Journal of the Korean Chemical Society
2005, *Vol. 49, No. 6*
Printed in the Republic of Korea

단 신

S-2-피리딜 싸이오카바메이트와 Grignard 시약으로부터 *N*-메톡시-*N*-메틸 아마이드의 새로운 합성

이재인* · 정혜진
덕성여자대학교 자연과학대학 화학과
(2005. 9. 20 접수)

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

Jae In Lee* and Hye Jin Jung
Department of Chemistry, Duksung Women's University, Seoul 132-714, Korea
(Received September 20, 2005)

주제어: *N*-메톡시-*N*-메틸 아마이드, S-2-피리딜 싸이오카바메이트, 치환, 킬레이트
Keywords: *N*-Methoxy-*N*-methylamides, S-2-Pyridyl thiocarbamate, Substitution, Chelate

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.[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 coupling reagents is the most common. The treatment of carboxylic acids and $MeONH_2MeCl$ with coupling reagents such as Ph_3P/CBr_4,[2] CDI,[3] HOBT/ DCC,[4] 2-halo-1-methylpyridinium iodide,[5] BOP·PF_6,[6] HBTU,[7] and 2-chloro-4,6-dimethoxy[1.3.5]triazine (CDMT)[8] in the presence of base affords the corresponding activated esters, which are transformed into the corresponding *N*-methoxy-*N*-methylamides by subsequent addition of $MeONH_2MeCl$ 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·PF_6, HBTU, and CDMT are expensive. The treatment of carboxylic acids with pivaloyl chloride,[9] alkyl chloroformate (R=Me,[10a] Et,[10b] *i*-Bu[10c]), and phosphonate reagents[11] 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 $MeONH_2MeCl$. 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,[12] following by the addition of $MeONH_2MeCl$. 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,[13] esters,[14] lactones,[15] and oxazolidinone carboximides[16] using $MeONH_2MeCl$/pyridine, MeONMeM (M=Li, MgCl), $Me_2AlCl/MeONH_2MeCl$, and $Me_2AlN(OMe)Me$, 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-

samination.

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,[17] 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)dithiocarbonate (1.24 g, 5.0 mmol) in dichloromethane (20 mL) was added *N,O*-dimethylhydroxylamine hydrochloride (487.8 mg, 5.0 mmol) and triethylamine (697 μL, 5.0 mmol) at 0 °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 $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using 50% EtOAc/*n*-hexane as an eluant to give **1** (902.4 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60-8.63 (m, 1H), 7.70-7.72 (m, 2H), 7.25-7.30 (m, 1H), 3.83 (s, 3H), 3.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 152.6, 150.5, 137.3, 131.2, 123.7, 62.4, 34.8; FT-IR (film) 3050, 2977, 2937, 1672 (C=O), 1573, 1451, 1341, 1175, 1073, 985, 771 cm^{-1}; Ms *m/z* (%) 198 (M^-, 1), 167 (47), 138 (58), 110 (14), 78 ($C_5H_4N^-$, 100).

Preparation of *N*-methoxy-*N*-methyl-*p*-methoxybenzamide (4g) <typical procedure>. To a solution of **1** (396.7 mg, 2.0 mmol) in THF (6 mL) cooled to 0 °C was slowly added *p*-methoxyphenylmagnesium bromide (0.25 M in THF, 8.0 mL, 2.0 mmol) over 10 min under argon atmosphere. After being stirred for 10 min, the mixture was quenched with sat. NH_4Cl (3 mL) and THF was evaporated *in vacuo*. The mixture was poured into sat. NH_4Cl (30 mL) and extracted with dichloromethane (3×25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and evaporated to dryness *in vacuo*. The crude product 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. ^{1}H NMR (300 MHz, $CDCl_3$) 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*-CH_3O-$C_6H_4CO^-$, 100), 92 (12), 77 (14).

***N*-Methoxy-*N*-methylnonamide (4a)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.18 (s, 3H), 2.41 (t, *J*=7.6 Hz, 2H), 1.56-1.68 (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 [$CH_3(CH_2)_7CO^-$, 100], 71 (66), 61 (71), 57 (72), 55 (30).

