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TANDEM ORGANOMETALLIC ADDITION REACTIONS TO *N*-METHOXY-UREAS AND URETHANES IN THE PREPARATION OF UNSYMMETRICAL AND SYMMETRICAL KETONES

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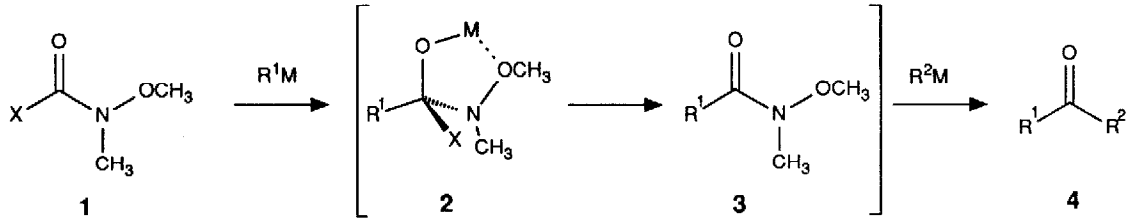
The use of the novel reagents ***1a-c*** *for the synthesis of ketones in a one pot reaction is described. An interesting leaving group effect was discovered in the fragmentation of the proposed complexes* ***2*** *to the intermediate N-methoxyamides* ***3****.*

The development of methods for the preparation of ketones by organometallic addition reactions to carbon dioxide and carbon monoxide equivalents has been a topic of special interest in the literature.[1] A particularly difficult task has been to devise a one pot reaction to yield unsymmetrical ketones through the tandem addition of two organometallic reagents to a carbon dioxide equivalent. This has been accomplished by Marchese and co-workers;[2] however, their method has the disadvantage of using heavy metal catalysis. This report describes a more advantageous one pot reaction for the preparation of unsymmetrical and symmetrical ketones in good yields without the use of heavy metals. Nahm and Weinreb have prepared unsymmetrical ketones through the addition of organolithium or Grignard reagents to various *N*-methoxy-*N*-methylamides (**3**).[3] Our method complements their method in that the methoxyamides **3** are formed in situ.



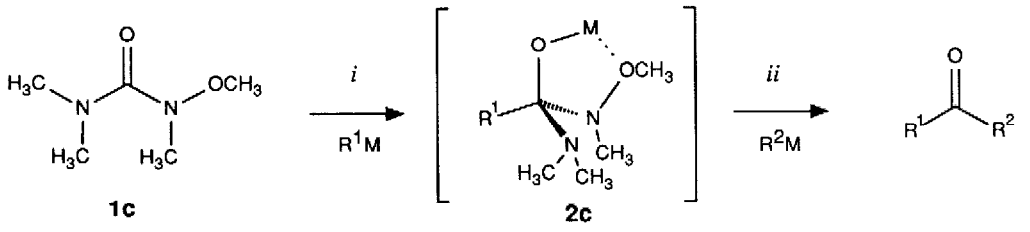
1 **2** **3** **4**

a X = OEt; **b** X = $NOCH_3$ (CH_3); **c** X = $N(CH_3)_2$

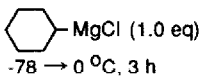
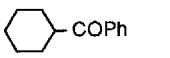
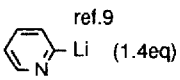
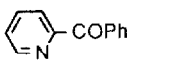
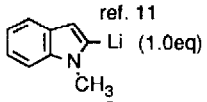
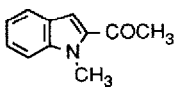
We wished to design a reagent such as **1** that would be useful as a carbon dioxide equivalent in addition reactions with organometallics. We reasoned that if the nucleophilic addition of an organolithium to **1** produced a discrete complex **2**, and the complex fragmented to give the methoxyamide **3** in situ, then reaction of a second organolithium would give the unsymmetrical ketone **4** in a one pot reaction. The *N*-methoxyurethane **1a** and *N,N'*-dimethoxyurea **1b** were not useful for this purpose. The urethane **1a** on addition to *n*-butyllithium or phenyllithium gave 5-nonanone and benzophenone, respectively, along with recovered starting material (**1a**). Addition of phenyllithium to **1a**, also gave a mixture consisting of benzophenone (24%) and methoxyamide **3** (R^1=Ph)(25%). The complex **2a** apparently fragments at a rate similar to the reaction of the organolithium with **1a**, thus giving mixtures. The *N,N'*-dimethoxyurea **1b** reacts with phenyllithium or with phenylmagnesium bromide (1.1 equivalent each) in tetrahydrofuran to give the methoxyamide **3** (R^1= Ph) in 95% and 91% isolated yields.[4,5] However, our attempts to prepare valerophenone by the reaction of *n*-butyllithium with the presumed

dicoordinate complex **2b** (R^1=Ph) were not successful. Treatment of the presumed complex **2b** with n-butyllithium with and without TMEDA in THF (RT to reflux) gave only methoxyamide **3** and decomposition products by TLC.

