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Reaction of Aldehyde O-Alkyl Oxime with Organometallic Compounds

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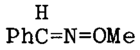
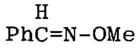
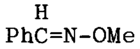
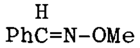
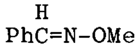
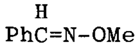
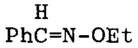
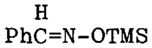
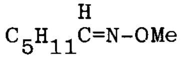
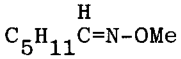
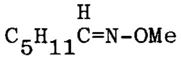
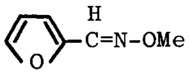
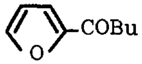
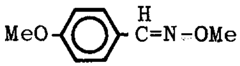
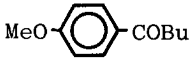
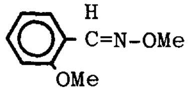
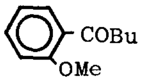
Summary: Aldehyde O-alkyl oximes were converted into ketones with high yields when they were treated with alkyllithium compounds or Grignard reagents followed by hydrolysis. Amines as reductive alkylation products of aldehyde O-alkyl oximes were also obtained by BH_3 reduction before hydrolysis.

Reactions of oximes with organometallic compounds have been known to derive various important synthetic intermediates. Ketone oximes or O-alkyl oximes having α-hydrogen react with alkyllithium compounds to result in the formation of dianion which could be alkylated on carbon with high regioselectivity.[1-4] Grignard reagent also react with oximes to yield amino alcohols or azirizines.[5,6] Aromatic aldehyde oxime such as benzaldehyde oxime react with Grignard reagent to give rearranged product phenyl alkylamine.[7] H. G. Richey, Jr., et. al. reported that reactions of a large excess of organolithium compounds with aldehyde oximes yielded hydroxylamines, which were sometimes accompanied by significant amount of other compounds.[8] However reactions of aldehyde O-alkyl oximes with organometallic compounds have not been studied systematically. We have found that alkyllithium compounds readily react with aldehyde O-alkyl oximes to give ketones after hydrolysis with high yield. We report here result showing that the conversion of aldehyde O-alkyl oximes into ketones can be efficiently carried out at 0°C using a two to one ratio of organometallic compound to aldehyde O-alkyl oximes. The experimental results are summarized in Table 1. The present method is one of the most efficient route for the ketone synthesis from aldehyde.[9]

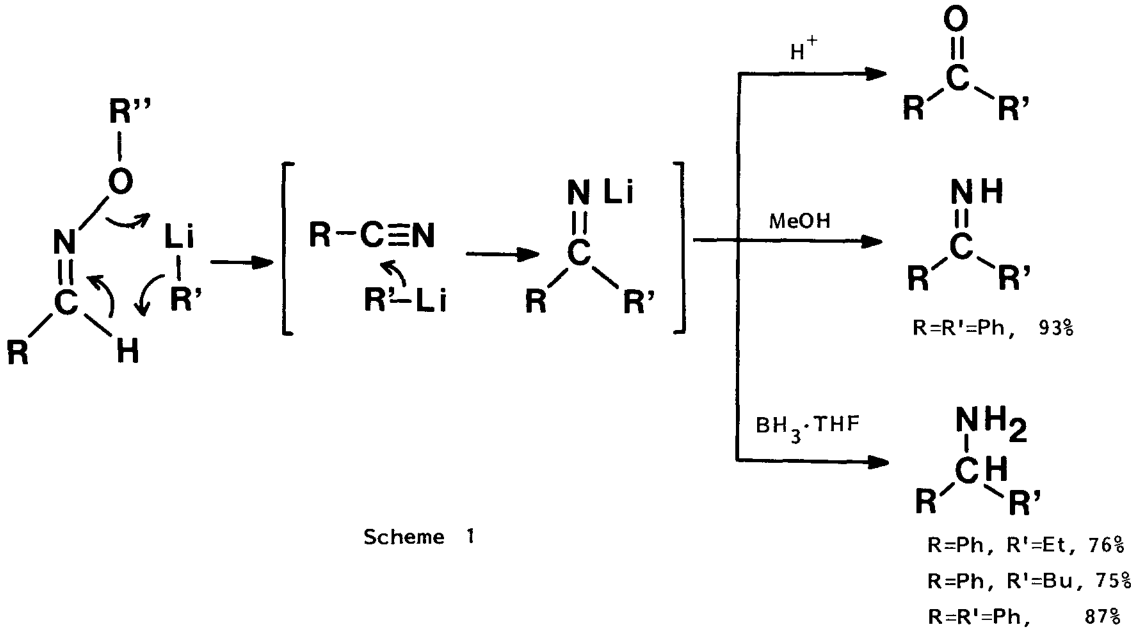
The following procedure for the synthesis of valerophenone is representative. A 1.2M freshly prepared solution in ether of n-butyllithium (16.7ml, 20mmol) was added dropwise (10min), under nitrogen, to a stirred solution of freshly distilled benzaldehyde O-methyl oxime (1.35g, 10mmol) in 50ml of dry THF at 0°C. After complete addition, the stirring was continued for 1h at the same temperature. Then the reaction was quenched by pouring the mixture into dilute hydrochloric acid and extracted with several portions of ether. The combined ether extracts were washed with aqueous $NaHCO_3$, water, and dried over $MgSO_4$. The solvents were removed and the residue was distilled to give 1.23g of valerophenone (76%yield).

