

# Synthesis of Cyclohexyl and Isopropyl Ketones from Benzimidazole Methiodide Salt and Grignard Reagents

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The reaction of 2-alkyl-1,3-dimethylbenzimidazolium salts with Grignard reagents gave addition products which were hydrolyzed to give ketones. A new method for the preparation of cyclohexyl ketones and isopropyl ketones is provided.

**Keywords** benzimidazolium salt, cyclohexyl ketones, isopropyl ketone, synthesis

## Introduction

The coenzyme  $N^5, N^{10}$ -methenyltetrahydrofolate uses 2-imidazoline ring in the transfer of a single carbon at the carboxylate oxidation level. The methods to mimic such processes have been developed.<sup>1</sup> New methods for the preparation of aldehydes and ketones via imidazoline as tetrahydrofolate coenzyme model have been provided.<sup>2</sup> In this paper, the reaction of 2-alkyl-1,3-dimethylbenzimidazolium salts with Grignard reagents was reported, the products were hydrolyzed to give ketones. As a new tetrahydrofolate coenzyme model, benzimidazolium salts transfer substituted single carbon at the carboxylate oxidation level in the reaction, cyclohexyl ketones and isopropyl ketones were prepared via this reaction.

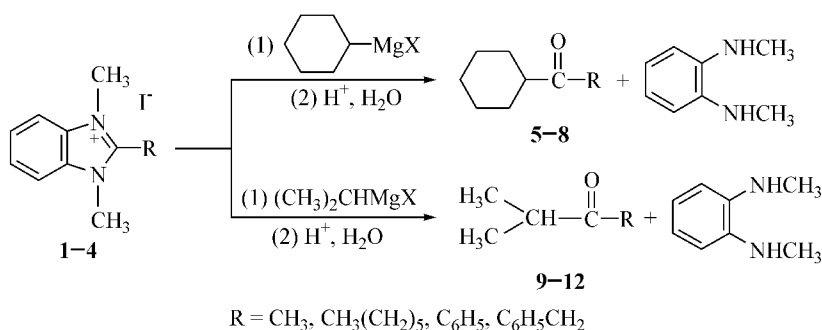
Addition of Grignard reagents to benzimidazolium salts in dry tetrahydrofuran led to formation of benzimidazolidines, which could be hydrolyzed in acidic solution (5% hydrochloric acid) to give ketones. The addition-hy-

drolysis reaction is shown in Scheme 1.

Carbonyl compounds are obviously of most important in synthetic organic chemistry. Methods for converting carboxylic acid into ketones generally make use of the controlled partial reduction of esters using diisobutylaluminum hydride, or partial reduction of acid chlorides with lithium tri-*t*-butoxyaluminum hydrides or Grignard reagents in the presence of special catalyst at very low temperature.<sup>3,4</sup> Methods by using heterocyclic compounds and Grignard reagents were also reported.<sup>5,6</sup> But at the same time, Meyers<sup>7</sup> found that the Grignard reagents appear to complex with the heterocyclic oxygen or sulfur, resulting in ring cleavage by virtue of addition of a second equivalent of the Grignard reagent.

In the method described in this paper, the intermediate benzimidazolidine produced from the reaction of Grignard reagent with benzimidazolium salt is stable, and it can not be decomposed to ketone which can react with Grignard reagent further under the same reaction conditions. Benzimidazolium salts could be prepared from methyl iodide and benzimidazole which could be prepared from carboxylic acid and *o*-phenylenediamine. The syntheses of cyclohexyl ketones and isopropyl ketones are difficult, so the above-mentioned route provides a useful method for synthesizing cyclohexyl ketones and isopropyl ketones from carboxylic acid and *o*-phenylenediamine.

## Scheme 1



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## Experimental

Melting points were taken on a model X<sub>4</sub> melting point apparatus and uncorrected. Infrared spectra were recorded on a EQUINOX55 spectrophotometer. Reactions were monitored by thin layer chromatography using Alugram silica gel/UV<sub>254</sub>. Solvents were purified by standard methods.

### Preparation of benzimidazolium salts

Benzimidazolium salts were prepared by the reported procedures.<sup>8,9</sup> The experimental data are listed in Table 1. Grignard reagents were conveniently prepared by general method.

### General procedure for the preparation of ketones

Grignard reagent (0.015 mol) in dry tetrahydrofuran (200 mL) was prepared in a three-necked round-bottomed flask, then benzimidazolium salt (0.01 mol) was added to the Grignard reagent solution in small portions over 30

min. The suspension was stirred at refluxing temperature for about 28–30 h till the reaction was finished. Tetrahydrofuran was removed by distillation and the residue was shaken with 5% hydrochloric acid (50 mL) in a separatory funnel. The aqueous layer was separated, extracted twice with ether or chloroform (2 × 30 mL). The combined organic layers were washed with sodium chloride solution, dried over anhydrous magnesium sulfate and evaporated to give ketones on distillation.

## Results and discussion

The results of experiments were summarized in Table 2. As shown in Table 2, expected ketones were synthesized in good yields under mild conditions except **7** and **11**.

The reaction described in this paper can be reasonably explained by the addition reaction of Grignard reagent with quaternary C=N bond of benzimidazolium iodide and the formation of benzimidazolidine which can be hydrolyzed to give ketone in acidic solution. The mechanism for the addition-hydrolysis reaction is shown in Scheme 2.

