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Regiocontrolled Synthesis of β-Trimethylsilyloxy Carbonyl Compounds through an Aldol-Grignard Elaboration Sequence.

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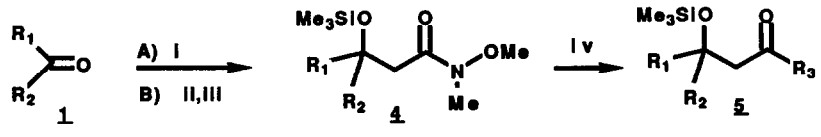
Abstract: Reaction of carbonyl compounds with α-lithio- or α-halozinc N-methoxy-N-methylamides, followed by silylation and Grignard addition resulted in a regiocontrolled synthesis of β-trimethylsilyloxy carbonyl compounds.

The aldol addition of an enolate anion derived from a carbonyl compound for the construction of a carbon-carbon bond is one of the most important operations in organic synthesis[1]. Among various problems associated with this process, the controlled cross-aldol addition between two dissimilar carbonyl compounds becomes of crucial importance[2]. Although modern variants and selective procedures have been developed to solve this problem[3], the introduction of new and simple methodologies to obtain one of the possible regio-aldols is still of considerable interest. Yamamoto[4] introduced the Reformatsky type reaction between α-halo ketones and carbonyl compounds induced by zinc in combination with dialkylaluminium chloride as an approach to the above problem[5]. However, from this methodology, regioespecific formation of the corresponding α-halo ketones as starting materials is required. Reported here is a general method for a regiocontrolled synthesis of β-trimethylsilyloxycarbonyl compounds through an aldol-Grignard elaboration sequence. Our approach to this problem is based on the straightforward conversion of the N-methoxy-N-methyl amide function into a carbonyl group discovered by Weinreb and Nahm[6]. We have found that α-bromo N-methoxy-N-methylacetamide **2** (10mmol) reacted with carbonyl compounds **1** (5mmol) in the presence of zinc powder (15mmol) and trimethylchlorosilane[7] (15mmol) in tetrahydrofuran as solvent, to provide the corresponding β-trimethylsilyloxy carbonyl compounds **4** in good to excellent isolated yield. Conversion of **1** into **4**, usually proceeds at room temperature within 1h and 1.5h, and the reaction works well with both enolizable and nonenolizable carbonyl compounds[8]. The final step of the method was easily accomplished by addition of the desired organometallic reagent to the amide function under standard protocol[6]. Results in Table 1 (Method A) illustrate the general utility of this simple aldol type-Grignard sequence. In general, the addition of the organometallic reagent (1.5 equiv.) proceeded smoothly at -40ºC in tetrahydrofuran or diethyl ether as solvents to provide after workup the desired β-trimethylsilyloxy carbonyl compound in good isolated yield. The overall sequence could also be carried out in a single operation by addition of the Grignard reagent (1.3equiv.) to the reaction mixture of the Reformatsky adduct.



Scheme 1. Reagents and Conditions: **A**: **i**, $BrCH_2CON(Me)OMe$ **2**, Zn, $ClSiMe_3$, THF, r.t. **B**: **ii** $MeCON(Me)OMe$ **3**, LDA, THF,-78ºC. **iii**, NEt_3, $ClSiMe_3$ **iv**, R_3MgX, THF or Et_2O, -40ºC—>r.t.;1h.

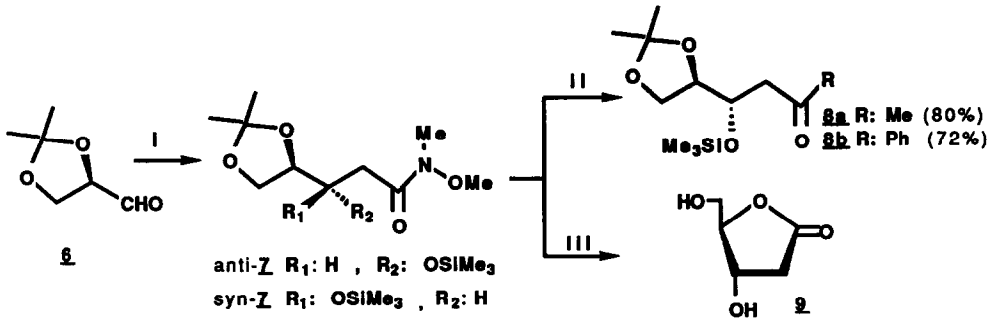
To determine the scope of the method, we next explored the addition of the lithium enolate of N-methoxy-N-methylacetamide **3** to the carbonyl compound **1**. The choice of **3** was based on Rathke's[9] success in reactions of other amide enolates with various electrophiles. Conversion of **1** into **4** was accomplished in the usual way by adding a solution of **1** to the preformed lithium enolate of **3**[10] (1.2 equiv.) in tetrahydrofuran at -78°C. After stirring for 1h at room temperature, triethylamine (1 equiv.) and trimethylchlorosilane (1.1equiv.) were added and the mixture was further stirred (1h, r.t.). After usual workup, the corresponding β-trimethylsilyloxy amides **4** were isolated in comparable yields as above.

