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Tandem Nucleophilic Reaction of 1,3-Dicarbonyl Compounds to Methyl α-Bromoacrylate: [3+2]Heteroannulation Leading to Hydrofuran Derivatives

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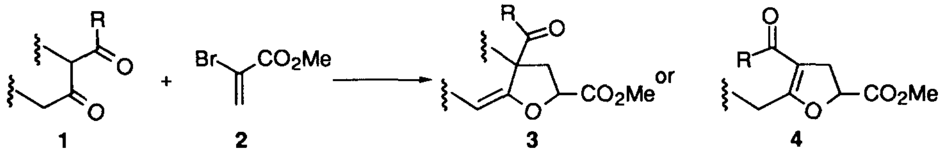
Abstract: Enolates of 1,3-dicarbonyl compounds **1** add in a [3+2] manner to methyl α-bromoacrylate **2** to furnish hydrofuran derivatives **3** or **4** in the presence of DBU in THF. © 1997 Elsevier Science Ltd.

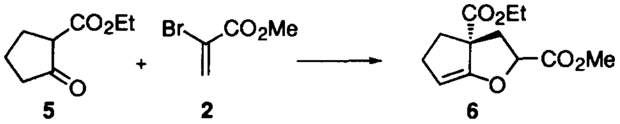
A number of methods have been developed so far in order to synthesize furan derivatives,[1] because many naturally-occurring compounds possess the furan moiety as a basic skeleton.[2]

Our ongoing interest has been directed toward the nucleophilic cascade reaction[3] for construction of polycyclic molecules in a one-pot operation. We delineate herein a new synthesis towards hydrofuran derivatives **3** or **4** by tandem nucleophilic reaction of 1,3-dicarbonyl compounds **1** to methyl α-bromoacrylate **2** (Scheme 1), the utility of which has been overlooked as a partner for cascade bond-forming processes.[4] These hydrofuran derivatives **3** or **4** would be versatile intermediates for substituted furans and some other oxygenated compounds. This procedure formally constitutes a [3+2]heteroannulation[5] of enolates to electron-deficient olefins.



Scheme 1

Some typical non-nucleophilic bases were tested for the reaction of carboethoxycyclopentanone **5** and methyl α-bromoacrylate **2** (Scheme 2) due to high reactivity of **2** as a Michael acceptor,[4] and it was found that DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) gave the desired product in THF (Table 1, entry 3).

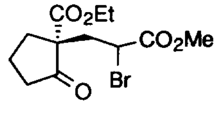


Scheme 2

Table 1

Entry	Base	Solvent	Reaction Condition	Yield[a]
1	Et_2NTMS (0.5 eq)	—[b]	room temp. 12hr	0[c]
2	K_2CO_3 (2eq)	MeOH	room temp. 3.3hr	0[d]
3	DBU (3 eq)	THF	−50°C, 7.5hr	86%

[a] Yield is based on **5**.
[b] Solvent was not used.
[c] A Michael adduct **7** was isolated in 39% yield.
[d] A mixture of unidentified products were obtained.