**Table 1** Preparation of benzimidazolium salts

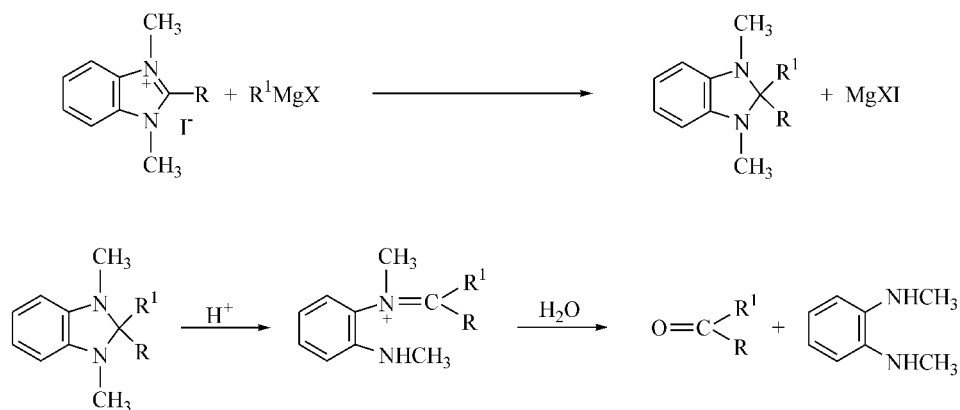
Comp.	R	Color and state	m.p. (°C)	Yield (%)
<b>1</b>	CH <sub>3</sub>	Colorless needles	254–255 (255) <sup>g</sup>	72
<b>2</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	Colorless needles	180–182 (182–184) <sup>g</sup>	72
<b>3</b>	C <sub>6</sub> H <sub>5</sub>	Bright platelets	272–273 (273) <sup>g</sup>	62
<b>4</b>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	Colorless prisms	278–280 (278–280) <sup>g</sup>	53

**Table 2** Preparation of ketones

Comp.	R	Color and state	m.p. (b.p.) (°C)	$\nu$ (cm <sup>-1</sup> )	Yield (%)
<b>5</b>	CH <sub>3</sub>	Yellow liquid	115–117 (117) <sup>0 a</sup>	1720	67
<b>6</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	Yellow liquid	200–202 (93 kPa) <sup>1</sup>	1715	64
<b>7</b>	C <sub>6</sub> H <sub>5</sub>	—	—	—	—
<b>8<sup>b</sup></b>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	Colorless oil	140–141 (140) <sup>2 c</sup>	1720	53
<b>9</b>	CH <sub>3</sub>	Yellow liquid	176–177 (177) <sup>3 c</sup>	1710	71
<b>10</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	Colorless oil	110–115 (140 Pa) <sup>4</sup>	1710	68
<b>11</b>	C <sub>6</sub> H <sub>5</sub>	—	—	—	—
<b>12<sup>b</sup></b>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	Colorless oil	138–140 (700 Pa) <sup>5</sup>	1705	49

<sup>a</sup> m.p. of 2-*A*-dinitrophenylhydrazone. <sup>b</sup> Should be stored at low temperature under nitrogen atmosphere. <sup>c</sup> m.p. of semicarbazone.

### Scheme 2



The formation of quaternary ammonium salt probably assists the addition reaction by increasing the polarity of C=N double bond being attacked by Grignard reagent, since the C=N bond itself does not successfully undergo the reaction with Grignard reagent. Further investigation on this kind of reaction is being continued in our laboratory.

## References

- 1 Bieraugel, H. ; Plemp, R. ; Hiemstra, H. C. ; Pandit, U. K. *Tetrahedron* **1983**, *39*, 3971.
- 2 Anderson, M. W. ; Jones, R. C. F. ; Saunders, J. J. *Chem. Soc., Chem. Commun.* **1982**, 282.
- 3 Shirley, D. A. *Org. React.* **1954**, *8*, 28.
- 4 Bergbreiter, D. E. ; Killough, J. M. *J. Org. Chem.* **1976**, *41*, 2750.
- 5 Degani, I. ; Fochi, R. *Gazz. Chim. Ital.* **1975**, *105*, 907.
- 6 Meyers, A. I. ; Temple, D. L. *J. Am. Chem. Soc.* **1970**, *92*, 6644.
- 7 Meyers, A. I. ; Collington, E. W. *J. Am. Chem. Soc.* **1970**, *92*, 6676.
- 8 El 'tsov, A. V. ; Muravich, Kh. L. *Zh. Org. Khim.* **1965**, *1*, 1307.
- 9 Craig, J. C. ; Erwiribe, N. N. *Synthesis* **1981**, 303.
- 10 Bunce, S. C. ; Clemans, S. D. ; Bennett, B. A. *J. Org. Chem.* **1975**, *40*, 961.
- 11 Heilborn, I. *Dictionary of Organic Compounds*, Chapman and Hall, New York, **1982**.
- 12 Krapcho, A. P. ; Kashdan, D. S. ; Jahngen, E. G. ; Lovey, A. J. *J. Org. Chem.* **1977**, *42*, 1189.
- 13 Hell, C. ; Schaal, O. *Chem. Ber.* **1907**, *40*, 4163.
- 14 Lythgoe, B. ; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2429.
- 15 Inaba, S. ; Rieke, R. D. *J. Org. Chem.* **1985**, *50*, 1373.

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