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Reactions of *In Situ* Formed Acyl Tributylphosphonium Ions with Grignard Reagents as an Effective Route to Ketones from Acid Chlorides

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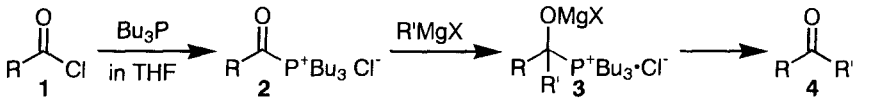
Abstract: The reactions of acyl tributylphosphonium ions *in situ* generated from acid chlorides and Bu_3P in THF at -22°C with primary alkyl and arylmagnesium halides have proved to be a convenient and simple procedure to prepare ketones from acid chloride in one-pot.

It is well known that reactions of Grignard reagents with acid chlorides can not provide a synthetically useful access to ketones due to the inevitable formation of tertiary alcohols,[1] unless the reaction is carried out not only at very low temperature in THF but also with high excess of acid chlorides in many cases.[2] Therefore, it has been recommended for preparation of ketones with Grignard reagents to utilize *N*-acylimidazoles,[3] 8-acyloxyquinolines,[4] *S*-(2-pyridyl) thioates,[5] mixed carboxylic anhydrides with *o*-anisoyl moiety,[6] *N*-methylamino pyridinylamides,[7] or *N*-methoxy-*N*-methylamides[8] in place of acid chlorides. However, these well-designed carboxylic acid derivatives are generally prepared from acid chlorides, and hence preparation of ketones with Grignard reagents requires two steps from the acid chlorides, except for the method with the mixed anhydrides.[6] Thus, it seems worthwhile to develop novel carboxylic acid derivatives, which can be easily generated from acid chlorides and enter *in situ* Grignard reactions to give ketones, although it was demonstrated that transformation of acid chlorides into ketones with Grignard reagents can be effectively catalyzed by $Fe(acac)_3$[9] or $NidppeCl_2$.[10]

Our study on the electrochemical reaction of carboxylic acids in the presence of Bu_3P has revealed that anodically generated acyl tributylphosphonium ions are reduced at more positive potential over 0.6 V than the corresponding acid chlorides, leading to the generation of novel acyl anion or radical equivalents.[11] The striking characteristic of acyl tributylphosphonium ions has been emphasized by the following fact: acid chlorides can not be reduced by Zn or a Zn-Cu couple, while the corresponding acyl tributylphosphonium ions generated chemically from acid chlorides and Bu_3P can undergo partial reduction to aldehydes in the presence of these metals.[12] The impressive capability of acyl tributylphosphonium ions as electron acceptors has allowed us to expect that they will be highly reactive carboxylic acid derivatives as acylating reagents as well. Thus, we examined the reactivity of acyl tributylphosphonium ions as electrophiles. For this purpose, Grignard reagents were first chosen as nucleophiles for the reason mentioned above. In this paper, we wish to describe the reactions of *in situ* formed acyl

Scheme 1



tributylphosphonium ions (**2**) from Bu_3P and acid chlorides (**1**) with Grignard reagents as an effective route to ketones from **1** (Scheme 1).

The effects of reaction conditions on the formation of ketones from **1** *via* **2** were explored first, utilizing decanoyl chloride (**1a**) and benzoyl chloride (**1b**) as model compounds. The results are summarized in Table 1. When the mixture of **1a** and Bu_3P (1.1 eq. on **1a**) in THF was stirred at 0°C for 20 min, followed by addition of a THF solution of MeMgBr (1.0 eq. on **1a**) at the same temperature, vigorous gas evolution was observed. GLC analysis of the crude products showed that 2-undecanone (**4a**) was obtained only in 30 % yield, although no formation of a tertiary alcohol **5a** was recognized at all (run 1). At -22°C, however, **4a** was formed selectively in 91 % yield (run 2). No further improvement in the yield of **4a** was observed even when the reaction temperature was lowered to -42°C (run 3). As shown in run 4, the Grignard reaction with 1.1 eq. of MeMgBr induced the formation of **5a** in 9 % yield, resulting in a lower yield of **4a**. In contrast to **1a**, **1b** smoothly entered the reaction course even at 0°C, giving acetophenone (**4b**) in 95 % yield, although a tertiary alcohol **5b** was also formed in a trace amount (run 6). When the reaction was carried out at -22°C, **4b** was exclusively obtained (run 7). Similarly to the case of **1a**, the selective formation of **4b** was disturbed in the reaction with excess MeMgBr (run 8). When the reaction was performed without the pre-reaction of **1a** or **1b** with Bu_3P, the Grignard reactions were quite slow at -22°C. After stirring for 10 min (see below), TLC analysis showed that a large amount of **1a** or **1b** still remained and the following work-up gave only a small amount of **4** accompanied with **5** as the major product (runs 5 and 9).

