, 1101, 759, 690 cm⁻¹; Ms m/z (%) 189 (M⁺, 2), 130 (14), 129 (C₆H₅CO⁺, 100), 101 (6), 75 (10).

**N-Methoxy-N-methylbenzamide (4d)**: ¹H NMR (300 MHz, CDCl₃) δ 7.65-7.69 (m, 2H), 7.39-7.45 (m, 3H), 3.55 (s, 3H), 3.36 (s, 3H); FT-IR (film) 3060, 2971, 2936, 1644 (C=O), 1380, 1214, 788, 707 cm⁻¹; Ms m/z (%) 165 (M⁺, 2), 106 (8), 105 (C₆H₄CO⁺, 100), 77 (50).

**N-Methoxy-N-methyl-o-methylbenzamide (4e)**: ¹H NMR (300 MHz, CDCl₃) δ 7.17-7.32 (m, 4H), 7.53 (s, 3H), 3.30 (s, 3H); FT-IR (film) 3063, 2970, 2935, 1650 (C=O), 1380, 1063, 773 cm⁻¹; Ms m/z (%) 179 (M⁺, 2), 120 (10), 119 (o-C₆H₄-CH₃CO⁺, 100), 91 (53), 65 (14).

**N-Methoxy-N-methyl-p-methylbenzamide (4f)**: ¹H NMR (300 MHz, CDCl₃) δ 7.59 (d, J=8.0 Hz, 2H), 7.19 (d, J=8.0 Hz, 2H), 3.55 (s, 3H), 3.34 (s, 3H), 2.38 (s, 3H); FT-IR (film) 3029, 2967, 2934.
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1643 (C=O), 1613, 1377, 1181, 830 cm⁻¹; Ms m/z (%) 179 (M⁺, 2), 120 (10), 119 (p-CH₃-C₆H₄-CO⁺, 100), 91 (44).

N-Methoxy-N-methyl-p-chlorobenzamide (4h)  
¹H NMR (300 MHz, CDCl₃) δ 7.65 (d, J=6.8 Hz, 2H), 7.27 (d, J=6.8 Hz, 2H), 3.53 (s, 3H), 3.35 (s, 3H); FT-IR (film) 3067, 2971, 2935, 1646 (C=O), 1594, 1380, 1091, 840 cm⁻¹; Ms m/z (%) 199 (M⁺, 2), 141 (34), 139 (p-Cl-C₆H₄-CO⁺, 100), 113 (11), 111 (34), 75 (16).

N-Methoxy-N-methyl-α-naphthalamide (4i): M.p. 38 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.86-7.91 (m, 3H), 7.46-7.56 (m, 4H), 3.52 (s, 3H), 3.42 (s, 3H); FT-IR (KBr) 3056, 2971, 2934, 1650 (C=O), 1592, 1374, 1102, 800, 778 cm⁻¹; Ms m/z (%) 215 (M⁺, 8), 156 (13), 155 (C₆H₄-CO⁺, 100), 128 (9), 127 (70).

N-Methoxy-N-methyl-2-thiophene carboxamide (4j): ¹H NMR (300 MHz, CDCl₃) δ 7.97 (dd, J=3.8 Hz, J=1.1 Hz, 1H), 7.56 (dd, J=5.0 Hz, J=1.1 Hz, 1H), 7.11 (dd, J=5.0 Hz, J=3.8 Hz, 1H), 3.78 (s, 3H), 3.38 (s, 3H); FT-IR (film) 3096, 2974, 2936, 1633 (C=O), 1423, 1383, 1208, 979, 728 cm⁻¹; Ms m/z (%) 171 (M⁺, 10), 112 (7), 111 (C₆H₄SCO⁺, 100), 83 (8).

RESULTS AND DISCUSSION

S-2-Pyridyl thiocarbamate (1) was prepared by the addition of N,N-dimethylhydroxylamine hydrochloride (3) and triethylamine to a solution of S,S-di(2-pyridyl)dithiocarbonate (2) in dichloromethane at 0 °C (Scheme 1). The reaction proceeded smoothly with the selective substitution of 2-thiopyridyl group by 3 within 1 h at 0 °C. After usual aqueous workup, the condensed residue was purified by silica gel column chromatography using 50% EtOAc/n-hexane as an eluant to give 1 in 91% yield. The reagent 1 could be stored in a refrigerator for several months without any decomposition.