***N*-Methoxy-*N*-methylcyclohexanecarboxamide (4b)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.18 (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 (39), 83 (*c*-$C_6H_{11}^-$, 100), 55 (44).

***N*-Methoxy-*N*-methylphenylpropiolamide (4c)**: M.p. 37 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 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 ($C_6H_5C_2CO^-$, 100), 101 (6), 75 (10).

***N*-Methoxy-*N*-methylbenzamide (4d)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.68 (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 ($C_6H_5CO^-$, 100), 77 (50).

***N*-Methoxy-*N*-methyl-*o*-methylbenzamide (4e)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.32 (m, 4H), 3.53 (s, 3H), 3.30 (s, 3H), 2.34 (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*-CH_3-$C_6H_4CO^-$, 100), 91 (53), 65 (14).

***N*-Methoxy-*N*-methyl-*p*-methylbenzamide (4f)**: ^{1}H NMR (300 MHz, $CDCl_3$) 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,

1643 (C–O), 1613, 1377, 1181, 830 cm^{-1}; Ms *m/z* (%) 179 (M^+, 2), 120 (10), 119 (*p*-CH_3-$C_6H_4CO^+$, 100), 91 (44).

***N*-Methoxy-*N*-methyl-*p*-chlorobenzamide (4h)**: ^1H NMR (300 MHz, $CDCl_3$) 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-$C_6H_4CO^+$, 100), 113 (11), 111 (34), 75 (16).

***N*-Methoxy-*N*-methyl-α-naphthamide (4i)**: M.p. 38 °C; ^1H NMR (300 MHz, $CDCl_3$) 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 ($C_{10}H_7CO^+$, 100), 128 (9), 127 (70).

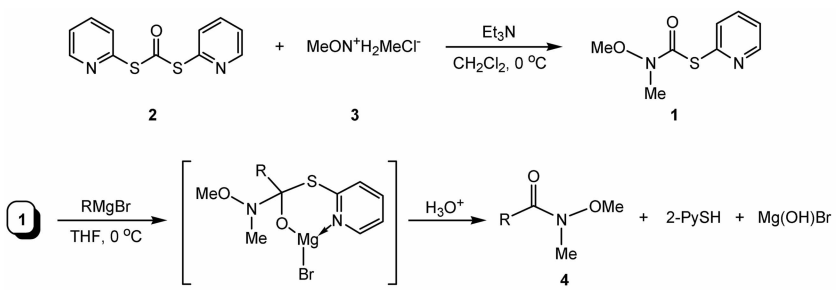
***N*-Methoxy-*N*-methyl-2-thiophenecarboxamide (4j)**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, J_1=3.8 Hz, J_2=1.1 Hz, 1H), 7.56 (dd, J_1=5.0 Hz, J_2=1.1 Hz, 1H), 7.11 (dd, J_1=5.0 Hz, J_2=3.8 Hz, 1H), 3.78 (s, 3H), 3.38 (s, 3H); FT-IR (film) 3096, 2974, 2936, 1633 (C=O), 1423, 1383, 1208, 979, 728 cm^{-1}; Ms *m/z* (%) 171 (M^+, 10), 112 (7), 111 ($C_4H_3SCO^+$, 100), 83 (8).

RESULTS AND DISCUSSION

S-2-Pyridyl thiocarbamate (**1**) was prepared by the addition of *N,O*-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/ring 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 (**4c**), *o*-methylphenylmagnesium bromide (**4e**), and α-naphthylmagnesium bromide (**4i**) required 1.5 equiv of Grignard reagent due to the decreased nucleophi-



Scheme 1.

Table 1. Preparation of *N*-methoxy-*N*-methylamides from S-2-pyridyl thiocarbamate and Grignard reagents[a]

