Synthesis of Ketones from Carboxylic Acids with R(PrNH)Mg

Maria Ohki and Morio Asaoka*
Department of Chemical and Biological Sciences, Faculty of Science, Japan Women's University,
2-8-1 Mejirodai, Bunkyo-ku, Tokyo 112-8681

(Received June 4, 2009; CL-090537; E-mail: asaoka-m@fc.jwu.ac.jp)

A widely applicable procedure for the preparation of ketones from carboxylic acids via sodium salts with R(PrNH)Mg is described.

Preparation of ketones from carboxylic acids is one of the most important transformations in organic synthesis. It is well known that the treatment of carboxylic acids with alkyl- or aryllithiums gave the corresponding ketones.[1] Although Grignard reagents are more easily prepared and handled than the corresponding organolithium compounds, Grignard reagents cannot be used in place of lithium reagents in the above ketone synthesis because of low yields of ketones and formation of tertiary alcohols.[2] Fiandanese et al. reported the synthesis of diaryl and aryl alkyl ketones by the reaction of carboxylic acids with Grignard reagents in the presence of Ni catalyst.[3]

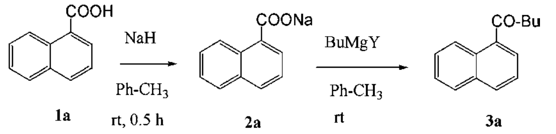
To develop more widely applicable ketone synthesis from carboxylic acids, we carried out the reaction with various magnesium reagents since the versatility and ready availability of Grignard and related magnesium reagents are well documented.[4]

In view of molecular economy of magnesium reagents, sodium carboxylates prepared in situ were used in the following reactions.

After conversion of 1-naphthoic acid (**1a**) into its sodium salt **2a** with NaH, various magnesium reagents were allowed to react. The reaction of a Grignard reagent with **2a** gave the corresponding tertiary alcohol as a major product, i.e., the reaction of BuMgCl at rt for 4 h gave ketone **3a** in 17% yield and the corresponding tertiary alcohol, 5-(1-naphthyl)-5-nonanol, in 46% yield. In contrast, Bu_2Mg gave ketone **3a** in 91% yield (Table 1, Entry 1). Since half of the R source in R_2Mg is sacrificed, one of the R groups was replaced with an unreactive group Y.

Reactions with unsymmetrical magnesium reagents, BuMgY, were surveyed. As a nontransferable group, 1-hexynyl residue was chosen and reacted with **2a**. Ketone **3a** was obtained in good yield (71%, Entry 2). Heteroatom-containing "dummy" ligands were also examined. When PrNH residue was introduced,[5] **3a** was obtained in 77% yield (Entry 3). Inferior results were obtained by the introduction of Ph–NH or CH_3O residues (Entries 4 and 5). In these cases, prolonged reaction periods did not cause improvement of the yields. Presumably, the reactivity depends on the basicity of Y^-.

Table 1. Reaction of BuMgY with **1a** via its sodium salt **2a**



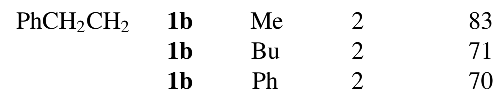
Entry	Y[a]	Time/h	Yield/%[b]	
			3a	**1a**
1	Bu	4	91	5
2	BuC≡C	6	71	3
3	PrNH	4	77	2
4	PhNH	4	39	30
5	MeO	4	37	48

[a]Two equivalents of BuMgY were used. [b]Isolated yield.

On the basis of the above results, we have chosen two types of magnesium reagents, R_2Mg and R(PrNH)Mg, and carried out their reactions with various sodium carboxylates.

The reaction of R_2Mg with two types of sodium carboxylates was carried out and the results are summarized in Table 2.[6] Primary alkyl and phenyl groups of R_2Mg were easily transferred to give the corresponding ketones in good to high yields (Entries 1, 2, 3, 6, 7, and 8). However, $(s\text{-}Bu)_2Mg$ gave the corresponding ketones in fair yields (Entries 4 and 9). Only a trace amount of ketone was obtained when $(t\text{-}Bu)_2Mg$ was used (Entry 5) and a large amount of the starting acid was recovered.