Table I. Tandem Organometallic Additions to Give Unsymmetrical Ketones.



1c **2c**

Entry	Reaction Conditions *i*	Reaction Conditions *ii*	Product	Isolated Yield(%)[4]	mp (°C) (Lit. mp)
1	PhLi (1.0eq) -78 °C, 1h	–	PhCONOCH$_3$ CH$_3$	90	oil
2	PhLi (1.0eq) -78 °C, 1.5 h	n-BuLi (1.1eq) -78 °C → RT, 2 h	PhCO-n-Bu	60	165-166.5[a] (167-168)[8]
3	PhLi (1.0 eq) -78 °C, 1 h	n-BuLi (5 eq) -78 °C → RT, 5 h	PhCO-n-Bu	62	oil
4	 -78 → 0 °C, 3 h	PhLi (1.1eq) 0 °C → RT, 1.5 h		41	55-57 (59-60)[7]
5	PhLi (1.0eq) -78 °C, 30 min	ref.9  -78 °C → RT, 5 h		60	124-126[b] (122-123)[10]
6	ref. 11  -78 → -20 °C, 1 h	MeLi (1.1eq) -78 °C → RT, 1.5 h		79	67-69 (71-72)[12]

a) As the 2,4-dinitrophenylhydrazone.
b) As the picrate.

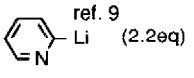
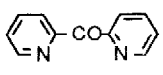
Based on the reactivity of **1a** and **1b**, we anticipated that the *N*-methoxyurea reagent (**1c**) would possess the proper reactivity and solve our synthetic problem. The dimethylamide group is a poorer leaving group than ethoxide and treatment of **1c** with phenyllithium would give a monocoordinate lithium species **2c** that should be more stable than **2a**. Indeed, the addition of **1c** to phenyllithium followed by the addition of *n*-butyllithium -78 °C → RT afforded valerophenone in 60% isolated yield (Table 1, entry 2). The reaction of excess *n*-butyllithium (5 equiv.) with **2c** (R^1=Ph) also gave valerophenone without the detection of the carbinol. The presumed

intermediate methoxyamide **3** was obtained in 90% yield on workup of the complex **2c** after 1 h at -78 °C (Table 1, entry 1). The major pathway for the reaction appears to proceed via fragmentation of the complex **2c** (R^1=Ph) in situ to give **3** and not *N,N*-dimethylbenzamide. The basis for this statement rests on the observation that at room temperature for 2 h the reaction of **2c** with *n*-butyllithium is complete. In a separate experiment the complex **2c** was formed as before and stirred at room temperature for 2 h. The major component of the reaction by GC was the methoxyamide **3** (R^1=Ph)(77%) with only 16% of *N,N*-dimethylbenzamide present.

This reaction does have some limitations regarding the nature of the organometallic reagent employed. Grignard reagents are not well behaved in these reactions. The reaction of phenylmagnesium bromide with **1c** followed by the addition of *n*-butyllithium gave the methoxyamide **3** (R^1=Ph)(43%) and *N,N*-dimethylbenzamide (36%). No valerophenone was detected. The addition of cyclohexylmagnesium chloride to **1c** followed by phenyllithium gave cyclohexyl phenylketone in only 41% yield (table 1, entry 4), while reversing the mode of addition afforded a complex mixture (TLC,GC). The best results are obtained when an aryl- or heteryllithium is added first to **1c** (table 1, entries 2,5,6), since treatment of **1c** with methyllithium and *n*-butyllithium afforded mixtures by GC. Nonetheless, the tandem addition of organolithium reagents to the *N*-methoxyurea **1c** to yield unsymmetrical ketones remains a useful one pot reaction.

Symmetrical ketones have been prepared through the addition of organolithium and Grignard reagents to *N,N*-dialkylurethanes, e.g. butylmagnesium bromide and *n*-heptyllithium were reported to give symmetrical ketones only in 53% and 25%, respectively.[6] The urethane reagent **1a** has proven to be a very useful reagent for the preparation of several symmetrical ketones (Table 2) in very good yields as the sole products. In addition, the ureas **1b** and **1c** on treatment with phenyllithium gave benzophenone in 75% and 97% yield, respectively.

Table II. Preparation of Symmetrical Ketones.