Table. Preparation of β-trimethylsilyloxy Carbonyl Compounds[a,b]

Carbonyl compound **1**	Method	Product 4		Product 5		
		Yield[c],%	b.p. °C/mmHg[d]	R_3	Yield[c],%	b.p. °C/mmHg[d]
C_6H_5CHO	A	73	120/0.05	Me	81	135/0.01
	B	82	———	$MeOC_6H_4$	73	160/0.005
$4\text{-}ClC_6H_4CHO$	A	76	135/0.01	Et	65	180/0.005
	B	70	———			
$C_6H_5CH(Me)CHO$	A	68	200/0.02	$CH_2CH{=}CH_2$	76	120/0.01
	B	70	———			
$(E)C_6H_5CH{=}C(Me)CHO$	A	70	160/0.02	C_6H_5	61[e]	
	B	81	———			
cyclohexanone	B	72	95/0.02	Me	70	70/0.01
pinacolone	B	63[f]	170/15[f]			

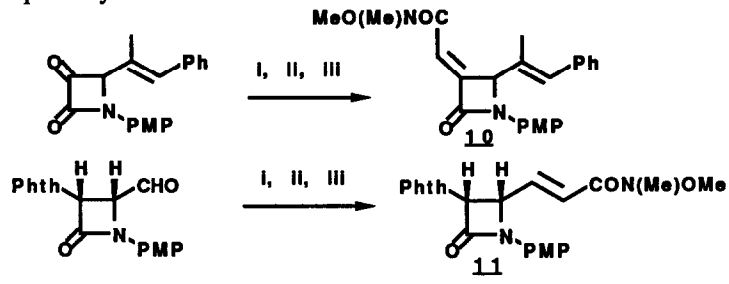
[a]Reactions conducted on 5mmol scale. [b]All compounds gave consistent analytical and spectroscopic data [c]Yields were not optimized and refer to isolated pure products. [d]Uncorrected boiling points observed during distillation with Kügelrohr apparatus. [e]Isolated as 1,5-diphenyl-4-methyl-2,4-pentadien-1-one [m.p: 76-78°C (MeOH)]. [f]Reaction carried out in Et_2O. Only desilylated product (β-hydroxyamide) was obtained.

In view of the results obtained, the reaction sequence was examined from 2,3-O-isopropylidene-D-glyceraldehyde **6** as starting material (Scheme 2). The choice of this aldehyde was based on its increasing utility as chiral building block for organic synthesis[11]. The aldol reaction was first carried out by adding the aldehyde over the preformed lithium anion of **3** at -78°C and warming the reaction mixture to room temperature for 2h. After silylation and workup of the reaction crude, a mixture of *anti*-**7** and *syn*-**7** (molar ratio: 81/19) was obtained in 78% isolated yield. When the reaction was performed entierely at -78°C, the *anti/syn* ratio could be increased up to 95/5. The subsequent treatment of **7** with Grignard reagents, afforded the compounds **8** as single isomers in good yields[12]. The *anti* relative configuration of compound **7** was confirmed by its transformation into **9**, following a protocol similar to this described by.Kita et al.[13].



Scheme 2. Reagents and Conditions: **i** MeCON(Me)OMe **3**, LDA, THF, -78°C, 2h. then, NEt_3, $ClSiMe_3$, -78°C, 2h **ii**, RMgX, THF or Et_2O, **iii** F_3C-CO_2H-H_2O (1:1), reflux, 2h.

On the other hand, the procedure can also be applied to the preparation of α,β-unsaturated carbonyl compounds by dehydration[7b] of compounds **4** and subsequent Grignard addition[14]. For example, this sequence was successfully used for the synthesis of β-lactams derivatives **10** and **11** in 71% and 59% overall yields, respectively.



Scheme 3. Reagents and Conditions: **i** MeCON(Me)OMe **3**, LDA, THF, -40°C, 1h. **ii** $MeSO_2Cl$, NEt_3, CH_2Cl_2 **iii** DBU, C_6H_6, 80°C, 30min. **PMP**: 4-methoxyphenyl group. **Phth**: phthalimido group.

In conclusion, our method represents a novel alternative to achieve regiocontrolled aldol additions. Further studies are currently under way in our laboratory for its extension to other synthetic applications.

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REFERENCES AND NOTES:

1. Hajos, Z.G. *Carbon-Carbon Bond Formation*, vol. 1; Augustine, R.L. Ed.; Marcel Dekker: New York. 1979, p. 1.
2. (a) House, H.O. *Modern Synthetic Reactions* ; 2nd ed.; Benjamin, W.A.; Reading, Mass.; 1972; p.

629. (b) Negishi, E.-I. *Organometallics in Organic Synthesis*; John Wiley: New York. 1980; p. 201. (c) Heathcock, C. *Asymmetric Synthesis*, vol. 2. Morrison, J.M. Ed.; Academic Press: New York. 1983. (d) Mukaiyama, T. *Pure and Appl. Chem.* **1983**, *55*, 1749. (e) Carruthers, W. *Some Modern Methods of Organic Synthesis*; 3rd ed.; Cambridge: London. 1986; p. 48.