Table 2. Reaction of R_2Mg with sodium carboxylates



Entry	R′	**1**	R[a]	Time/h	Yield/%[b]
1	1-Naphthyl	**1a**	Me	4	77
2		**1a**	Bu	4	91
3		**1a**	Ph	4	80
4		**1a**	*s*-Bu	4	37
5		**1a**	*t*-Bu	4	trace
6	$PhCH_2CH_2$	**1b**	Me	2	83
7		**1b**	Bu	2	71
8		**1b**	Ph	2	70
9		**1b**	*s*-Bu	2	8

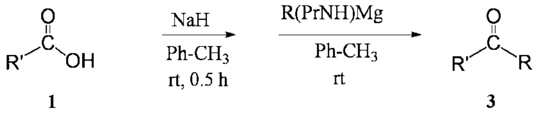
[a]Two equivalents of R_2Mg were used. [b]Isolated yield.

While the above reaction worked reasonably well, an alternative method with R(PrNH)Mg was also examined.

Usually, alkylmagnesium amides [R(R″NH)Mg] are prepared by the reaction of dialkylmagnesiums (R_2Mg) with the corresponding amine ($R''NH_2$),[4] however, in view of availability and atom economy, we prepared the alkylmagnesium amide reagents, R(PrNH)Mg, by the reaction of RMgX with PrNHLi, which in turn was prepared from $PrNH_2$ and CH_3Li (or BuLi).[8]

As shown in Table 3, the reaction of various R(PrNH)Mg with sodium salts of aromatic and aliphatic carboxylic acids proceeded smoothly to give various aryl and alkyl ketones in good to high yields.[8] Not only primary alkyl groups but also secondary alkyl groups were successfully transferred to give the corresponding ketones, i.e., isopropyl and cyclohexyl keones, in good

Table 3. Reaction of R(PrNH)Mg with sodium carboxylates



Entry	R′	1	R^{a}	Time/h	Yield/%^{b}
1	1-Naphthyl	**1a**	Me	4	80
2		**1a**	Et	4	72
3		**1a**	Pr	4	70
4		**1a**	Bu	4	77
5		**1a**	Dec	4	71
6		**1a**	Ph	4	82
7		**1a**	*i*-Pr	4	57
8	$PhCH_2CH_2$–	**1b**	Me	1	90
9		**1b**	Et	1	85
10		**1b**	Pr	2	73
11		**1b**	Bu	1	84
12		**1b**	Dec	1	68
13		**1b**	Ph	1	81
14		**1b**	*i*-Pr	1	35
15	$CH_3(CH_2)_8$–	**1c**	Et	0.1	67
16		**1c**	Bu	0.1	67
17	Ph	**1d**	Pr	1	84
18		**1d**	*i*-Pr	1	86
19		**1d**	Bu	1	81
20		**1d**	Dec	1	89
21		**1d**	*c*-Hex	1	82

^{a}Two equivalents of R(PrNH)Mg were used. ^{b}Isolated yield.

to moderate yields (Entries 7, 14, 18, and 21). The reaction of *t*-Bu(PrNH)Mg with **2a** was sluggish and a large amount of **1a** was recovered under the same reaction conditions. Among the solvents examined (toluene, ether, and THF), toluene is the best choice, and when the reaction was carried out in THF, formation of some by-products was observed. Even the use of THF solutions of Grignard reagent for the preparation of R(PrNH)Mg caused depression of the yields of ketones **3**. Therefore, Grignard reagents in Et_2O solvent were used for the preparation of R(PrNH)Mg.

In almost all the cases, formation of appreciable amount of the corresponding tertiary alcohols was not observed.

In conclusion, a new synthesis of various ketones from carboxylic acids via their sodium salts with R(PrNH)Mg was demonstrated.

References and Notes

1 M. J. Jorgenson, *Org. React.* **1970**, *18*, 1; T. M. Bare, H. O. House, *Org. Synth.* **1955**, Coll. Vol. *V*, 775; R. Levine, M. J. Karten, *J. Org. Chem.* **1976**, *41*, 1176; D. E. Nicodem, M. L. P. F. C. Marchiori, *J. Org. Chem.* **1981**, *46*, 3928.