Reagent	RLi[a]	Product	Isolated Yield (%)[4]
1a	PhLi (2.2eq)	PhCOPh	93
1a	n-BuLi (2.2eq)	n-Bu-CO-n-Bu	82
1a	 ref. 9		67
1b	PhLi (5.0eq)	PhCOPh[b]	75
1c	PhLi (2.2eq)	PhCOPh	97

a) The reagent 1a, 1b, or 1c (10 mmol in 8 mL of THF) was added dropwise to a 0.4 M solution of RLi in THF at -78°C and under N_2. The cooling bath was removed, stirring continued for 1-3 h, and the reaction was worked up as described in the typical experimental.
b) 5% of N-methoxy-N-methylbenzamide was also isolated.

N-Methoxy-N,N',N'-trimethylurea **(1c):** To a stirred suspension of 42.9 g (0.44 mol) of *O,N*-dimethylhydroxylamine hydrochloride and 2.4 g (20 mmol) of 4-dimethylaminopyridine in 400 mL of methylene chloride at -20 °C (ice-methanol bath) was added dropwise 37 mL (0.4 mol) of dimethylcarbamoyl chloride followed by 81 mL (1.0 mol) of pyridine. The reaction mixture was stirred overnight at room temperature and then diluted with methylene chloride, and the organic layer was washed successively with water

ice cold 5% aqueous 3-dimethylaminopropylamine, water, ice cold 6N HCl, and water. The organic layer was dried over magnesium sulfate, filtered, and concentrated to a pale yellow liquid (38.3 g). Vacuum distillation gave 30.4 g of **1c** (57%) as a colorless liquid; bp 83-87 °C (25 mm Hg); IR (film) 1667 cm^{-1}; NMR ($CDCl_3$) δ 2.94 (s) and 2.95 (s) (9H), 3.59 (s, 3H); C^{13} NMR ($CDCl_3$) δ 162.94, 58.68, 37.66, 36.08; MS (CI), m/e 133 (MH^+); Anal. ($C_5H_{12}N_2O_2$) C, H, N.

The urethane **1a**[13,14] and the *N,N'*-dimethoxyurea **1b**[15] were prepared analogously to **1c** in 88% and 81% distilled yields from ethyl chloroformate and phosgene, respectively.

Typical Procedure - Valerophenone: To a clear brown stirred solution of 5.0 mL (10 mmol) of 2.0 M phenyllithium in cyclohexane/diethylether and 25 mL of tetrahydrofuran at -78 °C and under nitrogen was added dropwise over 9 min a solution of 1.32 g (10 mmol) of the *N*-methoxyurea **1c** in 8 mL of tetrahydrofuran. After completion of the addition, the reaction mixture was stirred at -78 °C for 1.5 h and to the resultant clear yellow solution was added 4.5 mL (11 mmol) of a 2.44 M solution of *n*-butyllithium in hexanes. The cooling bath was removed and stirring was continued 2 h. The cloudy tan mixture was cooled in an ice bath and 20 mL of 6N HCl was added. The tetrahydrofuran was removed on a rotovap and the residue was diluted with water and extracted with methylene chloride (3X). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated to give 1.65 g of a yellow oil. Flash chromatography on silica gel (50 mm x 10 in column) eluted with 2% ethyl acetate in hexanes gave 0.98 g (60%) of a pale yellow oil.

Footnotes and References:

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4. The products were purified by flash chromatography on silica and were homogeneous by TLC. All known compounds had physical (mp) and spectral properties consistent with the literature and in the case of oils, were identical by TLC and GC mobility to known samples.
5. The reagent **1b** through the addition of organolithium or Grignard reagents could prove very useful in the synthesis of *N*-methoxy-*N*-methylamides **3** that are not readily available from the corresponding acid chlorides and *O,N*-dimethylhydroxylamine.
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12. Bailey, A. S.; Barnes, C. J.; Wilkinson, P. A. *J. Chem. Soc. Perkin Trans. 1*, **1974**, 1321.
13. **1a:** bp 64-66 °C (33 mm Hg) (lit. bp 150-155 °C (atm.))[14]; IR (film) 1735, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (t, J=12 Hz, 3H), 3.15 (s, 3H), 3.69 (s, 3H), 4.22 (q, J=12 Hz, 2H); MS (CI) m/e 134 (MH^+).
14. Major, R. T.; Fleck, E. E. *J. Am. Chem. Soc.*, **1928**, *50*, 1479.
15. **1b:** bp 35-42 °C (0.1 mm Hg); IR (film) 1664 cm^1; NMR ($CDCl_3$) δ 3.07 (s, 6H), 3.66 (s, 6H); C^{13} NMR ($CDCl_3$) δ 163.23, 60.34, 35.96; MS (CI) m/e 149 (MH^+); Anal. ($C_5H_{12}N_2O_3$) C,H,N.

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