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N-METHOXY-N-METHYLAMIDES AS EFFECTIVE ACYLATING AGENTS

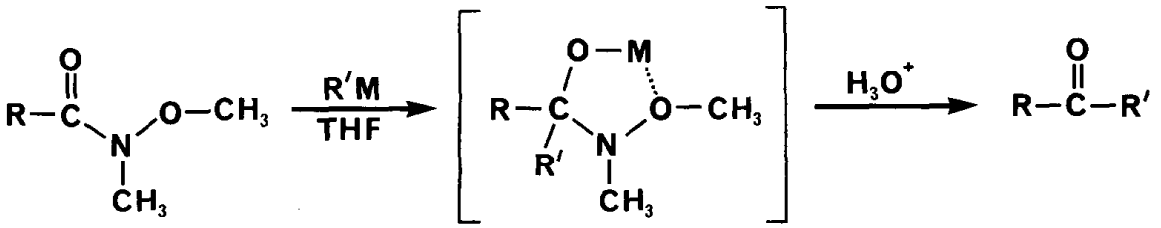
Steven Nahm and Steven M. Weinreb*

Department of Chemistry
The Pennsylvania State University
University Park, PA 16802

Summary: Readily preparable N-methoxy-N-methylamides couple in good yields with Grignard and organolithium reagents to produce ketones, and are reduced with hydrides to afford aldehydes.

Synthesis of ketones from compounds in the carboxylic acid oxidation state via coupling with various organometallics has been extensively investigated over the past few decades.[1] One major difficulty generally associated with this type of method is the propensity of reactive Grignard and organolithium reagents to overadd to the substrate, producing a tertiary alcohol. Several elegant solutions to this problem have been described recently,[1] but most require carefully controlled, low-temperature addition of one equivalent or less of organometallic to an appropriate carboxylic acid derivative.

We have discovered that N-methoxy-N-methylamides combine cleanly with both Grignard reagents and organolithium species in THF to form ketones (Scheme I). Significantly, these reactions do not produce teriary alcohols even when large excesses of organometallic are used, and do not require the stringent experimental conditions crucial to the success of many other methods. We believe that this conversion procedes through a very stable metal-chelated intermediate (Scheme I), which probably accounts for the observed lack of over-addition products.



Scheme I

N-Methoxy-N-methylamides are routinely prepared from commercially available N,O-dimethylhydroxylamine hydrochloride and an acid chloride or other activated derivative. These compounds

show normal tertiary amide stability and thus require no special handling or storage.

Table 1 shows the reaction conditions and purified yields of ketones isolated in a number of tests of this method. As can be seen, product yields are high if reactions are run with 1.1 equivalent of organometallic reagent, or if any sort of excess is used. No significant amounts of over-addition products have been detected in the examples listed.

We have also found that N-methoxy-N-methylamides can be conveniently reduced to aldehydes (Table 1). Reduction with a large excess of $LiAlH_4$ produces primarily aldehyde along with only a small amount of the corresponding primary alcohol. Dibal reduction similarly yields the aldehyde with trace amounts of alcohol detectable in some cases.[3]

We believe that the chemistry described here provides a superior method for acylation of various organometallics, and for reduction of compounds in the carboxylic acid oxidation state to aldehydes.[5]

Preparation of N-Methoxy-N-methylamides. In a typical procedure 1 mmol of acid chloride and 110 mg (1.1 mmol) of N,O-dimethylhydroxylamine hydrochloride was dissolved in 10 mL of ethanol-free chloroform at room temperature.[6] The solution was cooled to 0°C and 185 mg (2.2 mmol) of pyridine was added. The mixture was stirred at ambient temperature for 1h and evaporated in vacuo. The residue was partitioned between brine and a 1:1 mixture of ether and methylene chloride. The organic layer was dried with sodium sulfate and concentrated to afford the amide which was purified by silica gel chromatography or by distillation.

General Procedure for Acylation Reactions and Reductions. To a solution of 1 mmol of N-methoxy-N-methylamide in 10 mL of dry THF was added the desired amount of organometallic reagent at low temperature. The reaction mixture was stirred at the desired temperature (Table 1) until TLC showed no starting amide. The reaction was poured into 5% HCl in ethanol at 0° and the mixture was partitioned between brine and a 1:1 mixture of ether and methylene chloride. The organic extract was dried with Na_2SO_4 and evaporated in vacuo. The product was purified by preparative TLC on silica gel, affording pure material in the yield shown in Table 1.

