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# Preparation of Trifluoromethylphenyl Magnesium Halides in the Presence of LiCl and Synthesis of 2'-Trifluoromethyl-Aromatic Ketones

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# ABSTRACT

The effect of LiCl-promoted insertion of magnesium turnings into halogenated-trifluoromethylbenzenes for Grignard reagent synthesis was investigated. In the presence of less than 1.0 equivalent of LiCl, chloro(trifluoromethyl)benzene Grignard reagents were easily generated. The 2-trifluoromethylphenyl magnesium chloride Grignard reagent was obtained in high yield and 2'-trifluoromethyl-substituted aromatic ketone was synthesized through reaction of the obtained Grignard reagent with a carboxylic anhydride in an 83% yield.

Keyword: Grignard reagents synthesis, Halogenated benzotrifluorides, LiCl Aromatic ketone,

## **INTRODUCTION**

In general, aromatic ketones are synthesized using a Friedel-Crafts reaction where aromatic substrates react with acyl halides or carboxylic anhydrides in the presence of a Lewis acid such as aluminum chloride;<sup>1</sup> however, this reaction is limited to the acylated position on the aromatic ring. Moreover, aromatic ketones are difficult to obtain using the Friedel-Crafts route in cases where the substrate contains a strong electron-withdrawing group that reduces its reactivity.

When trifluoromethylbenzene is used as the substrate, *ortho-* and *para-*acylated trifluoromethylbenzene are difficult to obtain because acylation occurs at the *meta-*position. Therefore, methods other than the Friedel-Crafts reaction is required when *orth-* or *para-*acylated trifluoromethylbenzene is desired.<sup>2</sup>

The ferrocenyl ketones are obtained via the in situ-ganerated mixed anhydride;<sup>3</sup> however, the method has problems in their industrial use from the viewpoint of the handling on corrosive substance and inexpensive method because an equimolar amount of trifluoroacetic anhydride is necessary.

The synthesis of 3,5-bis(trifluoromethyl)acetophenone was examined through the reaction of a Grignard reagent derived from 3,5-bis(trifluoromethyl)bromobenzene with acetic anhydride. In a previous report, the Grignard reagent was not obtained with Mg turnings due to poor reactivity; therefore, highly reactive Mg dust or a metal-halogen exchange method with *i*PrMgBr was used in the Grignard reagent synthesis. However, halogenated trifluoromethylbenzenes can react dangerously with Mg dust.<sup>5</sup> Moreover, the Grignard reagent decomposition caused by instability occurred with a strong exothermic reaction.<sup>6</sup>

Knochel et al. found that LiCl mediates metal insertion reactions of aryl halides using zinc

powder.<sup>7</sup> LiCl likely increases the solubility of the formed organozinc compound, supplies a clean metal surface due to the formation of a LiCl-complex Grignard reagent, aids in electrophilic activation of aromatic compound,<sup>8</sup> facilitates charge separation from the high ionic strength of LiCl, and accelerates metal insertion.<sup>9</sup> Recently, LiCl was reported to promote preparation of aryl magnesium reagents, as well as aryl zinc halides.<sup>5</sup> In the presence of LiCl (1.25 equivalent) in THF at 0 °C, safe and rapid magnesium insertion into 4-boromo(trifluoromethyl)benzene proceeds with magnesium turnings, and the obtained Grignard reagent is stable. Moreover, the Grignard reagent was cross-coupled with ethyl 4-iodobenzoate, resulting in the biphenyl derivative with high yield.<sup>5</sup> Studer et al. reported that using a Sonogashira-type cross-coupling reaction with an aryl Grignard reagent complexed with LiCl and an alkynyl Grignard reagent, *ortho*-substituted aryl compounds are obtained in high yield;<sup>10</sup> however, there are still few studies reporting on the effects of LiCl on Grignard reagent synthesis and the reaction of aryl Grignard reagents complexed with LiCl.

