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A CONVENIENT SYNTHESIS OF KETOXIMES FROM GRIGNARD REAGENTS AND NITRO COMPOUNDS ACTIVATED BY N,N-DIMETHYLCHLOROMETHYLENIMINIUM CHLORIDE

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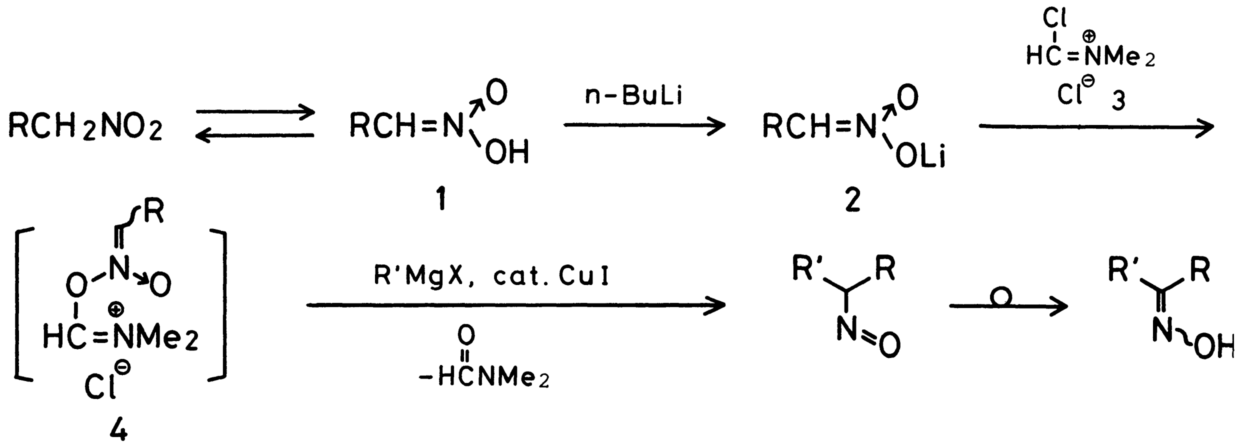
Ketoximes were synthesized in high yields with a new carbon-carbon bond formation by regioselective nucleophilic attack of Grignard reagents at the α-position of aci-nitroalkanes activated by *N*,*N*-dimethylchloromethyleniminium chloride in the presence of a catalytic amount of copper(I) iodide under mild conditions.

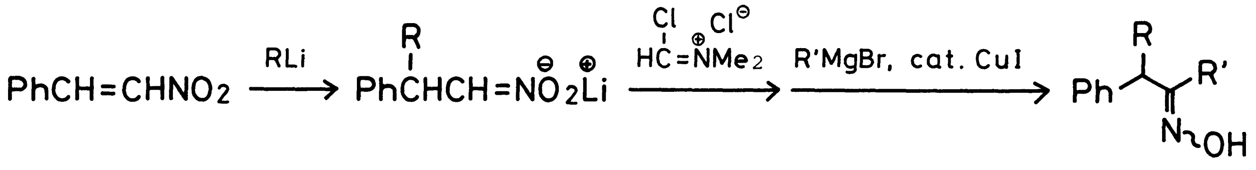
We wish to report here a novel ketoxime synthesis by the carbon-carbon bond forming reaction of Grignard reagents with nitroalkanes activated by *N*,*N*-dimethylchloromethyleniminium chloride (3). Ketoximes are well known as good synthetic intermediates to give ketones,1) nitro compounds,2) amines,3) amides,4) and heterocycles.5) The dianions of them have been shown to be useful enolate anion equivalent.6) Condensation of ketones with hydroxylamine, reductive conversion of nitro compounds,7,8) and reaction of active methylene compounds with nitrosation reagents9) are known as the synthetic methods of ketoximes. However, these methods are only functional conversion ones without the extension of carbon skeleton. An alkylation reaction of silyl nitronate with two equivalents of alkyllithium10) is a method to give ketoximes by a new carbon-carbon bond formation, but the yields of ketoximes are not so high. On the other hand, *N*,*N*-dimethylchloromethyleniminium chloride (3), prepared easily from *N*,*N*-dimethylformamide and oxalyl chloride, has been reported to be a most effective condensation reagent of carboxylic acids with various nucleophiles11) to give acyl chlorides,12) esters,13) acyl azides,14) amides,15) aldehydes,16) and alcohols.17) These results suggest that lithium salts of aci-nitro compounds (2) react with the iminium chloride 3 to give aci-nitroiminium chlorides (4) which are subjected to nucleophilic attack of Grignard reagents at the α-position to yield ketoximes *via* nitroso compounds with liberating *N*,*N*-dimethylformamide.

Thus, when the lithium salt of aci-nitroethane, prepared from nitroethane and butyllithium, was treated with the iminium chloride 3 in THF at -60 °C, followed by addition of copper(I) iodide (20 mol%) and β-phenethylmagnesium bromide (1 equiv) at -30 °C, the desired ketoxime of 4-phenyl-2-butanone was obtained in 52% yield. When THF-CH_2Cl_2 (3:1) and THF-HMPA (20:1) systems were used as a mixed solvent, the yields were 71% and 33%, respectively. The use of two equivalents of the Grignard reagent increased remarkably the yield of the ketoxime up to 97%. The amount of the copper catalyst affected also the yield. In the reaction of 1-nitropropane (1 equiv) with β-phenethylmagnesium bromide (2 equiv), the yield of the ketoxime of 1-phenyl-3-pentanone was 74% without the catalyst, and the use of 5, 10, and 20 mol% of copper(I) iodide gave the ketoxime in 86, 94, and 99% yields, respectively.



