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Zinc-mediated Alkylation and Acylation of 1,3-Dicarbonyl Compounds

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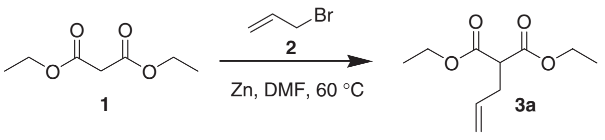
1,3-Dicarbonyl compounds undergo smooth allylation, benzylation, propargylation, and acylation with halides using metallic zinc in DMF at 60 °C to afford the corresponding allyl, benzyl, 2-propynyl, and acylated 1,3-diesters in good yields. In the case of cyclic 1,3-diketones, the corresponding enol ethers are obtained as sole products instead of *C*-alkylation.

The development of new methods for efficient C–C bond formation via alkylations and acylations of active methylene compounds are important chemical transformations in organic synthesis.[1] Earlier approaches for monoalkylation and acylation require the use of catalyst and the stoichiometric amount of bases such as non-ionic super base $P(MeNCH_2CH_2)_3N$,[2a] $PdCl_2/K_2CO_3$,[2b] (3*S*,4*S*)-1-benzyl-3,4-dihydroxy-1-methylpyrrolidinium iodide,[2c] *n*-BuLi,[2d] BaH_2,[2e] Et_3N, and $SmCl_3$.[2f] In recent years, there have been some interesting reports for this transformation which involve silicon-controlled alkylation of 1,3-dioxocompounds using allyltrimethylsilane and ceric ammonium nitrate[3] and *C*-alkylation by Mitsunobu reagents.[4]

The β-ketoenol ethers are also widely adaptable intermediates in organic synthesis.[5] During recent years, activated zinc has been used as a versatile promoter in organic synthesis and has attracted great interest.[6] Previously, we have reported some zinc-catalyzed organic transformations.[7]

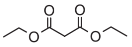
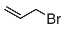
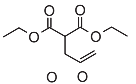
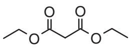
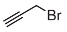
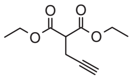
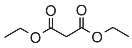
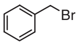
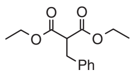
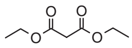
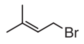
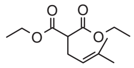
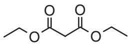
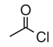
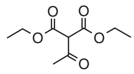
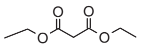
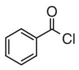
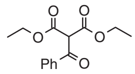
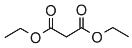
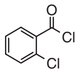
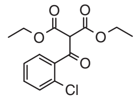
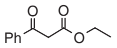
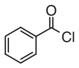
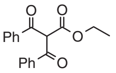
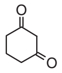
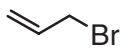
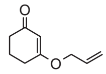
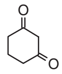
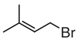
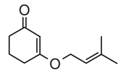
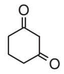
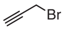
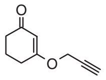
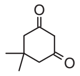
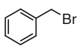
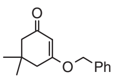
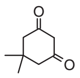
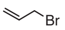
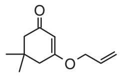
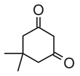
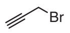
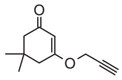
In continuation of our work on zinc-mediated reactions for various transformations,[8] we report herein a novel and simple method for the monoalkylation and acylation of 1,3-dicarboxylates and β-ketoesters using activated zinc metal. Initially, we have attempted the coupling of diethyl malonate (**1**) with allyl bromide (**2**) using zinc metal. The reaction proceeds smoothly in DMF at 60 °C and the corresponding monoallyl derivative **3a** was obtained in 75% yield (Scheme 1).

Similarly, 2-propynyl bromide, benzyl bromide, and prenyl bromide reacted effectively with diethyl malonate to give the corresponding 2-propynyl, benzyl, and prenyl derivatives of malonates respectively, in good yields (Entries **b**–**d**, Table 1). Besides alkylation, we have attempted the acylation of diesters as well. Interestingly, 1,3-dicarbonyl compounds such as 1,3-diesters and β-ketoesters underwent smooth acylation with acid chlorides. For instance, diethyl malonate reacted smoothly with acetyl chloride, benzoyl chloride, and 2-chlorobenzoyl chloride to furnish *C*-acyl or *C*-benzoyl derivatives of malonates respectively (Entries **e**–**g**, Table 1). In addition to malonate, β-ketoester, for instance, ethyl benzoylacetate also participated well in *C*-benzoylation (Entry **h**, Table 1). In the case of cyclic 1,3-diketones, the corresponding β-ketoenol ethers[9] were obtained as sole products (Scheme 2, Entries **i**–**n**, Table 1).

