

## COMMUNICATIONS TO THE EDITOR

A Mild Condition for C-Alkylation of  $\beta$ -Ketoester

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$\beta$ -Ketoesters are important building blocks and are widely used in synthetic organic chemistry. The acidic nature of the methylene protons provides a convenient way of introducing various electrophiles at that position. However reactions require relatively strong base such as sodium alkoxide or sodium hydride in a solvent like DMF and the reactions tend to give a mixture of the C-alkylated, O-alkylated and dialkylated products depending on the reaction condition.<sup>1</sup> Herein we would like to report a condition which requires a weaker organic base and which gives the mono C-alkylated product exclusively.

When the mixture of ethyl acetoacetate, diisopropylethylamine and benzyl bromide was refluxed in the presence of 1 eq. of LiCl, the desired mono C-alkylated product was obtained in high yield. The other possible O-alkylated product was not detected.

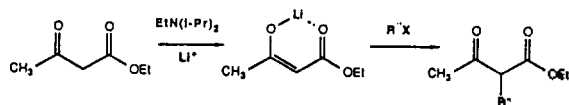


Figure 1.

We found that the role of LiCl in this reaction is crucial and unique since no alkylation occurs in the absence of LiCl (entry 4 in Table 1). This kind of a crucial role of the Li cation has been observed in other system<sup>2</sup> and has been explained in details.<sup>3-6</sup> Other alkaline cation such as K<sup>+</sup> or Na<sup>+</sup> does not have a function of the Li cation in catalyzing this reaction, since neither cation provides the alkylation product (entry 2 & 3 in Table 1).

Diethyl malonate behaves similarly to give the desired C-alkylated product. However, to our surprise, acetylacetone does not react under this condition. Presumably the complexation between the lithium cation and the carbonyl oxygen is too stable to undergo the alkylation.

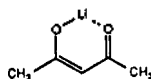


Figure 2.

We also observed the solvent effect on the reaction. When

Table 1

Entry	Starting material	Condition	Solvent	Isolated Yield <sup>a</sup>
1	Ethyl acetoacetate	+ LiCl	THF	85%
2	Ethyl acetoacetate	+ NaCl	THF	b
3	Ethyl acetoacetate	+ KCl	THF	b
4	Ethyl acetoacetate	no M <sup>+</sup> Cl <sup>-</sup>	THF	b
5	Diethyl malonate	+ LiCl	THF	87%
6	Acetylacetone	+ LiCl	THF	b
7	Ethyl acetoacetate	+ LiCl	CH <sub>3</sub> CN	64% <sup>c</sup>
8	Ethyl acetoacetate	+ LiCl	benzene	89% <sup>d</sup>

\* Condition: A mixture of 1 eq. of  $\beta$ -ketoester (or acetylacetone), 1 eq. of benzyl bromide and 2 eq. of diisopropylethylamine in a specified solvent was refluxed for 24 hours with or without a metal chloride as indicated in the condition column. <sup>a</sup> Isolated yield for mono C-alkylated product. <sup>b</sup> No reaction takes place. Unreacted starting material was recovered. <sup>c</sup> Di C-alkylated product was obtained in 18% yield. <sup>d</sup> Reaction requires 48 hours of reaction time.

acetonitrile was used, the reaction progressed faster than in THF but a significant amount of the dialkylated product was obtained (entry 7 in Table 1). In benzene, although the reaction progressed much slower than in THF, mono C-alkylated product was obtained exclusively (entry 8 in Table 1).

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