Table 1 1) Bu_3P, 2) MeMgBr

RCOCl → R(C=O)Me (**4a**/**4b**) + R(OH)(Me)Me (**5a**/**5b**)

1a: R=$CH_3(CH_2)_8$- **1b**: R=Ph-

Run	Acid chloride	Reaction temp.	Molar ratio MeMgBr / 1	Yield (%)[a] of 4	5
1	**1a**	0°C	1.0	30	-
2	"	-22°C	"	91	-
3	"	-42°C	"	90	-
4	"	-22°C	1.1	79	9
5[b]	"	"	1.0	12	22
6	**1b**	0°C	"	95	trace
7	"	-22°C	"	98	-
8	"	"	1.1	87	9
9[b]	"	"	1.0	14	26

a) Determined by GLC. b) Without Bu_3P.

Based on the results described so far, preparation of ketones through the reactions of *in situ* formed **2** with Grignard reagents was carried out on various **1**. A typical procedure is as follows: to a THF solution of **1** (3.0 mmol) cooled to -22°C in dry ice-CCl_4 bath, Bu_3P (3.3 mmol) was added under N_2 atmosphere and the resulting mixture was stirred for 20 min. To the well-stirred mixture, a THF solution of Grignard reagent (3.0 mmol) was added rapidly by a syringe. After stirring for 10 min at the same temperature, the reaction was quenched by the addition of 1M HCl (5 ml). The whole mixture was poured into 1M HCl (100 ml) and extracted with ether (60 ml x 3). The combined organic layer was washed with 1% $NaHCO_3$ and brine (200 ml each), and dried over $MgSO_4$. After removal of the solvent, the residue was subjected to column chromatography (SiO_2; hexane-AcOEt) to afford a pure product.

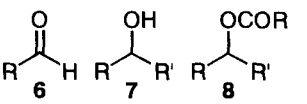
As can be seen in Table 2, the reaction works very well in most cases with MeMgBr, *n*-C_4H_9MgCl, and PhMgBr, giving various ketones in high isolated yields (runs 1~8, 15~19): the presence of an ester or

Table 2 Preparation of Ketones (**4**) by the Reaction of Grignard Reagents with Acyl Tributylphosphonium Ions (**2**) *In Situ* Generated from Acid Chlorides (**1**) and Bu_3P

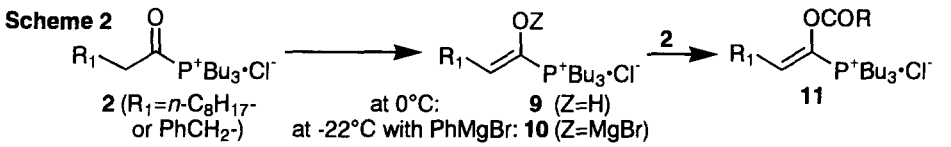
Run	1	Grignard reagent	Yield (%) of 4	Run	1	Grignard reagent	Yield (%) of 4
1	$PhCH_2CH_2COCl$	MeMgBr	85	11	$PhCH_2CH_2COCl$	*iso*-C_3H_7MgBr	35[c]
2	*p*-MeO-C_6H_4COCl	"	96	12	*p*-MeO-C_6H_4COCl	"	43[d]
3	*p*-Br-C_6H_4COCl	"	89	13	$CH_3(CH_2)_8COCl$	PhMgBr	5[e]
4	*p*-NC-C_6H_4COCl	"	89	14	$PhCH_2CH_2COCl$	"	7[f]
5	*p*-MeO_2C-C_6H_4COCl	"	90	15	*iso*-C_3H_7COCl	"	80
6	$PhCH_2CH_2COCl$	*n*-C_4H_9MgCl	97	16	*cyclo*-$C_6H_{11}COCl$	"	86
7	$EtO_2CCH_2CH_2COCl$	"	89	17	*t*-C_4H_9COCl	"	70
8	*cyclo*-$C_6H_{11}COCl$	"	96	18	*p*-MeO-C_6H_4COCl	"	100
9	*p*-MeO-C_6H_4COCl	"	78[a]	19	*p*-MeO_2C-C_6H_4COCl	"	91
10	*p*-MeO_2C-C_6H_4COCl	"	80[b]				

a) **6**, **7**, and **8** were obtained in a 7 % combined yield. b) **7** was afforded in 5 % yield. c) **6** and **7** were obtained in trace amounts. d) **6**, **7**, and **8** were afforded in a 22 % combined yield. e,f) The corresponding carboxylic acids were obtained in 78 and 90 % yields, respectively.

