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1-DIPHENYLPHOSPHONIO-1-METHOXYMETHYLLITHIUM,

A USEFUL REAGENT FOR THE SYNTHESIS OF ALDEHYDES FROM HINDERED KETONES

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Summary: A new reagent, 1-diphenylphosphonio-1-methoxymethyllithium, has been found to be highl effective for the transformation $R_2CO \rightarrow R_2CHCHO$ with sterically hindered, enolizable ketones.

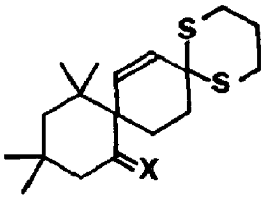
The replacement of ketonic oxygen by hydrogen and formyl, $R_2CO \rightarrow R_2CHCHO$, is an important a commonly used tactic in synthesis for which several different standard reagents are available.[1] our experience, however, none of these reagents is satisfactory for hindered ketones possessing or more alpha hydrogens.[2] The most common reagent methoxymethylenetriphenylphosphorane (1) ofte fails to provide the intermediate methyl enol ethers[2,3] in acceptable yield, and although the analogous phosphine oxide reagent 2 can be more effective,[4] its use is also limited. For exampl 2 was not satisfactory in the case of the substrate 3 since it afforded almost equal amounts of desired enol ether 4 and starting ketone (as a consequence of alpha deprotonation) even under op conditions.

$CH_3OCH{=}PPh_3$

1

$\underset{\displaystyle Li}{CH_3O\underset{|}{C}HPOPh_2}$

2



3 X=O

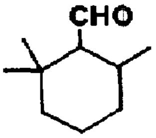
4 X=CHOCH$_3$

During the course of research leading to the total synthesis of the antiviral agent aphidic we noted the <u>complete</u> failure of reagents 1, 2 and a variety of others to generate a complex cyc hexane carboxaldehyde derivative from the corresponding cyclohexanone (which was similar to 3 in possessing an α-methylene group and two α' substituents, but even more hindered) and as a consequence were motivated to investigate alternative reagents. The lithio reagent 5 seemed obvious choice since its steric requirements are expected to be less than 1 or 2 and since it appeared readily accessible by the following process:

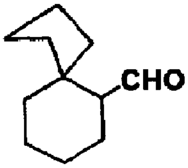
$$Ph_2PCl \xrightarrow{Li-NH_3} Ph_2PLi \xrightarrow{CH_3OCH_2Cl} \underset{6}{Ph_2PCH_2OCH_3} \longrightarrow \underset{5}{Ph_2PCHLiOCH_3}$$

Anions derived from diphenyl alkyl phosphines have been described,[6] but their utility remaine largely unexplored.

Phosphine 6 was prepared in nearly quantitative yield by treatment of lithiodiphenyl phos with chloromethyl methyl ether.[7] The phosphide was obtained by addition of diphenylchlorophos to a blue solution of lithium in tetrahydrofuran (THF)-liquid ammonia at -78°C. Formation of anion is indicated by its bright red color. Phosphine 6 can be metallated efficiently to 5 by treatment with *sec*-butyllithium. Reaction of ketone 3 with an excess of 5, followed by *in sit* generation of the betaine by treatment with methyl iodide results in complete conversion to th ether 4, a clear indication of the usefulness of this new reagent. In a further attempt to es its utility, the reaction with a series of hindered ketones was examined with the results expr in the following figure (reaction products, % yield).



91%



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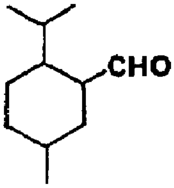
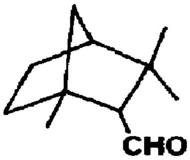
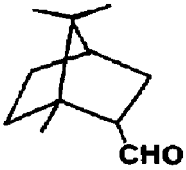


73%



79%



ca. 10%

With the exception of camphor, the enol ethers so obtained were free of starting material the infrared spectra of crude reaction mixtures showed no carbonyl absorption. Hydrolysis to corresponding aldehydes proceeded in high overall yield. The failure in the case of camphor sumably occurs because of competing enolization. A representative experimental procedure foll

Dihydrocyclocitral from 2,2,6-Trimethylcyclohexanone:[8] A solution of 5 equiv. of diphenyl methoxymethyl phosphine (9.2 ml. of a 100 mg./ml. solution in THF) was added at -95°C (toluene-liquid nitrogen bath) to a stirred solution of 4.5 equiv. of *sec*-butyllithium in 5 ml. of THF ove 30 min. (argon atmosphere). After 15 min. the addition was complete; 100 mg. of 2,2,6-trimethylcyclohexanone, dissolved in a minimum amount of THF, was added dropwise. The mixture was allowed to warm to room temperature (~2 hr.) and the excess reagent was quenched with methanol. Methyl iodide was added (2 ml.) and the mixture stirred for 3 hr. The reaction mixture was partitioned between ether and water, dried ($MgSO_4$) and concentrated. The enol ether was hydrolyzed to the aldehyde in 3 ml. of methylene chloride with 4 equiv. of trichloroacetic acid. Purification of t product by column chromatography on silica gel (5% THF in hexane solvent) furnished 101 mg. (91%) of dihydrocyclocitral as a mixture (2:1) of *trans* and *cis* isomers, showing pmr ($CDCl_3$) peaks at 9.59 δ (d, J = 5 Hz, CHO) and 9.89 δ (d, J = 6 Hz, CHO); ir$_{max}$ 1720 cm^{-1} (neat), mass spectrum *m/e* 154 (P) and 139 ($P-CH_3$).

Diphenyl methoxymethyl phosphine:[8] A solution of 40.5 cm. of 1/8" diameter lithium wire (0.2% Na) in 200 ml. of liquid ammonia containing 100 ml. of ether was treated at -78°C with an ethereal solution of 20 ml. of diphenylchlorophosphine (exothermic!). This was followed by the addition of a solution of chloromethyl methyl ether in THF. The disappearance of the bright red color of lithium diphenylphosphide indicates the endpoint of the addition. The ammonia was evaporated from the solution under a current of argon and the residue partitioned between ether a water. The organic phase was filtered through potassium carbonate into a dry, argon-filled Schle tube, and the solvent was removed under vacuum. A solution containing 100-200 mg./ml. of the residue in THF was of sufficient purity for use in the reaction with ketones. The yield of diphenyl methoxymethyl phosphine[7a] was quantitative by nmr analysis: ($CDCl_3$) 7.35 δ (m, 10H, Ph) 4.18 δ (d, J = 5 Hz, 2H, CH_2), 3.45 δ (s, 3H, OCH_3).

Anion **5** should be considered the reagent of choice for methoxymethylenation of hindered keto Although numerous other methods for performing this transformation are known,[1] none are suited fo hindered substrates, and all give diminished yields in such cases.[9]

References and Notes

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8. This reaction should be conducted in a fume hood.
9. This research was assisted by a grant from the National Science Foundation.

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