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ADDITION OF ESCHENMOSER'S SALT TO KETONE, ESTER, & LACTONE ENOLATES. A CONVENIENT SYNTHESIS OF α-METHYLENE CARBONYLS VIA MANNICH INTERMEDIATES.[1]

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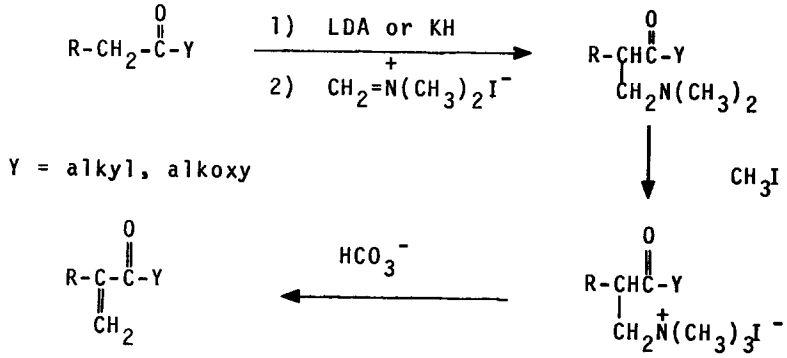
Synthetic routes to α-methylene carbonyl compounds have received considerable attention recently[4] because of the importance of this class of compounds as useful synthetic intermediates and the growing number of naturally occurring substances which contain an α-methylene lactone moiety.[4,5] In a search for an improved olefin synthesis via the amine oxide route, we found that addition of Grignard and lithium reagents to Eschenmoser's salt[6] proved to be an excellent method for introducing the dimethylaminomethylene group.[7] The recent report by Danishefsky and coworkers[8] on the use of Eschenmoser's salt to introduce the α-methylene lactone moieties in vernolepin prompts us to report related studies with ketone, ester, and lactone enolates. In each case we obtained good to excellent yields of Mannich intermediates which could be converted via elimination of the ammonium salts to the corresponding α-methylene ketone, ester, or lactone. The general sequence of reactions is outlined below. Specific experimental procedures which have been optimized for the best yield of products are presented.



Procedure A (Lactones and Esters). To a stirred solution of 2.02 g (20 mmol) of diisopropylamine in 20 ml of anhydrous tetrahydrofuran maintained at 4° was added 8.34 ml

of a hexane solution which was 2.35 M (20 mmol) in butyl lithium. The solution was stirred for 15 minutes and cooled to -78° before 1.60 g (19 mmol) of γ-butyrolactone were added, followed, after 45 minutes at -78°, by 7.4 g (40 mmol) of dimethyl(methylene)ammonium iodide. The resulting suspension was stirred at -78° for 30 minutes and gradually allowed to warm to room temperature. Solvent was removed at reduced pressure; the residue was dissolved in 20 ml of methanol; excess (15 ml) of methyl iodide was added; and the resulting mixture was stirred at room temperature for 24 hours. Solvent was removed at reduced pressure, giving a white solid which was shaken with 70 ml of 5% aqueous sodium bicarbonate (44 mmol) and 50 ml of dichloromethane until all of the solids dissolved. The aqueous layer was extracted with five 40 ml portions of dichloromethane. The combined organic extracts were dried over magnesium sulfate and solvent was removed at reduced pressure to afford 2.4 g of a pale yellow oil. Medium pressure chromatography of the residue on silica gel with 9:1 dichloromethane:acetone afforded 1.21 g (67%) of tulipalin A[9], which gave a single peak on a 500' X 0.03' open tubular column coated with SF-96-50. The IR and NMR spectra of the α-methylene lactone were identical to those reported in the literature.[10a]