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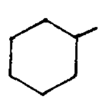
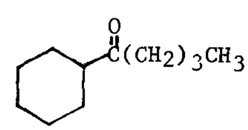
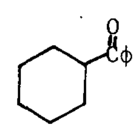
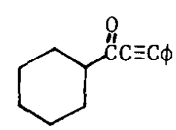
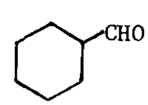
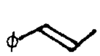
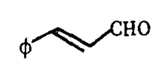
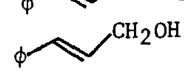
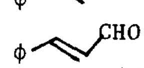
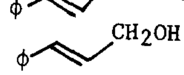
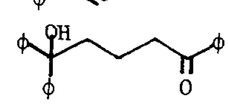
Table 1. Addition of Organometallics and Hydrides to N-Methoxy-N-methylamides in THF (Scheme I).

R	R'M (equiv.)	Reaction Time	Reaction Temperature(°C)	Product(s)	Isolated Yield (%)[4]
φ-	CH_3MgBr (1.1)	1h	0°	φC(O)CH_3	93
	CH_3MgBr (3)	1h	0°		95
	CH_3MgBr (75)	1h	0°		96
	n-BuMgCl (3)	1h	0°	φC(O)$(CH_2)_3CH_3$	91
	n-BuLi (2)	1h	0°		84
	φMgBr (3)	1h	0°	φC(O)φ	93
	φLi (2)	1h	0°		95
	φC≡CMgBr (1.5)	1.5h	65°	φC(O)C≡Cφ	92
	φC≡CLi (1.1)	1h	20°		90
	$LiAlH_4$ (xs)	8 min	-78°	φCHO +	67
				φCH_2OH	5
	Dibal (xs)	1h	-78°	φCHO	71
n-$C_{17}H_{35}$-	CH_3MgBr (2)	1h	0°	n-$C_{17}H_{35}$C(O)CH_3	94
	Dibal (xs)	30 min	0°	n-$C_{17}H_{35}$CHO	71
	$LiAlH_4$ (xs)	5 min	-78°	n-$C_{17}H_{35}$CHO +	50
				n-$C_{17}H_{35}CH_2OH$	25
	n-BuMgCl (1.5)	1.5h	25°		97
	n-BuLi (1.5)	30 min	0°		86
	n-BuLi (15)	30 min	0°		94
	φMgBr (6)	1h	65°		100
	φLi (3.3)	1h	65°		92
	φC≡CMgBr (1.1)	1h	65°		92
	φC≡CLi (1.1)	1h	65°		87
	Dibal (xs)	30 min	0°		74
	$LiAlH_4$(xs)	7 min	-78°	 +	70
					14
	Dibal (xs)	30 min	0°	 +	76
					3
CH_3OC(O)$(CH_2)_3$-	φMgBr (6)	45 min	65°		98

References and Notes

(1) see inter alia: (a) Shirley, D.A. Org. React. 1954, 8, 28. (b) Jorgenson, M.J. Org Reac 1970, 18, 1. (c) Mukaiyama, T. Araki, M.; Takai, H. J. Am. Chem. Soc. 1973, 95, 4763. (d) Meyers, A.I.; Comins, D.L. Tetrahedron Lett. 1978, 5179. (e) Kende, A.S.; Scholz, D.; Schneider, J. Syn. Commun. 1978, 59. (f) Sato, F.; Inoue, M.; Oguro, K.; Sato, M. Tetrahedron Lett. 1979, 4303. (g) Kikkawa, I.; Yorifuji, T. Synthesis 1980, 877.

(2) Available from Aldrich; Sigma; Pfaltz and Bauer.

(3) We have not attempted these reductions with stoichiometric amounts of hydride.

(4) Yields have not been optimized and most reactions were run only once.

(5) Interestingly, 1,2,2-trimethylhydrazides are generally unreactive towards addition of nucleophiles to the carbonyl group: Knapp, S.; Toby, B.H.; Sebastian, M.; Krogh-Jesperson, K.; Potenza, J.A. J. Org. Chem. 1981, 46, 2490; Knapp, S.; Calienni, J. Synth. Commun. 1980, 10, 837.

(6) Ethanol was removed by washing the chloroform with water, drying and distilling immediately before use.

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