Herein, we report the effect of LiCl-promotion and the position of halogen-substituted trifluoromethylbenzene on Grignard reagent synthesis. Furthermore, the reaction of the synthesized Grignard reagent with carboxylic anhydrides to form trifluoromethyl-substituted aromatic ketones was examined.

# **RESULTS AND DISCUSSION**

Although aromatic chlorides are generally less expensive and more available than bromides, aromatic chlorides are less reactive.<sup>5</sup> The halogenated trifluoromethylbenzenes in this study exhibit the same behavior.

Table 1. Grignard reagent synthesis from bromo(trifluoromethyl)benzenes (BTFBs).



BTFB

1a : ortho-, 1b : meta-, 1c : para-

Entry	Substrate	LiCl/Substrate (molar ratio)	Conversion (%)	Product	Yield (%)
1	ortho-BTFB	-	∼100	1a	98
2	ortho-BTFB	0.3	∼100	1a	98
3	<i>meta</i> -BTFB	-	∼100	1b	97
4	<i>meta</i> -BTFB	0.3	∼100	1b	96
5	para -BTFB	-	∼100	1c	90
6	para -BTFB	0.3	<b>~</b> 100	1 <b>c</b>	93

Conditions: THF/Mg = 5.0 (molar ratio), Mg/substrate = 1.04 (molar ratio), reaction temp. 40  $^{\circ}$ C, time = 4 h

The bromo(trifluoromethyl)benzenes (BTFBs) in this study were readily transformed into Grignard reagents, regardless of the position of bromine substituent. The presence of LiCl was not observed to affect the rate of formation or the yield of the Grignard reagent, which is likely due to the high reactivity of the BTFBs. Therefore, it can be noted that LiCl is not always necessary for Grignard reagents synthesis of BTFBs. In case of *para*-BTFB, which is reported to be unstable and highly reactive, a decrease in the yield of the Grignard reagent (Table 1, formation of 4,4'-bis(trifluoromethyl)biphenyl, the homo-coupled Grignard reagent (Table 1,

# entries 5, 6).

Table 2. Grignard reagent synthesis from chloro(trifluoromethyl)benzenes (CTFBs)



CTFB

2a : ortho-, 2b : meta-, 2c : para-

Entry	Substrate	LiCl/Substrate (molar ratio)	Temp (°C)	Time (h)	Conversion (%)	Product	Yield (%)
1	ortho -CTFB	-	50	4	91	2a	90
2	meta-CTFB	-	50	7	62	2b	60
3	para -CTFB	-	50	7	0	2c	—
4	ortho -CTFB	0.3	50	4	98	2a	97
5	ortho -CTFB	0.5	50	4	99	2a	98
6	ortho -CTFB	1.0	50	4	98	2a	97
7	<i>meta</i> -CTFB	1.0	50	7	94	2b	86
8	para -CTFB	1.0	50	7	51	2c	49

Conditions: THF/Mg = 5.0 (molar ratio), Mg/substrate = 1.04 (molar ratio).

In case of chloro(trifluoromethy)lbenzenes (CTFBs), the reactivity was found to depend on the position of chloro substituent (Table 2, entries 1–3). An exothermic reaction was observed as soon as drops of *ortho*-CTFB were added into the activated Mg tunings in THF at 50 °C. *ortho*-CTFB was converted to a Grignard reagent with 90% yield after 4 h. In contrast, *meta*-CTFB did not exhibit an exothermic reaction and the rate of metal insertion is slower than that of *ortho*-CTFB. After a 7 h reaction time, ~40% substrate remained (Table 2, entry 2). In the case of *para*-CTFB, the reaction did not proceed, even after intense stirring for 7 hours (Table 2, entry 3).

On the other hand, it is conformed that in the presence of LiCl in THF, the rate of Grignard reagent formation for *ortho-*, *meta-*, and *para-*CTFBs considerably increases (Table 2,

entries 4–6). *ortho*-CTFB was transformed into the Grignard reagent after 4 h in more than 97% yield. The reaction promoting effect can be achieved using only 0.3 equivalent of LiCl, which is less than the relative equivalent of the substrate used. Furthermore, LiCl was seen as a precipitate in the solution after the reaction when more than 1.0 equivalent was used, indicating that less than an equivalent of LiCl is sufficient.

