Tetrahedron Letters,Vol.25,No.42,pp 4805-4808,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

# IRON CATALYZED CROSS-COUPLING REACTIONS OF ACYL CHLORIDES WITH GRIGNARD REAGENTS. A MILD, GENERAL, AND CONVENIENT SYNTHESIS OF ALIPHATIC AND AROMATIC KETONES.

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Summary: Acyl chlorides couple with Grignard reagents at room temperature in the presence of catalytic amounts of tris(acetylacetonate)iron(III), $Fe(acac)_3$. The reaction is general with respect to both reactants and provides a very mild and convenient method for the synthesis of aliphatic and aromatic ketones.

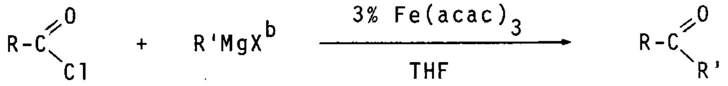
In principle, the coupling reaction of carboxylic acids or their derivatives with Grignard reagents represents one of the most straightforward methods for the synthesis of ketones. However, in spite of the inherent simplicity, its synthetic usefulness is severely limited, due mainly to the simultaneous formation of undesired tertiary and/or secondary alcohols[1].

As part of our study on the carbon-carbon bond formation by the use of transition metal catalyzed Grignard reactions[2], we have recently reported that in the presence of a nickel(II)-phosphine complex as a catalyst, the reaction of Grignard reagents with carboxylic acids leads to ketones in satisfactory yields without significant formation of alcohols[3].

To clarify the scope and limitations of this procedure, we have considered convenient to extend the catalyzed Grignard cross-coupling reactions to carboxylic acid derivatives. With this aim acyl chlorides were chosen. Indeed, for the latter compounds, in order to prevent the formation of undesired carbinols, other kinds of organometallics such as zinc[4], cadmium[5], copper[6], manganese[7], or rhodium[8] derivatives are preferred to Grignard reagents[9]. On the other hand, although in isolated cases addition of catalytic amounts of transition metal compounds, such as $FeCl_3$[10] or CuCl[11], has been reported to improve the yields of ketones by direct reaction of Grignard reagents and acyl chlorides, none of these reactions appear to be general. Therefore, transition metal catalyzed

## TABLE

Cross-Coupling Reactions of Acyl Chlorides with Grignard Reagents in the Presence of $Fe(acac)_3$ as a Catalyst[a].



| Entry | R | R' | Temp | Yield in Ketone[c] % |
|---|---|---|---|---|
| 1 | $CH_3(CH_2)_9$ | $CH_3$ | r.t. | 84 |
| 2 | $CH_3(CH_2)_4$ | $CH_3(CH_2)_4$ | r.t. | 82 |
| 3 | $CH_3$ | $CH_3(CH_2)_8$ | r.t. | 82 |
| 4 | $CH_3$ | $CH_3(CH_2)_9$ | r.t. | 80 |
| 5 | $CH_3(CH_2)_2$ | $(CH_3)_2CH$ | r.t. | 80 |
| 6 | $CH_3(CH_2)_2$ | $(CH_3)_3C$ | r.t. | 70 |
| 7 | $CH_3(CH_2)_2$ | $C_6H_5$ | r.t. | 67 |
| 8 | $CH_3(CH_2)_2$ | $C_6H_5$ | 0°C | 83 |
| 9 | $(CH_3)_2CH$ | $(CH_3)_2CH$ | r.t. | 80 |
| 10 | $(CH_3)_2CH$ | $C_6H_5$ | r.t. | 75 |
| 11 | $(CH_3)_2CH$ | $C_6H_5$ | 0°C | 92 |
| 12 | $(CH_3)_3C$ | $C_6H_5$ | 0°C | 80 |
| 13 | $C_6H_5$ | $CH_3$ | r.t. | 80 |
| 14 | $C_6H_5$ | $CH_3(CH_2)_3$ | r.t. | 90 |
| 15 | $C_6H_5$ | $(CH_3)_2CH$ | r.t. | 84 |
| 16 | $C_6H_5$ | $(CH_3)_3C$ | r.t. | 70 |
| 17 | $C_6H_5$ | $C_6H_5$ | r.t. | 63 |
| 18 | $C_6H_5$ | $C_6H_5$ | 0°C | 75 |

[a] All reactions were performed on a 5 mmol scale with the same procedure as described in the text. The molar ratio of Grignard reagent and acyl chloride was 1:1. [b] All Grignard reagents were prepared in THF from the corresponding chlorides (entries 1, 5, 6, 9, 13, 15, and 16) or bromides (other entries ). [c] The yields refer to pure products isolated by distillation. In reactions with $C_6H_5MgBr$, diphenyl formed as by-product was removed by short-path column chromatography on silica gel, eluting with hexane/ether 9/1. All products were identified by comparison of gc retention times and n.m.r. spectra with those of commercial authentic samples.

coupling reactions of acyl chlorides with Grignard reagents or organolithium compounds, generally, are not considered applicable for the synthesis of ketones[12].

We report here results showing that in the presence of tris(acetylacetonate)iron(III), $Fe(acac)_3$, as a catalyst, the conversion of acyl chlorides into ketones can be efficiently carried out at room temperature using a one to one ratio of Grignard reagent to acyl chloride. The experimental results are summarized in the Table. No significant amounts of tertiary and/or secondary alcohols have been detected in the examples listed. As illustrated by the entries in the Table, various ketones can be synthesized by this method in high isolated yields. The reaction works well with both aliphatic and aromatic acyl chlorides, including the highly hindered pivaloyl chloride which gives the corresponding ketone in 80% yield (entry 12). Similarly, aromatic and primary, secondary, and tertiary aliphatic Grignard reagents can be efficiently used. With phenylmagnesium bromide at room temperature both aliphatic and aromatic acyl chlorides lead to the corresponding ketones in yields of 63-75% (entries 7,10, and 17). However, these can be increased carrying out the reaction at 0°C (entries 8,11, 12, and 18).

In conclusion, we believe that the iron-catalyzed coupling reaction of acyl chlorides with Grignard reagents provides a mild and convenient procedure for synthesizing aliphatic and aromatic ketones which is superior or complementary to existing methods. In fact, the present method has the following advantages: i) it is general both with respect to the Grignard reagents and the acyl chlorides; ii) no excess of reactants is necessary and an equimolar ratio is sufficient to ensure complete reaction; iii) low temperatures are not required; iv) the yields are high in most cases, and v) there are virtually no side reactions which complicate isolation and purification of the products.

The following procedure for the synthesis of valerophenone is representative. A 0.84 M freshly prepared solution in THF of n-butylmagnesium bromide (6 ml, 5 mmol) was added dropwise (30 min), under nitrogen, to a stirred solution of freshly distilled benzoyl chloride (0.7g, 5 mmol) and $Fe(acac)_3$ (0.053g, 0.15 mmol) in 50 ml of dry THF at room temperature. After complete addition, the stirring was continued for 10 min 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 aq $NaHCO_3$, water, and dried over $Na_2SO_4$. The solvent was removed and the residue was distilled to give 0.73g of valerophenone (90% yield).

Acknowledgement: This work was supported by a grant from the "Progetto Finaliz-

zato di Chimica Fine e Secondaria" of Italian National Research Council (CNR), Rome.

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(Received in UK 15 June 1984)