Entry 4	RMgBr, R	Reaction time, h	Product	Isolated yield, %
a	$CH_3(CH_2)_7$[b]	0.3	$CH_3(CH_2)_7CON(Me)OMe$	91
b	*c*-C_6H_{11}[b]	0.5	*c*-$C_6H_{11}CON(Me)OMe$	84
c	$C_6H_5-C\equiv C$[c]	2[d]	$C_6H_5-C\equiv C-CON(Me)OMe$	75
d	C_6H_5	0.3	$C_6H_5CON(Me)OMe$	84
e	*o*-CH_3-C_6H_4[c]	2[d]	*o*-CH_3-$C_6H_4CON(Me)OMe$	74
f	*p*-CH_3-C_6H_4	0.3	*p*-CH_3-$C_6H_4CON(Me)OMe$	89
g	*p*-CH_3O-C_6H_4	0.3	*p*-CH_3O-$C_6H_4CON(Me)OMe$	90
h	*p*-Cl-C_6H_4	0.3	*p*-Cl-$C_6H_4CON(Me)OMe$	90
i	α-Naphthyl[c]	1.5[d]	α-Naphthyl-CON(Me)OMe	82
j	2-Thienyl	1.5	2-Thienyl-CON(Me)OMe	85

[a]The Grignard reagents were added at 0 °C over 10 min. [b]RMgCl was used.
[c]1.5 equiv was used. [d]The reaction was carried out between 0 °C and room temperature.

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.

Acknowledgment. We are very grateful to Duksung Women's University for its financial support (2005).

REFERENCES

1. (a) For a review on the applications of *N*-methoxy-*N*-methylamides: Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (c) Liu, J.; Ikemoto, N.; Petrillo, D.; Armstrong, J. D. *ibid.* **2002**, *43*, 8223.
2. Einhorn, J.; Einhorn, C.; Luche, J. L. *Synth. Comm.* **1990**, *20*, 1105.
3. Poss, M. A.; Reid, J. A. *Tetrahedron Lett.* **1992**, *33*, 1411.
4. Brenner-Weiß, G.; Giannis, A.; Sandhoff, K. *Tetrahedron* **1992**, *48*, 5855.
5. Sibi, M. P.; Stessman, C. C.; Schultz, J. A.; Christensen, J. W.; Lu, J.; Marvin, M. *Synth. Comm.* **1995**, *25*, 1255.
6. (a) Fehrentz, J. A.; Castro, B. *Synthesis* **1983**, 676. (b) Shreder, K.; Zhang, L.; Goodman, M. *Tetrahedron Lett.* **1998**, *39*, 221.
7. Wen, J. J.; Crews, C. M. *Tetrahedron: Asymmetry* **1998**, *9*, 1855.
8. (a) Luca, L. D.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534. (b) Hioki, K.; Kobayashi, H.; Ohkihara, R.; Tani, S.; Kunishima, M. *Chem. Pharm. Bull.* **2004**, *52*, 470.
9. Raghuram, T.; Vijaysaradhi, S.; Singh, I.; Singh, J. *Synth. Comm.* **1999**, *29*, 3215.
10. (a) Lucet, D.; Gall, T. L.; Mioskowski, C.; Ploux, O.; Marquet, A. *Tetrahedron: Asymmetry* **1996**, *7*, 985. (b) Falorni, M.; Giacomelli, G.; Spanedda, A. M. *ibid.* **1998**, *9*, 3039. (c) Angelastro, M. R.; Peet, N. P.; Bey, P. *J. Org. Chem.* **1989**, *54*, 3913.
11. (a) Irako, N.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1992**, *48*, 7251. (b) Dechantsreiter, M. A.; Burkhart, F.; Kessler, H. *Tetrahedron Lett.* **1998**, *39*, 253.
12. Woo, J. C. S.; Fenster, E.; Dake, G. R. *J. Org. Chem.* **2004**, *69*, 8984.
13. Aidhen, I. S.; Ahuja, J. R. *Tetrahedron Lett.* **1992**, *33*, 5431.
14. (a) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461. (b) Andres, J. M.; Pedrosa, R.; Perez-Encabo, A. *Tetrahedron* **2000**, *56*, 1217. (c) Iseki, K.; Asada, D.; Kuroki, Y. *J. Fluorine Chem.* **1999**, *97*, 85.
15. Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685.
16. Davis, F. A.; Kasu, P. V. N. *Tetrahedron Lett.* **1998**, *39*, 6135.
17. (a) Lee, J. I.; Park, H. *Bull. Korean Chem. Soc.* **2001**, *22*, 421. (b) Lee, J. I.; Park, H. *ibid.* **2002**, *23*, 521.