DSC analysis (nitrogen sealed stainless-steel pressure-resistant cell) was performed on the prepared Grignard reagent 2a, as shown in Table 2, entry 4. The onset temperature of exothermal behavior is 115 °C and the calorific value is 95 J/g. Intense decomposition behavior was not observed. The stability of 2a may be improved by the presence of LiCl.

The *meta*-CTFB was transformed into **2b** in a 60% yield in the absence of LiCl after 7 h. In contrast, the yield reached 86% in the presence of LiCl (Table 2, entries 2, 7).

In the case of *para*-CTFB, the reaction did not proceed in the absence of LiCl, but formed **2c** in a 49% yield after 7 h in the presence of 1.0 equivalent of LiCl (Table 2, entry 8).

The presence of LiCl on Grignard formation with CTFBs, and particularly *ortho*-CTFB, resulted in the formation of the desired products, confirming the reaction promoting effect of LiCl; however, although the reaction promoting effect was observed with *meta*- and *para*-CFTBs, the reaction rate is still insufficient for industrialization.

Furthermore, formation of trifluoromethyl-substituted aromatic ketones through coupling with carboxylic anhydrides was examined using the obtained Grignard reagents (**2a** : Table 2, entry 4; **1b** : Table 1, entry 4; and **1c** : Table 1, entry 6).

Table 3. Synthesis of aromatic ketones substituted with a trifluoromethyl group.



Entry	Grignard reagent	Carboxylic anhydride <sup>a)</sup>	Product	Yield <sup>b)</sup> (%)
1	2a	(CH <sub>3</sub> CO) <sub>2</sub> O	3a	83
2	1	$(C_2H_5CO)_2O$	4a	73
3	1	$(C_3H_7CO)_2O$	5a	74
4	1a	(CH <sub>3</sub> CO) <sub>2</sub> O	3a	83
5	1b	$(CH_3CO)_2O$	3b	52
6	1c	1	3c	35

Reaction conditions: reaction temp. 30 °C, time 2 h

a) Carboxylic anhydride/substrate = 1.5 (mol/mol)

b) Calculated with respect to substrate

The reaction of **2a** with carboxylic anhydride to 2'-trifluoromethyl aromatic ketones proceeded rapidly under the mild conditions in a 70% yield, regardless of the identity of the carboxylic anhydrides (Table 3, entries 1-3) and the yield of 2'-trifluoromethyl aromatic ketones was the same (Table 3, entries 1, 4).

In case of **1b** or **1c**, the yield substantially decreased compared to **2a**. The reaction of these Grignard reagents (**1b** or **1c**) with carboxylic anhydrides yielded byproducts (Scheme 1, compounds **6** and **7**), which were identified by GCMS analysis. Compound 6 was formed through reaction of the desired aromatic ketone with additional Grignard reagent, and compound **7** was formed through reaction of 6 with additional carboxylic anhydride.

The higher yield of 2'-trifluoromethyl aromatic ketones compared to 3'- or 4'-trifluoromethyl aromatic ketones is likely due to steric interference by the trifluoromethyl

group next to the acyl group, that is, 3'- or 4'-trifluoromethyl aromatic ketones are subjected to attack by the Grignard reagent as indicated below (Scheme 1). Conversely, 2'-trifluoromethyl aromatic ketones are hard to recieve the attack of the Grignard reagent.



Scheme 1. Formation of byproducts

Table 4. Optimization of the reaction temperature on formation of2'-trifluoromethylpropiophenone



Reaction conditions: carboxylic anhydride/substrate = 1.0 (mol/mol), reaction time 2 h a) Calculated with respect to substrate

The influence of the reaction temperature was investigated for the synthesis of 2'-trifluoromethylpropiophenone 4a through reaction with 2a and propionic acid anhydride. When the temperature was more than 50 °C, the yield of 4a was reduced, due to the formation of byproducts 6 and 7.