nitrile functionality, liable to react with Grignard reagents, did not interfere with the coupling reactions at all; secondary and tertiary **1** smoothly entered the reaction course. The coupling reactions of *n*-C_4H_9MgCl with aromatic **2** also gave **4** in good yields (runs 9 and 10). However, the aromatic **2** seemed to undergo Meerwein-Pondorff-Verley type reduction as well, inducing the formation of **6**, **7**, and/or **8** although the yields were not significant. Such hydride transfer reaction would be attributed to the much more positive reduction potential of aromatic **2** than that of aliphatic ones as previously reported.[11a] Although **2** derived from secondary and tertiary aliphatic **1** reacted efficiently with PhMgBr to afford **4** in good yields (runs 15~17), the Grignard reagent could not add effectively to primary aliphatic **2**, resulting in the formation of **4** only in poor yields, where the corresponding carboxylic acids were obtained in large amounts (runs 13 and 14). In the case of the reactions of *iso*-C_3H_7MgBr with **2** generated from primary aliphatic and aromatic **1**, **4** were obtained in moderate yields (runs 11 and 12): the products such as **6**, **7**, and/or **8** were also obtained, although the amounts were negligible in the former reaction.



Several points regarding to the mechanism are worthy of comment. Before the present work was undertaken, it was expected that the preferential formation of ketones by the present reactions would be achieved even with excess Grignard reagents through the formation of a stable adduct **3** as depicted in Scheme 1, based on our results that α-hydroxy tributylphosphonium ions, a protonated analogue of **3**, are not decomposed into carbonyl compounds unless they are subjected to aqueous work-up.[11,12] However, the results of the reactions with excess Grignard reagents have demonstrated that **4** is formed during the reaction by the decomposition of **3**. Thus, it can be concluded that the selective formation of ketones by the present reaction is ascribed to the higher reactivity of Grignard reagents toward **2** than **4**. The reaction paths of primary aliphatic **2** seemed to be somewhat complicated, compared with those of other aliphatic **2** as well as aromatic **2**. It has been reported that acetic anhydride reacts with Bu_3P to give acetyl tributylphosphonium ion as an initial intermediate, which seems to be transformed even at -8°C into an enolate intermediate such as **11** depicted in Scheme 2.[13] Accordingly, the significant effects of the reaction temperature upon the reaction of **2** generated from **1a** with MeMgBr (runs 1 and 2 in Table 1)



should be explained by allowing for the formation of **11**, which will be facilitated at 0°C, and will not take place at -22°C, leading to the predominant formation of **4a**: deprotonation at the allylic proton in **11** by MeMgBr will be responsible for the gas evolution observed in the reaction at 0°C. Similarly, the poor yields of **4** in the reaction of primary aliphatic **2** with PhMgBr (runs 13 and 14 in Table 2) could be ascribed to the formation of enolate species **10** and/or **11**, where PhMgBr would function mainly as a base. Alternatively, it can be proposed that the results will arise from the lower reactivity of primary aliphatic **2** toward PhMgBr than other **2**. And yet, this was ruled out by the following facts: no difference was observed in the results of the same reactions with stirring for 10 min and 1 h after the addition of PhMgBr; contrary to the expectation that PhMgBr would react slowly with **2** generated from t-C_4H_9COCl due to steric hindrance, the non-enolizable **2** smoothly reacted with the Grignard reagent (run 17 in Table 2). Thus, the formation of carboxylic acids in large amounts should be attributed to hydrolysis not of **2** themselves but of **10** and/or **11**. At present, it is not clear why secondary aliphatic **2** effectively reacted with PhMgBr to give **4**, even though they are also enolizable as primary aliphatic ones (runs 15 and 16 in Table 2). However, it might be speculated that severe steric interaction between one of the alkyl groups and the tributylphosphonium moiety anticipated in the enol species generated from secondary aliphatic **2** will prevent PhMgBr from working as a base, leading to the exclusive formation of **4**.

In conclusion, we believe that the reaction of *in situ* generated **2** with primary alkyl and arylmagnesium halides provides a convenient and simple procedure to prepare ketones from acid chlorides in one-pot, taking into consideration the facts that the reaction completes rapidly, excess amount of acid chlorides is not required, and the regenerated Bu_3P is easily removed from the products by acidic aqueous work-up. Further studies on the reactions of **2** with other organometallic compounds as well as the chemistry of enolates of **2** are under way.

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