In a similar sequence of reactions, 1.76 g (20 mmol) of methyl propionate were converted to the corresponding α-methylene ester[11] in 80% yield.[12] Elimination of the methyl iodide salt of the acyclic ester proved to be more difficult than for the lactone. The formation of the quaternary methyl iodide salt was carried out on the isolated Mannich intermediate at -20°C in 2 ml of methanol with 8.5 g (60 mmol) of methyl iodide. The salt was dissolved in 40 ml (1·1 equiv) of 5% aqueous sodium bicarbonate, 30 ml of methylene chloride was added and the resulting two phase system vigorously stirred for 24 hrs., after which it was worked up in the usual way. Both quaternisation and elimination reactions were quantitative. As before, IR and NMR spectra were identical to those reported in the literature.[13]

Alkylation of the enolate generated from cyclohexanone proved to be more difficult. In several early experiments (see Table 1), the salt was added to a rapidly stirred solution of

Table 1. REACTION WITH CYCLOHEXANONE

Base for Generation of Enolate	Order of Addition	Temp. °C	Rxn Time Min	Amine/Ketone[d]
silyl enol ether[a]	normal[c]	50	10	45/55
LDA	normal	25	15	50/50
LDA	normal	25	60	50/50
LDA[b]	normal	-78	45	60/40
LDA[b]	inverse	-78	10	80/20
KH	inverse	-78	60	96/4

a) Cleaved with methyl lithium. b) With HMPA. c) Salt added to enolate. d) Determined by glpc. The amine cleanly pyrolyzed to 2-methylenecyclohexanone upon injection. The ratio was determined before work-up with hydrochloric acid.

the enolate, and after work-up, 40-55% of the enolate was recovered as cyclohexanone. The low yields of amine were possibly due to equilibration of the less stable enolate of cycylohexanone with the newly formed ketoamine. Inverse addition gave improved conversions with the percentage of recovered starting ketone varying between 20-22% when lithium diisopropyl amide was used to generate the enolate and between 4-10% when potassium hydride served as the base. The potassium hydride procedure is described below.

Procedure B (Ketones). To a stirred solution of 0.27 g (6.7 mmol) of potassium hydride (Alfa-Ventron) in 5 ml of anhydrous tetrahydrofuran were added at 0°, 0.42 g (4.3 mmol) of dry cyclohexanone in 1 ml of tetrahydrofuran. After 5 minutes the contents of the flask were transfered via syringe to a cooled addition funnel (-78°) and slowly added to a rapidly stirred slurry of 1.6 g (8.6 mmol) of dimethyl(methylene)ammonium iodide in 10 ml of dry tetrahydrofuran at -78°. After addition was complete, the contents of the flask were allowed to warm to room temperature (ca. 30 minutes) and stirring was continued for an additional 30 minutes. Saturated sodium chloride solution (ca. 5 ml) was added, followed by enough water to just dissolve the salts. The layers were separated, and tetrahydrofuran was removed at reduced pressure. The water layer was made basic with aqueous sodium hydroxide, and the aqueous phase was extracted four times with pentane. The pentane extracts were added to the residue left after removal of tetrahydrofuran, and the resulting mixture was extracted with cold 5N hydrochloric acid. The aqueous layer was washed three times with pentane before addition of cold 10N sodium hydroxide. The resulting basic solution was extracted four times with pentane and the combined pentane extracts were washed with saturated sodium chloride solution before drying over sodium sulfate. Removal of solvent gave 0.60 g (90%) of a light yellow oil whose IR, NMR, and mass spectra (ei and ci) were consistent with the structure of the known[8] Mannich base. On a slightly larger scale, 1.05 g (88%) of the aminoketone was obtained.

The use of Eschenmoser's salt provides a convenient entry to Mannich intermediates which can easily be converted to the corresponding α-methylene carbonyl compounds. In those cases where the regiospecific generation of ketone enolates is not possible, the independent observations by Danishefsky et. al.[8] and Hooz et. al.[14] that Eschenmoser's salt reacts directly with silyl enol ethers and enol borinates contributes to the synthetic utility of the reaction.[15]

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