2 Although the early literature records a number of examples of ketone synthesis by the reaction of Grignard reagents with carboxylic acids or metal carboxylates they are less satisfactory than the corresponding organolithium method. M. S. Kharasch, O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ **1954**; B. J. Wakefield, *Organomagnesium Methods in Organic Synthesis*, Academic Press, UK, **1995**.

3 V. Fiandanese, G. Marchese, L. Ronzini, *Tetrahedron Lett.* **1983**, *24*, 3677.

4 *Handbook of Grignard Reagents*, ed. by G. S. Silverman, P. E. Rakita, CRC Press, New York, **1996**; *Grignard Reagents New Developments*, ed. by H. G. Richey, Jr., John Wiley & Sons, Ltd, UK, **2000**; *The Chemistry of Organomagnesium Compounds Part 1 and 2*, ed. by Z. Rappoport, I. Marek, John Wiley & Sons, Ltd, UK, **2008**.

5 There are only a limited number of reports on the reaction of organomagnesium amide reagents. B. Conway, E. Hevia, A. R. Kennedy, R. E. Mulvey, S. Weatherstone, *Dalton Trans.* **2005**, 1532; E. L. Carswell, D. Hayes, K. W. Hendarson, W. J. Kerr, C. J. Russell, *Synlett* **2003**, 1017; P. E. Eaton, M.-X. Zhang, N. Komiya, C.-G. Yang, I. Steele, R. Gilardi, *Synlett* **2003**, 1275; K. H. Yong, N. J. Taylor, J. M. Chong, *Org. Lett.* **2002**, *4*, 3553; K. H. Yong, J. M. Chong, *Org. Lett.* **2002**, *4*, 4139; M.-X. Zhang, P. E. Eaton, *Angew. Chem., Int. Ed.* **2002**, *41*, 2169; M. P. Sibi, Y. Asano, *J. Am. Chem. Soc.* **2001**, *123*, 9708; M. T. Reetz, N. Harmat, R. Mahrwald, *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 342; E. C. Ashby, G. F. Willard, *J. Org. Chem.* **1978**, *43*, 4094, and references contained in each.

6 A typical procedure: A mixture of NaH (55% in oil, 50 mg, 1.15 mmol) and 1-naphthoic acid (172 mg, 0.75 mmol) in dry toluene (30 mL) was stirred under argon at room temperature for 0.5 h. To the mixture was added a solution of Bu_2Mg prepared from BuMgCl (0.91 M in THF, 1.5 mmol) and BuLi (1.65 M in hexane, 1.5 mmol) at room temperature. After 4 h stirring, acetone (0.2 mL) and 2 M hydrochloric acid (4 mL) were added. Usual work-up followed by purification by p-TLC (hexane:AcOEt = 8:1) gave butyl 1-naphthyl ketone (145 mg, 91%).

The direct reaction of Bu_2Mg (3 equiv) with 1-naphthoic acid (**1a**) under the same reaction conditions furnished butyl 1-naphthyl ketone in 67% yield and 5-(1-naphthyl)-5-nonanol in 20% yield. The reaction of salt free Bu_2Mg, prepared by the method of Y. Saheki et al.,[7] with **2a** gave butyl 1-naphthyl ketone in 60% yield and 5-(1-naphthyl)-5-nonanol in 19% yield.

7 Y. Saheki, K. Sasada, N. Satoh, N. Kawaichi, K. Negoro, *Chem. Lett.*, **1987**, 2299.

8 A typical procedure: A mixture of NaH (55% in oil, 50 mg, 1.15 mmol) and 3-phenylpropionic acid (113 mg, 0.75 mmol) in dry toluene (7.5 mL) was stirred under argon at room temperature for 0.5 h. To the mixture was added a solution of Bu(PrNH)Mg prepared from BuMgBr (0.64 M in Et_2O, 1.5 mmol) and PrNHLi (1.5 mmol) which in turn was prepared from MeLi (1.09 M in Et_2O, 1.5 mmol) and $PrNH_2$ (1.5 mmol). After 1 h stirring, acetone (0.2 mL) and 2 M hydrochloric acid (8 mL) were added. Usual work-up followed by purification by p-TLC (hexane:AcOEt = 7:1) gave 1-phenyl-3-heptanone (121 mg, 84%).

Published on the web (Advance View) July 25, 2009; doi:10.1246/cl.2009.856