Table 1 Synthesis of Ketones[a]

Entry	Aldehyde O-Alkyl Oxime	Organometallic Compound	Temperature /°C	Product	Yield/%[b]
1	 $\overset{H}{\mathrm{PhC}}\mathrm{=N=OMe}$	EtLi	0	PhCOEt	84
2	 $\overset{H}{\mathrm{PhC}}\mathrm{=N-OMe}$	BuLi	r.t.	PhCOBu	65
3	 $\overset{H}{\mathrm{PhC}}\mathrm{=N-OMe}$	BuLi	0	PhCOBu	76
4	 $\overset{H}{\mathrm{PhC}}\mathrm{=N-OMe}$	BuLi	- 78	PhCOBu	81
5	 $\overset{H}{\mathrm{PhC}}\mathrm{=N-OMe}$	PhLi	0	PhCOPh	90
6	 $\overset{H}{\mathrm{PhC}}\mathrm{=N-OMe}$	EtMgBr	65	PhCOEt	57
7	 $\overset{H}{\mathrm{PhC}}\mathrm{=N-OEt}$	BuLi	0	PhCOBu	80
8	 $\overset{H}{\mathrm{PhC}}\mathrm{=N-OTMS}$	BuLi	0	PhCOBu	72
9	 $\mathrm{C_5H_{11}}\overset{H}{\mathrm{C}}\mathrm{=N-OMe}$	BuLi	0	$\mathrm{C_5H_{11}COBu}$	54
10	 $\mathrm{C_5H_{11}}\overset{H}{\mathrm{C}}\mathrm{=N-OMe}$	BuLi	- 78	$\mathrm{C_5H_{11}COBu}$	51
11	 $\mathrm{C_5H_{11}}\overset{H}{\mathrm{C}}\mathrm{=N-OMe}$	PhMgBr	65	$\mathrm{C_5H_{11}COPh}$	37
12		BuLi	0		42
13		BuLi	0		76
14		BuLi	0		80

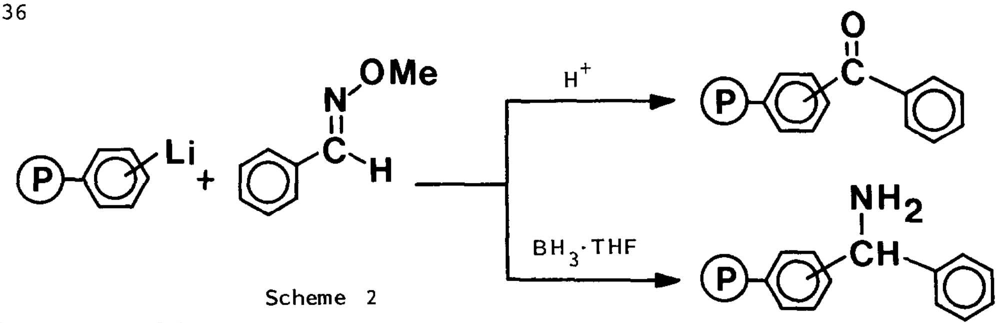
[a] All reactions were performed on a 10 mmol scale with the same procedure as described in the text. The molar ratio of organometallic compound and aldehyde O-alkyl oxime was 2 : 1. [b] Yields refer to products isolated by distillation. All products were identified by comparison of GC retention time and ^{1}HNMR data with those obtained using authentic samples.

As illustrated by the entries in the Table 1, various ketones can be synthesized by this method in medium to high isolated yields. In the use of n-butyllithium yield was increased carring out the reaction at -78°C (entry 4). Aldehyde O-methyl oxime derived from enolizable aldehyde yielded ketone in somewhat low yield (entries 9-11). Only a small amount of the desired ketone was obtained when aldehyde oxime was used in place of O-alkyl derivatives. Although Grignard reagents could be used efficiently, higher reaction temperature was required to give ketones (entries 6,11). In this reaction, two equiv of organometallic compound are required to give ketone. Products of the reaction of benzaldehyde O-methyl oxime with equimolar amount of n-butyllithium at 0° C included benzonitrile and valerophenone. Reaction of benzaldehyde O-methyl oxime with lithium diisopropylamide (LDA) gave only benzonitrile in 85% yield.[10] Thus the present reaction is considered to proceed via nitrile intermediate. One mole of n-butyllithium may be used for nitrile preparation by deprotonation. Produced nitrile would be added immediately by another one mole of n-butyllithium to give imine which is hydrolyzed to ketone.[11] (Scheme 1). Indeed, stable diphenylmethane imine was also isolated with high yield (93%) by the treatment with methanol instead of hydrolysis. The imine intermediate can be reduced with borane THF in situ to primary amines. Other reducing agents such as $LiAlH_4$ and $NaBH_4$ were unsuitable for this reaction.[12]



Scheme 1

The present method also allows preparation of polymer-bound ketone and amine from lithiated polystyrene beads[13,14] and aldehyde O-methyl oxime (Scheme 2). This is the efficient procedure for preparing benzhydrilamine resins which provide one of the most useful polymeric support for solid-phase peptide synthesis.[15]



Scheme 2

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12. In $LiAlH_4$ reduction, some primary amine appeared to be formed but was accompanied by significant amounts of other compounds. $NaBH_4$ could not reduce the intermediate.
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