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ACETYLATIONS OF STRONGLY BASIC AND NUCLEOPHILIC ENOLATE ANIONS WITH N-METHOXY-N-METHYLACETAMIDE

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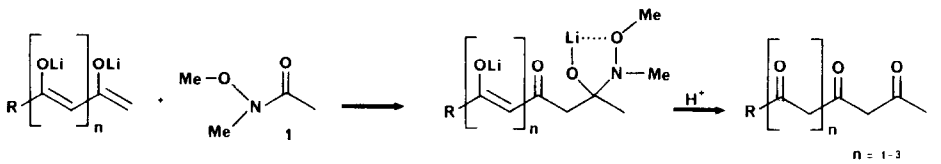
Summary: Efficient acetylation of the multiple anions of poly-β-carbonyl compounds is achieved by the use of N-methoxy-N-methylacetamide.

Methods for the stepwise acetylation of the multiple anions of oligo-β-carbonyl compounds are of interest for use in the formation of higher homologs; certain of the polycarbonyl compounds are intermediates in the biosynthesis of aromatic natural products.[1] Although the dianions of 2,4-diketones can be acetylated with ethyl acetate to give 2,4,6-triketones,[2] acetylations of the trianions of triketones and a number of other multiple anions have failed or have given only low yields because the strongly basic nucleophiles abstract a proton from the ester rather than attacking the carbonyl group.[1b,3] A variety of other acetylating agents have been investigated without success in attempts to circumvent this problem. Herein we describe the use of a new acetylating agent, N-methoxy-N-methylacetamide (1), for the acylation of lithium enolates of oligo-β-carbonyl compounds.

Amide 1 is readily prepared by treatment of commercially available O,N-dimethylhydroxylamine[4] with acetyl chloride and pyridine in methylene chloride, followed by aqueous work-up and distillation. In the reactions of 1 with nucleophiles, only one equivalent of anion is needed to achieve acetylation, in contrast to the 2:1 ratio required for acylation of anions with esters. The difference in stoichiometry is ascribed to the fact that in ester condensations the alkoxyl group is lost immediately and a second equivalent of nucleophile is expended in the ionization of the newly formed methylene group whereas in the present case the methoxylamine leaving group probably does not depart until after the reaction mixture is quenched with acid (see Scheme 1). Acetylation of the lithium salts of di-,[5] tri-,[6] and

Scheme 1

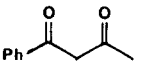
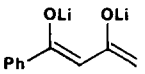
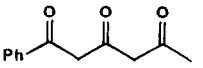
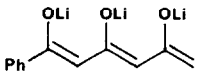
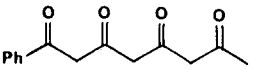
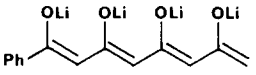
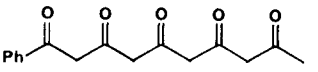
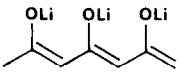
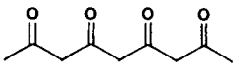


tetraanions[6b,7] of di-, tri-, and tetraketones, respectively, occurred in excellent yield, as shown in Table 1, when the nucleophiles were treated with one equivalent of 1 for 4-5 hours in THF at ambient temperatures. Work-up by evaporation of the solvent, addition of dilute acid, and extraction into ether gave material which by NMR and TLC was essentially pure. Further purification could be obtained by column chromatography but not without substantial losses of the polycarbonyl compounds on account of their unstable nature.[8] Interestingly, monoanions of simple ketones cannot be acetylated using 1; an attempted condensation of the lithium salt of acetophenone with 1 failed to give anything other than recovered starting materials even when the mixture was refluxed in THF.[9] The condensations of monoanions of ketones with esters requires ionization of the resulting β-diketone to drive an otherwise unfavorable reaction to completion. It is probable that the failure of the anion of acetophenone to condense with 1 is a thermodynamic rather than just a kinetic problem. On the other hand, the highly unstable anions of the multiple ketones achieve a degree of stabilization by condensation with 1.

Nahm and Weinreb have recently demonstrated the utility of various N-methoxyl-N-methylamides for the acylation of Grignard and organolithium reagents.[10] In these reactions the O,N-dimethylhydroxylamine also does not depart until the reaction mixture is

acidified (on account of chelation of the resulting alkoxy salt), thus avoiding the classical problem of tertiary carbinol formation during acylation of lithium and magnesium reagents with esters.

Table 1

Nucleophile	Time (hrs.)	Temperature (^{o}C)	Product	Yields,% Crude (purified)
	5	66		0
	4	25		86 (56)[2]
	5	25		80 (75)[5]
	5	25		88 (55)
	4	25		96 (60)[5]

Experimental Section:

N-Methoxy-N-methylacetamide (1): Pyridine (71.17 mL, 0.88 mol) was slowly added to a well stirred slurry of O,N-dimethylhydroxylamine hydrochloride (42.92 g, 0.44 mol) and acetyl chloride (28.44 mL, 0.40 mol) in CH_2Cl_2 (600 mL) under N_2 at 0°. The mixture was warmed to room temperature and stirred for 2 hrs, at which time 400 mL of brine and 600 mL of Et_2O were added. Separation of the layers, extraction with an additional 300 mL of Et_2O and evaporation of the combined organic layers, followed by distillation under reduced pressure (bp 40-44°, 20 mm) gave 26.7 g (65% yield) of 1: ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H), 3.18 (s, 3H), 3.70 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 19.58, 31.98, 60.86, 171.59; IR (neat) 2950, 1670, 1410, 1380 cm^{-1}.

Typical Acetylation Procedure: Preparation of 1-Phenyl-1,3,5,7,9-decanepentanone. 1-Phenyl-1,3,5,7-octanetetraone (0.4 g, 1.6 mmol) in THF (20 mL) was slowly added to a solution of lithium diisopropylamide (7.1 mmol) in THF (50 mL) at -10°. The solution was stirred 1 hr followed by addition of 1 (0.178 g, 1.7 mmol). After 5 hrs at room temperature the resulting light red solution was evaporated to dryness in vacuo, the residue was suspended in Et_2O (50 mL) at 0°, and acidified to pH 1 with 6 N HCl (3 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (2 x 25 mL). The combined organic phase was dried ($MgSO_4$), filtered and evaporated in vacuo. The residue was dissolved in a small amount of Et_2O, filtered and evaporated to give 0.41 g (88% yield) of essentially pure pentaketone. Flash chromatography on deactivated silica gel (55:45, EtOAc-hexane) gave 0.257 g (55% yield) of pure product, which could be crystallized from Et_2O/hexane to give light yellow crystals:

mp 63-66°; ^{1}H NMR showed a complex mixture of enol-keto tautomers ($CDCl_3$) δ 1.99, 2.05, 2.08, 2.26 (4 x s, CH_3's), 3.22, 3.27, 3.32, 3.42, 3.44, 3.59, 3.69, 3.98 (8 x s, CH_2's), 5.22, 5.31, 5.44, 5.58, 5.65, 5.73, 5.75, 5.89, 6.23, 6.28, 6.30 (11 x s, =CH-), 7.48, 7.83 (2 x m, C_6H_5), 14.15, 14.68, 15.14, 15.86 (4 x s, OH); IR (KBr) 3600-2700 (br), 1600, 1570 cm^{-1}; MS m/z (relative intensity) 288 ($M^{+\bullet}$, 6), 270 (5), 189 (15), 161 (16), 147 (39), 127 (10), 105 (100), 85 (31), 77 (45), 69 (50), 51 (13), 43 (60). Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.72, H, 5.70.

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