Conjugate Addition of RMgX–3MeLi to α,β-Unsaturated Amides and α,β-Unsaturated Carboxylic Acids

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In the presence of 3 equivalents of MeLi, various Grignard reagents reacted with secondary α,β-unsaturated amides and α,β-unsaturated carboxylic acids to give the corresponding Michael adducts in good yields.

In the course of our studies on the regioselective additions of RLi to 3-(trimethylsilyl)acrylamide and cinnamamide derivatives,[1] we have found that conjugate addition of MeLi is extraordinary sluggish compared with other alkyl- and aryl-lithium reagents.[2]

On the other hand, it is well-known fact that Grignard reagents are easily prepared and handled, however, one of the drawbacks of the reagents is their low reactivity compared with the corresponding organolithium reagents.[3] Thus, we envisioned to activate Grignard reagents with MeLi in the conjugate addition to secondary α,β-unsaturated amides and α,β-unsaturated carboxylic acids. Generally none of these Michael acceptors reacts with organocuprates or Grignard reagents.[3–6]

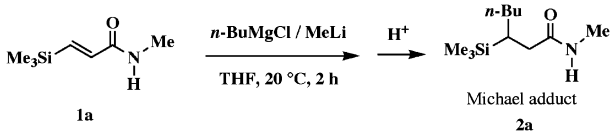
Actually, no Michael adduct **2a** was obtained by the reaction of *n*-BuMgCl with 3-(trimethylsilyl)acrylamide **1a** at 20 °C for 2 h (Entry 1 in Table 1). Then, the reaction was carried out in the presence of MeLi. When the reacion was carried out by sequential addition of the Grignard reagent and MeLi to **1a**, the yields of adduct were often variable and low. Thus, in the following reactions, *n*-BuMgCl and MeLi was mixed at 0 °C and stirred at that temperature for 20 min before use.[7]

In the presence of 1 equiv. of MeLi,[8] *n*-BuMgCl gave only a small amount of the Michael adduct **2a** under the same reaction conditions (Entry 2). Good yields of **2a** were obtained in the presence of 2–5 equiv. of MeLi (Entries 3–6, in Table 1). There was no remarkable difference when more than 3 equiv. of MeLi was used (Entries 4–6). Though the identification of actual active species is difficult, it can be pointed out that the formation of higher order ate complexes, $RMe_nMgLi_{(n-1)}$ ($n \geq 3$), plays an important role in this conjugate addition.[9] It is noteworthy that in all the above cases, *n*-Bu group of the complex was preferentially transferred and no Me group-transferred product was found.

Conjugate additions of three RMgX–3MeLi reagents to some secondary α,β-unsaturated amides were surveyed (Table 2). The reactions were carried out with 4 equiv. of RMgX–3MeLi since lack of reproducibility was observed when 2.5–3 equiv. of RMgX–3MeLi was used. In all the cases no addition product was obtained without MeLi under the same reaction conditions. As long as judged from the reaction temperature, the order of their reactivity is suggested as follows: *t*-BuMgCl–3MeLi > *n*-BuMgCl–3MeLi > PhMgBr–3MeLi. Addition of *t*-BuMgCl–3MeLi to crotonamide gave the Michael-adduct in good yield (Entry 4).

On the contrary, *t*-BuMgCl–3MeLi gave the corresponding contra-Michael adducts (2-*t*-butyl derivatives)[1] by the reaction with 3-trimethylsilyl- and 3-phenyl-substituted acrylamide derivatives (Entries 2 and 7). PhMgBr–3MeLi (Entries 1, 5, and 8) and *n*-BuMgCl–3MeLi (Entries 3 and 6) reagents gave the corresponding Michael-adducts in fair to good yields. In these cases also no Me group-transferred product was found. The results in Table 2 in conjunction with those reported by us[1] led us to the conclusion that RMgX–3MeLi reagents are more reactive than the corresponding Grignard reagents but less reactive than RLi.

Table 1. Effect of MeLi in the addition of *n*-BuMgCl to **1a**

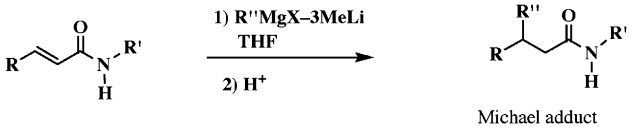


1a **2a**

Entry	Molar ratio (*n*-BuMgCl:MeLi)[a]	Yield/%[a] **2a**
1	—	—
2	1:1	7
3	1:2	54
4	1:3	82
5	1:4	78
6	1:5	83

[a]Molar ratio of **1a**:*n*-BuMgCl is 1:4. [b]Isolated yield.

