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REINVESTIGATION OF THE GRIGNARD REACTIONS WITH FORMIC ACID. A CONVENIENT METHOD FOR PREPARATION OF ALDEHYDES

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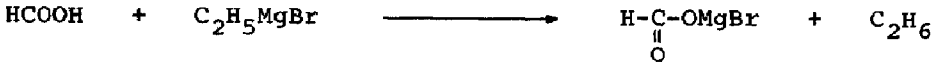
Summary: Grignard reagents react with formic acid in tetrahydrofuran to produce aldehydes in relatively good yields Various aldehydes such as alkyl, aryl, allyl, benzyl and vinyl aldehydes were prepared from the corresponding Grignard reagents. The reaction with vinyl Grignard reagents proceeded with retention of configuration.

Many methods have been reported for the preparation of aldehydes by the reactions of Grignard reagents with masked formic acid or formal derivatives.[1] However, the reaction with formic acid itself, which is obviously the most direct approach, was reported to afford aldehydes only in very low yields,[2,3] and, therefore, has not been used for aldehyde synthesis.[4]

Recently, a striking solvent effect of THF on Grignard reactions with acid chlorides was observed. In marked contrast to the reaction in ether, the reaction in THF gave ketones almost quantitatively.[5]
This finding prompted us to reinvestigate the reaction of Grignard reagents with formic acid in THF in expectation of production of aldehydes in better yields than in ether.

In the preliminary investigation, the reaction of two moles of hexylmagnesium bromide with a mole of formic acid in THF was carried out, and a satisfactory yield (72%) of heptanal was obtained. However, rather suprisingly, heptanal was found to be produced in a 55% yield even when ether was used as the solvent. The yield was lower than for the reaction in THF but not so low as previously reported.[2,3] Though the precise reason is not clear, we believe that insufficient drying of formic acid was responsible for the low yield of aldehydes in the previous investigations.[6]

In view of the potential economy of this aldehyde synthesis in THF, we decided to carry out the reaction which gives the magnesium salt of formic acid by treatment with an equimolar amount of a readily available Grignard reagent such as ethylmagnesium bromide, and then to treat the magnesium salt with one mole of the desired Grignard reagent as shown in eqs 1 and 2.



$$HCOOH + C_2H_5MgBr \longrightarrow \underset{\underset{O}{\|}}{H\text{-}C\text{-}OMgBr} + C_2H_6 \qquad (1)$$

$$\underset{\underset{O}{\|}}{H\text{-}C\text{-}OMgBr} + RMgBr \longrightarrow \underset{\underset{\underset{1}{}}{OMgBr}}{\overset{R}{H\text{-}C\text{-}OMgBr}} \xrightarrow{H_2O} \underset{\underset{O}{\|}}{R\text{-}C\text{-}H} \qquad (2)$$

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In a representative procedure, ethylmagnesium bromide in THF (0.84 M; 16 ml, 13.4 mmol) was added dropwise (20 min) to a solution of formic acid (0.45 ml, 11.9 mmol) in dry THF (15 ml) while stirring under argon at 0°C. Hexylmagnesiu bromide (0.79 M; 10.5 ml, 8.3 mmol) was then added (10 min) to this solution, and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was decomposed with 2N HCl,[8] extracted with ether, dried over Na_2SO_4, and then distilled under reduced pressure (62°C, 35 Torr) to afford heptanal (0.72 g, 75% yield).

The presumed intermediate (1) seemed stable under the reaction conditions and was converted to aldehyde only by hydrolysis, as the ^{1}H NMR analysis of the reaction mixture in THF showed no peak due to formyl protons before hydrolysis, whereas the peak appeared after the addition of 2N HCl to the sample in the NMR tube.

As illustrated by the entries in Table 1, the method can be readily extende to various Grignard reagents such as alkyl, aryl, benzyl, allyl and vinyl Grigna reagents. The listed yields were obtained using the above procedure without optimization for each substrate. It can be seen that the yields were satisfacto in all cases except for secondary aliphatic Grignard reagents. The reaction wi vinylic Grignard reagents followed by hydrolysis under neutral conditions (by a dition of H_2O)[8] afforded an α,β-unsaturated aldehyde with the same stereoconfiguration as the starting Grignard reagents, indicating that the reaction o vinylic Grignard reagents with formic acid proceeds with retention of configuration. Unfortunately, even if a Grignard reagent is prepared from a pure (E) or (Z)-1-alkenyl halide, it becomes a mixture of (E) and (Z)-1-alkenyl magnesium halides.[9,10,11] Therefore, pure (E) and (Z)-2-alkenals could not be obtained directly. However, as (Z)-2-alkenal is easily isomerized to the stabl (E)-isomer by acid,[12] pure (E)-2-alkenal may be obtained easily by the present method. Thus, pure (E)-cinnamaldehyde was prepared from the Grignard reagent

TABLE 1

$$HCOOMgBr \quad + \quad RMgBr \longrightarrow RCHO$$

RMgBr	RCHO[a]	Yield[b] %
$C_6H_{13}MgBr$	$C_6H_{13}CHO$	75
$C_8H_{17}MgBr$	$C_8H_{17}CHO$	70
$C_3H_7CH(CH_3)MgBr$	$C_3H_7CH(CH_3)CHO$	38[c]
$BrMg-(CH_2)_4-MgBr$	$OHC-(CH_2)_4-CHO$	55
C_6H_5MgBr	C_6H_5CHO	81
$C_6H_5CH_2MgBr$	$C_6H_5CH_2CHO$	61
$C_3H_7-CH=CH-CH_2MgBr$	$C_3H_7CH(CHO)-CH=CH_2$	50
$C_4H_9-CH=CH-MgBr$	$C_4H_9-CH=CH-CHO$	
E/Z = 15/85[d,e]	E/Z = 16/84[f]	60
E/Z = 65/35[g,e]	E/Z = 65/35[f]	58
$C_6H_5-CH=CH-MgBr$	$C_6H_5-CH=CH-CHO$	
E/Z = 89/11[h,i]	E/Z = 87/13[f]	67

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[a] Products were identified by IR, ^1H NMR and m.p. of their 2,4-dinitrophenylhydrazone derivatives. [b] Isolated yield by distillation, and based on RMgBr. [c] GLC yield. [d] Prepared from (Z)-1-bromo-1-hexene (98% pure). [e] The ratio was determined by ^1H NMR and is in accordance with the reported value[9]. [f] The ratio was determined by ^1H NMR analysis of the formyl protons. Chemical shifts were as follows (δ, ppm in CCl_4); 2-heptanal, 9.4(d) for E and 10.0(d) for Z-isomer; cinnamaldehyde, 9.6(d) for E and 9.9(d) for Z-isomer. [g] Prepared from (E)-1-bromo-1-hexene (98% pure). [h] Prepared from pure (E)-β-bromostyrene. [i] The ratio was determined by ^1H NMR of the product of hydrolysis with D_2O, and is in accordance with the reported value[10].

from either (E) or (Z)-β-bromostyrene by hydrolysis with 2N HCl after the reaction.

Most aldehyde syntheses by the reactions of Grignard reagents with formic acid derivatives in the literatures need the acidic hydrolysis step. Therefore, it seems difficult to prepare (Z)-2-alkenals by these methods. Therefore, it is important to note that the present aldehyde synthesis makes it possible to prepare (Z)-2-alkenals from (Z)-1-alkenylmagnesium halides.

References and Notes

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