The result of ketoxime synthesis from nitroalkanes and various kinds of Grignard reagents using the iminium chloride **3** is summarized in Table. Primary and secondary alkyl Grignard reagents gave the corresponding ketoximes in over 82% yields. Even in the case of a bulky tertiary Grignard reagent, tert-butylmagnesium chloride, the corresponding ketoxime was obtained in 73% yield. α,β-Unsaturated, β,γ-unsaturated, and aromatic ketoximes were also obtained in good yields by the reaction of vinyl, allyl, and phenyl Grignard reagents, respectively. The reaction of a β,γ-unsaturated nitro compound, 3-nitro-1-propene, with β-phenethylmagnesium bromide gave the corresponding α,β-unsaturated ketoxime of 5-phenyl-1-penten-3-one in a high yield of 83%.

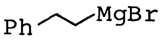
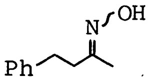
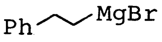
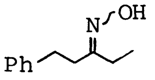
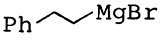
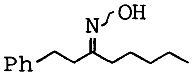
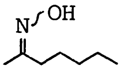
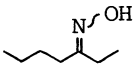
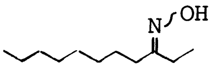
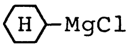
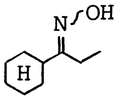
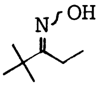
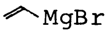
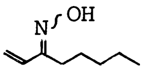
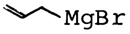
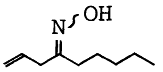
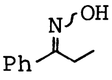
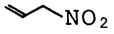
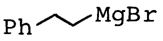
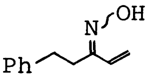
The reaction of α,β-unsaturated nitro compounds with organometallics is well known to afford the Michael adducts.7,18) Accordingly, the double alkylation reaction at the α- and β-position of α,β-unsaturated nitro compounds is possible by the Michael addition reaction with alkyllithium, followed by the present alkylation reaction. Thus, the Michael addition of β-nitrostyrene with methyllithium at -78 °C for 1 h, followed by treatment with iminium chloride **3** and then β-phenethylmagnesium bromide gave the dialkylated ketoxime of 1,4-diphenyl-3-pentanone in 83% yield. In a similar manner, double alkylation by butyllithium and methylmagnesium bromide gave the ketoxime of 3-phenyl-2-pentanone in 61% yield.



$R = CH_3$, $R' = PhCH_2CH_2$, 83%
$R = n\text{-}C_4H_9$, $R' = CH_3$, 61%

A typical procedure for the ketoxime synthesis from nitroalkane and Grignard reagent is as follows. To a solution of *N*,*N*-dimethylformamide (87.7 mg, 1.20 mmol) in dichloromethane (5 ml) was added an excess amount of oxalyl chloride (0.5 ml) at 0 °C. After stirring at the same temperature for 1 h, dichloromethane and excess oxalyl chloride were removed under a reduced pressure. Then, dichloromethane (5 ml) was added to the resulting white powder and cooled to -60 °C. To the

Table 1. Yields of Ketoximes from the Reaction of Grignard Reagents with Nitroalkanes Activated by *N*,*N*-Dimethylchloromethyleniminium Chloride[a)]

Entry	Nitroalkane	Grignard Reagent	Product[b)]	Yield/%[c)]
1	$C_2H_5NO_2$			97
2	n-$C_3H_7NO_2$			99
3	n-$C_6H_{13}NO_2$			97
4	n-$C_6H_{13}NO_2$	CH_3MgBr		90
5	n-$C_3H_7NO_2$	n-C_4H_9MgBr		82
6	n-$C_3H_7NO_2$	n-$C_8H_{17}MgBr$		90
7	n-$C_3H_7NO_2$			84
8	n-$C_3H_7NO_2$	t-C_4H_9MgCl		73
9	n-$C_6H_{13}NO_2$			86
10	n-$C_6H_{13}NO_2$			68
11	n-$C_3H_7NO_2$	PhMgBr		70
12				83

[a)] All reactions were performed by the same procedure described in the text. [b)] All products were identified by IR and NMR spectra and/or comparison with authentic materials. [c)] The yields were based on nitroalkane. Isolated yields of chromatographed (silica gel) products.

suspension was added the lithium salt of aci-nitroethane (1.20 mmol), prepared by the reaction of nitroethane with butyllithium in dry THF (8 ml) at -90 °C to -60 °C for 1 h, and stirred for 2 h elevating the temperature gradually to -30 °C. A suspension of copper(I) iodide (45.7 mg, 0.24 mmol) in THF (3 ml) and β-phenethylmagnesium bromide (3.3 ml of 0.80 M THF solution, 2.64 mmol) was added to this reaction mixture. After stirring the reaction mixture at -30 °C for 2 h, the reaction was quenched with a saturated aqueous ammonium chloride solution, and usual work-up afforded 4-phenyl-2-butanone oxime in 97% yield.

The present reaction is nucleophilic α-alkylation of nitroalkane transforming the nitro group into the oxime group. In contrast to the electrophilic alkylation at the α-position of nitroalkanes,[7,19)] in which the employable electrophiles were limited to primary alkyl and benzyl halides or tosylates, the use of wide range of Grignard reagents including primary, secondary and tertiary alkyl, vinyl, aryl, and allyl ones renders the present method attractive.

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