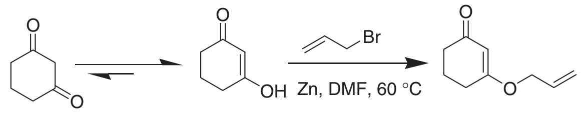


Scheme 1. *C*-Allylation of diethyl malonate with allyl bromide.

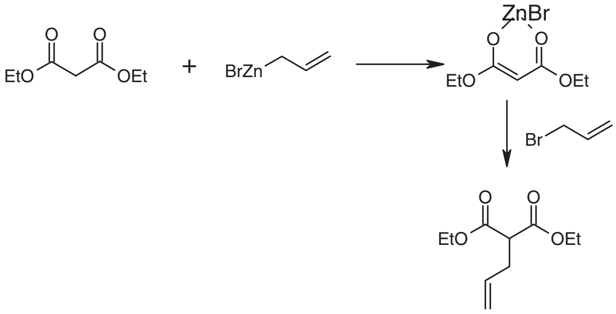
Table 1. Zinc-mediated alkylation and acylation of 1,3-dicarbonyl compounds

Entry	Substrate	Alkyl halide	Product[a]	Time/h	Yield/%[b]
a				5.0	75
b				10.0	82
c				6.0	80
d				9.0	70
e				6.0	68
f				5.0	75
g				4.0	77
h				6.0	76
i				7.0	68
j				9.0	66
k				10.0	76
l				5.0	86
m				7.0	63
n				12.0	68

[a]The products were characterized by NMR, IR, and mass spectrometry. [b]Yield refers to pure products after chromatography.



Scheme 2. *O*-Allylation of 1,3-cyclohexadione.



Scheme 3. A plausible reaction mechanism.

No *C*-alkylation was observed with cyclic 1,3-diketones under these conditions. In the absence of zinc metal, no alkylation or acylation was achieved in DMF alone. Furthermore, alkyl bromides such as propyl and butyl bromides were ineffective for this reaction. Similarly, aryl bromides also failed to give the desired product. Among various solvents such as CH_3CN, THF, and toluene studied for alkylation, DMF was found to give high conversions. No *bis*-alkylation was observed under the present reaction conditions whereas *bis*-alkylation was common under base-promoted alkylations. The effects of various metals such as zinc, indium, yttrium, and samarium were studied for the alkylation. Of these, zinc was found to be the best in terms of conversion. The present method may be useful for alkylation and acylation especially for base sensitive substrates. The results are presented in Table 1.[10]

Mechanistically, one equivalent of activated zinc and two equivalents of allyl bromide would be enough for this reaction (Scheme 3). But good yields were obtained when two equivalents of both zinc and allyl bromide were used. Therefore, further studies are in progress to explore the reaction mechanism.

In conclusion, we have developed a simple, convenient, and base-free protocol for the monoalkylation and acylation of active methylene compounds such as 1,3-diesters and β-ketoesters. This method is also effective for the preparation of enol ethers from cyclic 1,3-diketones. The use of readily available zinc metal makes this method simple, convenient, and practical.

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10 Experimental procedure: To a stirred suspension of activated zinc (86 mg, 1.24 mmol) in DMF (5 mL) under N_2 atmosphere at 60 °C was added diethyl malonate (100 mg, 0.624 mmol) and stirred for 5 min and then allyl bromide (149.8 mg, 1.24 mmol) was added. The resulting mixture was allowed to stir at 60 °C for specified time (Table 1). The progress of the reaction was monitored by TLC. After completion as monitored by TLC, the reaction mixture was quenched by saturated ammonium chloride solution and extracted with ether (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was further purified by column chromatography on silica gel (ethyl acetate/hexane, 1.5:98.5) to afford monoallyl derivative.