Formation of **4a** using Grignard reagents and propionic anhydride was found to be controlled by low reaction temperatures. **4a** was obtained after quenching the reaction with an aqueous solution, washing with aqueous NaCl, and distillation using a filling tower (number of theoretical plates = 3). Total yield was 59% and the purity was found to be 99.6% (GC area %) as a clear, colorless oil.

#### **EXPERIMENTAL SECTION**

#### **Grignard reagent synthesis (General Procedure)**

1 mol/L EtMgBr/THF solution (0.5 g) was added to a mixture of Mg turnings (5.1 g, 0.208 mol), LiCl (2.54 g, 0.06 mol) and THF (75.0 g) under nitrogen gas flow (for removing water) in a 200 mL flask at room temperature. EtBr (0.44 g, 0.004 mol) was added for removing the oxide film from the surface of the Mg turnings with a slight increase in temperature. 1-chloro-2-(trifluoromethyl)benzene (36.1 g, 0.2 mol) was added gradually using a dropping funnel to the mixture at ~50 °C; furthermore, the reaction mixture was stirred at 50 °C for 4 h to obtain the Grignard reagent. The reaction mixture was then diluted with toluene (10.8 g). A sample of the solution was hydrolyzed with a saturated aqueous ammonium chloride solution, and GC analysis was performed on a diethyl ether abstracted solution from that sample. The conversion and vield calculated relative the amount of were to 1-chloro-2-(trifluoromethyl)benzene.

### **Coupling with acid anhydride (General Procedure of 4a)**

The Grignard reagent was gradually added using a dropping funnel into a solution of propionic anhydride (26.0 g, 0.2 mol) and toluene (43.3 g) at 30 °C in a 200 mL flask under  $N_2$  flow in a water bath. Furthermore, the reaction mixture was stirred at 30 °C for 2 h. A sample of the solution was analyzed by GC. The yield was calculated relative to the amount of 1-chloro-2-(trifluoromethyl)benzene.

### **Coupling with acid anhydride (General Procedure of 3a)**

The Grignard reagent was gradually added using a dropping funnel into a solution of acetic anhydride (20.6 g, 0.2 mol) and toluene (43.3 g) at 30 °C in a 200 mL flask under  $N_2$  flow in a water bath. Furthermore, the reaction mixture was stirred at 30 °C for 2 h. A sample of the solution was analyzed by GC. The yield was calculated relative to the amount of 1-chloro-2-(trifluoromethyl)benzene.

**Coupling with acid anhydride (General Procedure of 5a)** 

The Grignard reagent was gradually added using a dropping funnel into a solution of butyric anhydride (31.6 g, 0.2 mol) and toluene (43.3 g) at 30 °C in a 200 mL flask under N<sub>2</sub> flow in a water bath. Furthermore, the reaction mixture was stirred at 30 °C for 2 h. A sample of the solution was analyzed by GC. The yield was calculated relative to the amount of 1-chloro-2-(trifluoromethyl)benzene.

## **Distillation (General Procedure)**

3 wt% aqueous HCl solution (39.2 g) was added dropwise into the reaction mixture. Furthermore, the solution was stirred for 1 h then left undisturbed to separate oil and water layers. The oil layer was removed and washed with a 0.015 wt% NaCl aqueous solution (18.6 g) twice. The oil was distilled under reduced pressure and the main fraction was collected at a temperature range of 85–89 °C at 1333 Pa.

**2'-Trifluoromethyl propiophenone 4a**: <sup>1</sup>H NMR  $\delta$  7.37–7.73 (m, 4H), 2.83–2.90 (q, *J* = 8 Hz, 2H), 1.18–1.24(t, *J* = 8 Hz, 3H); <sup>19</sup>F NMR  $\delta$  -59.29 (s).

**2'-Trifluoromethyl acetophenone 3a**: <sup>1</sup>H NMR  $\delta$  7.44–7.74 (m, 4H), 2.57–2.60 (s, 3H); <sup>19</sup>F NMR  $\delta$  -59.35 (s).

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