3. (a) Mukaiyama, T. *Angew. Chem. Int. Ed. Engl.*. **1977**, *16*, 817. (b) Nogradi, M. *Stereoselective Synthesis*; Verlag: Berlin. 1987; p. 193.
4. (a) Fukuzawa, S.I.; Tsuruta, T.; Fujinami, T.; Sakai, S. *J. Chem. Soc; Perkin Trans I*. **1987**, 1473. (b) Marouka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.*, **1977**, *99*, 7705. For related reactions, see: Dubois, J.-E.; Axiotis, G.; Bertounesque, E.; *Tetrahedron Lett.*. **1985**, *26*, 4371. Nozaki, N.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1041. Huang, Y.-Z.; Chem, C.; Shen, Y. *J. Chem. Soc; Perkin Trans I*. **1988**, 2855, and references therein.
5. For recent reviews on Reformatsky reaction, see: (a) Miginiac, L. *The Chemistry of the Metal-Carbon Bond*; Hartly, F.R. and Patai, S. Eds.; vol. 3; Wiley: New York, 1985; p. 99. (b) Fürstner, A. *Synthesis*, **1989**, 571.
6. Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.*. **1981**, *22*, 3815.
7. For the use of trimethylchlorosilane in related Reformatsky reactions, see: (a) Picotin, G.; Miginiac, P. *J. Org. Chem.* **1987**, *52*, 4796. (b) Palomo, C.; Aizpurua, J.M.; López, M.C.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31*, 2205. (c) Palomo, C.; Aizpurua, J.M.; Aurrekoetxea, N. *Tetrahedron Lett.*. **1990**, *31*, 2209. (d) Palomo, C.; Aizpurua, J.M.; López, M.C.; Aurrekoetxea, N.; Oiarbide, M. *Tetrahedron Lett.* **1990**, *31*, 6269.
8 For aromatic aldehydes, the products **4** were obtained toghether with the corresponding 1,2-bis(trimethylsilyloxy)-1,2-diarylethanes in less than 5%, see So, J.-H.; Park, M.K.; Budjouk, P. *J. Org. Chem.* **1988**, *53*, 5871.
9. Woodbury, R.P.; Rathke, M.W. *J. Org. Chem.* **1977**, *42*, 1688.
10. While our work was in progress, a paper dealing with the behaviour of N-methoxy-N-methylamides towards strong bases was appeared, see Graham, S.L.; Scholz, T.H. *Tetrahedron Lett.* **1990**, *31*, 6269.
11. For reviews, see: (a) McGarvey, G.J.; Kimura, M.; Oh, T.; Williams, J.M. *Carbohydr. Chem.* **1984**, *3*, 125. (b) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron*. **1986**, *42*, 447.
12. Representative data: *anti*-**7**: b.p: 150°C/0.02Torr. ^{1}H-NMR($CDCl_3$ δ ppm): 4.22 (m, 1H, $C_{(4)}H$), 3.93-4.01 (m, 2H, $C_{(5)}H_2$), 3.78 (m, 1H, J: 3.5Hz, J: 8.5Hz, $C_{(3)}H$), 3.65 (s, 3H, OCH_3), 3.13 (s, 3H, N-CH_3), 2.35-2.74 (m, CH_2CO), 1.36 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 0.12 (s, 9H, $SiMe_3$). MS: *m/e* (M^+-15): 290. **8a**: b.p. 85°C/0.01Torr. ^{1}H-NMR($CDCl_3$ δ ppm): 4.11 (m, 1H, CHOC), 3.96, 3.88 (m, 1H,1H, CH_2O), 3.73 (m, 1H, CHOSi), 2.59, 2.54 (dd, 1H, 1H, CH_2CO), 2.13 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 0.06 (s, 9H, $SiMe_3$). MS: *m/e* (M^+-15): 245. **11**: Syrup. ^{1}H-NMR($CDCl_3$ δ ppm): 7.85-7.72 (m, 4H, arom.), 7.39 (d, 2H, arom.), 6.95 (dd, 1H, CH=, J: 6.4Hz, J: 15.8Hz), 6.87 (d, 2H, arom.), 6.74 (d, 1H, CH=, J: 15.8 Hz), 5.65 (d, 1H, $C_{(3)}H$, J: 5.6Hz), 5.05 (dd, 1H, $C_{(4)}H$, J: 6.4Hz, J: 5.7Hz), 3.78 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.12 (s, 3H, CH_3). Anal. calcd. for $C_{23}H_{21}N_3O_6$: C, 63.44; H, 4.86; N, 9.65. Found: C, 63.83; H, 5.04, N, 9.72.
13. Kita, Y.; Tamura, O.; Itoh, F.; Yasuda, H.; Kishino, H.; Ke, Y.Y.; Tamura, Y. *J. Org. Chem.* **1988**, *53*, 554. See also, Heathcock, C.H.; Young, S.D.; Hagen, J.P.; Pirrung, C; White, C.T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846.
14. Nuzillard, J.M.; Boumendjel, A.; Massiot, G. *Tetrahedron Lett.* **1898**, *30*, 3779.

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