The successful preparation of N-methoxy-N-methylamides (4) using 1 depends largely on the selective substitution of 2-thiopyridyl group. We anticipated that 2-thiopyridyl group capable of forming 6-membered chelate would be more reactive than N-methoxy-N-methylamino group toward Grignard reagent. Thus, the treatment of 1 with 1 equiv of p-methoxyphenylmagnesium bromide at 0 °C over a period of 10 min gave N-methoxy-N-methyl-p-methoxybenzamide (4g) in 90% yield without appreciable side products. The preferential formation of 4 is presumably due to the stability of 6-membered chelate between magnesium atom of Grignard reagent and carbonyl oxygen/nitrogen atom of 1, which dissociates to give 4 after hydrolysis.

As shown in Table 1, various N-methoxy-N-methylamides were synthesized in high yields (74-91%) by this method. The reaction proceeded smoothly for both aliphatic (4a-4c) and aromatic Grignard reagents (4d-4j). Furthermore, the kind of electron donating (4f, 4g) and electron withdrawing group (4h) in p-substituted phenylmagnesium bromide didn't influence on the selective substitution of 2-thiopyridyl group. However, the reaction of 1 with phenylethynylmagnesium bromide (4e), α-methylphenylmagnesium bromide (4e), and α-naphthylmagnesium bromide (4i) required 1.5 equiv of Grignard reagent due to the decreased nucleophi-

Scheme 1.
licity or steric effect for the high yield formation of the corresponding N-methoxy-N-methylamides.

In conclusion, the present method provides a new synthesis of N-methoxy-N-methylamides using 1 from alkyl halides in connection with (i) availability of starting material (ii) convenience of one step operation (iii) high yield of 4 and may be utilized in many synthetic applications.

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REFERENCES


Table 1. Preparation of N-methoxy-N-methylamides from S-2-pyrrolid thio carbamate and Grignard reagents a

<table>
<thead>
<tr>
<th>Entry</th>
<th>RMgBr, R</th>
<th>Reaction time, h</th>
<th>Product</th>
<th>Isolated yield, %</th>
</tr>
</thead>
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<tr>
<td>a</td>
<td>CH3(CH3)2</td>
<td>0.3</td>
<td>CH3(CH3)2CON(Me)OMe</td>
<td>91</td>
</tr>
<tr>
<td>b</td>
<td>C6H5</td>
<td>0.5</td>
<td>C6H5CON(Me)OMe</td>
<td>84</td>
</tr>
<tr>
<td>c</td>
<td>CH3-C=CH2</td>
<td>2</td>
<td>CH3-C=CH-CON(Me)OMe</td>
<td>75</td>
</tr>
<tr>
<td>d</td>
<td>C6H5</td>
<td>0.3</td>
<td>C6H5CON(Me)OMe</td>
<td>84</td>
</tr>
<tr>
<td>e</td>
<td>α-CH3-C6H5H</td>
<td>2</td>
<td>α-CH3-C6H5CON(Me)OMe</td>
<td>74</td>
</tr>
<tr>
<td>f</td>
<td>p-C6H4-C6H5H</td>
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<td>p-C6H4-C6H5CON(Me)OMe</td>
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</tr>
<tr>
<td>g</td>
<td>p-C6H4-C6H5H</td>
<td>0.3</td>
<td>p-C6H4-C6H5CON(Me)OMe</td>
<td>90</td>
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<tr>
<td>i</td>
<td>α-Naphthyl</td>
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<td>α-Naphthyl-CON(Me)OMe</td>
<td>82</td>
</tr>
<tr>
<td>j</td>
<td>2-Thienyl</td>
<td>1.5</td>
<td>2-Thienyl-CON(Me)OMe</td>
<td>85</td>
</tr>
</tbody>
</table>

a The Grignard reagents were added at 0 °C over 10 min. b RMgCl was used.

1.5 equiv. was used. c The reaction was carried out between 0 °C and room temperature.