Table 2. Conjugate addition of R″MgX–3MeLi to secondary α,β-unsaturated amides

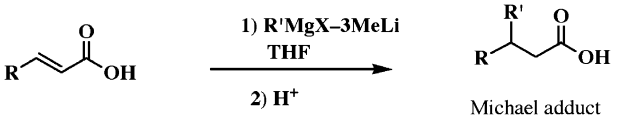


1 **2**

Entry	R	R′	R″MgX	Temp/Time °C/h	Yields/%[a] **2**
1	Me_3Si	Me	PhMgBr	rt/2	77
2			*t*-BuMgCl	rt/2	69[b]
3	Me	Ph	*n*-BuMgCl	0/5	40
4			*t*-BuMgCl	−10/1	66
5			PhMgBr	rt/3	43
6	Ph	Ph	*n*-BuMgCl	−10/2	74
7			*t*-BuMgCl	−30/1	59[b]
8			PhMgBr	rt/3	59

[a]Isolated yield. [b]The product was not the Michael adduct **2** but the contra-Michael adduct (2-*t*-butyl derivative).[1]

Table 3. Conjugate addition of R′MgX–3MeLi to α,β-unsaturated carboxylic acids



3 4

Entry	R	R′MgX	Temp/Time °C/h	Yields/%[a] **4**
1	Ph	*n*-BuMgCl	−15/1.5	60
2		*s*-BuMgCl	−15/1.5	60
3		PhMgBr	40/3.5	58
4	$PhCH_2CH_2$	*n*-BuMgCl	−15/1.5	50[b]
5		*t*-BuMgCl	−30/1.5	67[b]
6		PhMgBr	rt/3	36[b]

[a]Isolated yield. [b]Isolated as the corresponding methyl ester.

Conjugate addition of RMgX–3MeLi reagents to α,β-unsaturated carboxylic acids was also demonstrated (Table 3). In some cases, esterification with DMF dimethylacetal (at 80 °C for 2 h) was carried out to facilitate the purification of addition products by p-TLC.[11]

Though the conjugate addition of *t*-BuMgCl–3MeLi to cinnamic acid was unsuccessful, *n*-BuMgCl–3MeLi, *s*-BuMgCl–3MeLi, and PhMgCl–3MeLi reacted with cinnamic acid to give the corresponding Michael adducts in good yields (Entries 1–3). The reaction of *n*-BuMgCl–3MeLi, *t*-BuMgCl–3MeLi, PhMgCl–3MeLi with 5-phenyl-2-pentenoic acid gave Michael adducts in good yields (Entries 4–6). In the above cases also, no Michael adduct was obtained without MeLi under the same reaction conditions and transfer of Me group from RMgX–3MeLi reagents was not observed.

In conclusion, though the mechanistic investigations still remain, activation of Grignard reagents with 3 equiv. of MeLi was demonstrated.

We are grateful to Dr. K. Takenaka, of this university, for measurement of MS spectra.

References and Notes

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7 A typical procedure for secondary α,β-unsaturated amides: To a solution of *n*-BuMgCl (0.89 M in THF, 2.3 mL, 2 mmol) was added MeLi (1.13 M in Et_2O, 5.3 mL, 6 mmol) at 0 °C. After stirring for 20 min at that temperature, **1a** (75 mg, 0.5 mmol) in THF (5 mL) was added and the reaction mixture was stirred under Ar at 20 °C for 2 h. Quenching with aqueous NH_4Cl (2 mL), extraction with ethyl acetate, and purification by silica gel TLC (hexane:AcOEt = 1:1) gave **2a** in 82% yield as a colorless oil.

8 Presumably, the following equilibration presents under the reaction conditions.

$$2n\text{-BuMeMg} \rightleftarrows (n\text{-Bu})_2\text{Mg} + \text{Me}_2\text{Mg}$$

9 The equilibration of methyl groups in mixtures of MeMgX and MeLi is believed to proceed via the formation of a series of complexes as illustrated below.[10]

$$\text{MeMgX} \overset{\text{MeLi}}{\rightleftarrows} \text{Me}_2\text{Mg} \overset{\text{MeLi}}{\rightleftarrows} \text{Me}_3\text{MgLi}$$
$$\overset{\text{MeLi}}{\rightleftarrows} \text{Me}_4\text{MgLi}_2 \overset{\text{MeLi}}{\rightleftarrows} \text{Me}_5\text{MgLi}_3$$

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11 A typical procedure for α,β-unsaturated carboxylic acid: To a solution of *t*-BuMgCl (1.01 M in THF, 1.0 mL, 1.0 mmol) was added MeLi (1.13 M in Et_2O, 2.7 mL, 3 mmol) at 0 °C. After stirring for 30 min at that temperature, the mixture was cooled to −30 °C. 5-Phenyl-2-pentenoic acid (45 mg, 0.25 mmol) in THF (4 mL) was added and the reaction mixture was stirred under Ar at −30 °C for 1.5 h. Quenching with 2 M HCl (4 mL), extraction with ethyl acetate, and concentration gave a crude oil which was treated with *N*,*N*-dimethylformamide dimethyl acetal (300 μL) at 80 °C for 2 h. Condensation and purification by silica gel TLC (hexane:AcOEt = 10:1) gave methyl 3-*t*-butyl-5-phenyl-2-pentenoate in 67% yield as a colorless oil.

Published on the web (Advance View) May 9, 2007; doi:10.1246/cl.2007.736