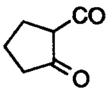
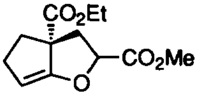
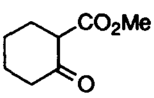
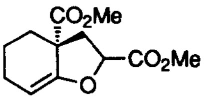
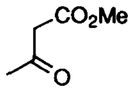
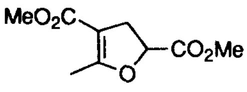
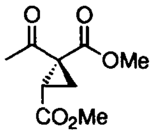
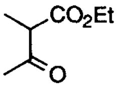
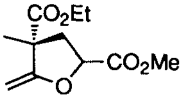
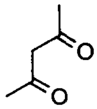
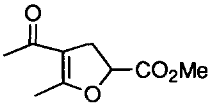
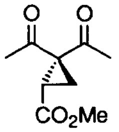
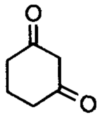
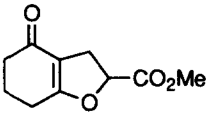
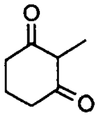
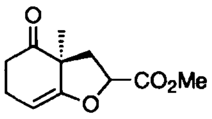
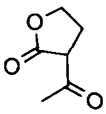
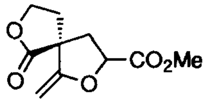
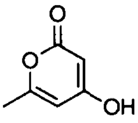
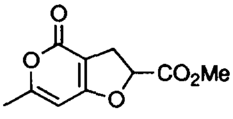
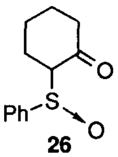
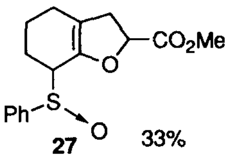
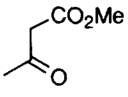
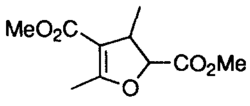
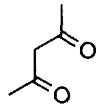
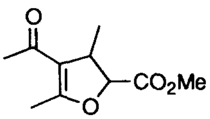
7

Under our optimized reaction conditions, reactions of some representative 1,3-dicarbonyl compounds were investigated and the results are listed in Table 2. Both cyclic and acyclic 1,3-dicarbonyl compounds gave satisfactory results. In the reaction of acetyl-γ-butyrolactone **22**, a spirocyclic hydrofuran derivative **23** was obtained (entry 8). In entry 10, initial Michael addition occurred at the α-methylene carbon unexpectedly, not at the more acidic α-methylene carbon in the reaction of 2-phenylsulfinylcyclohexanone **24**. Except entries 3, 5, 6 and 9, dihydrofuran derivatives were mixtures of diastereomers. In entries 3 and 5, cyclopropane derivatives **12** and **17** were also isolated as a result of intramolecular C-alkylation of the intermediary enolate of the initial Michael adduct.

In entries 11 and 12, methyl α-bromocrotonate **28** afforded hydrofuran derivatives **29** and **30**, albeit in low yield. Reactions with cyclic 1,3-dicarbonyl compounds gave none of the desired products, probably because of the difficulty in completing the initial Michael addition due to steric reasons.

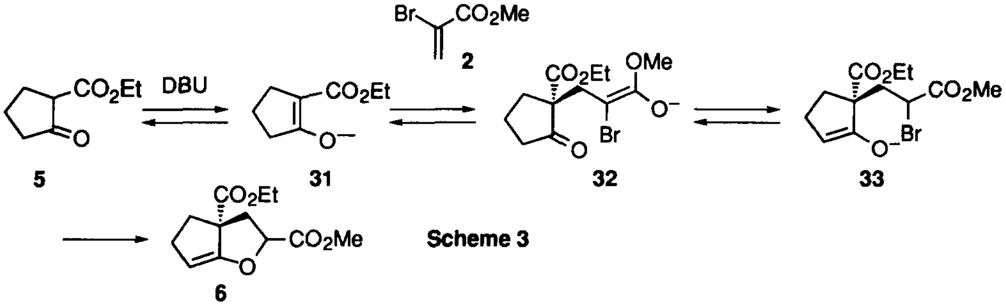
Since treatment of the Michael adduct **7** (Table 1, entry 1) with DBU in THF afforded the hydrofuran derivative **6** in 45% yield, the reaction pathway of the present reaction is explained by initial intermolecular Michael addition of the C of the enolate **31** of 1,3-dicarbonyl compound **5** followed by intramolecular O-alkylation of the enolate **33** as shown in Scheme 3.

Table 2. Reactions of 1,3-dicarbonyl compounds with methyl α-bromoacrylate **2**.[a]

Entry	Starting Material	Product
1	 **5**	 **6** 86%
2	 **8**	 **9** 87%
3	 **10**	 **11** 82%  **12** 9%
4	 **13**	 **14** 78%
5	 **15**	 **16** 75%  **17** 17%
6	 **18**	 **19** 83%
7	 **20**	 **21** 92%
8	 **22**	 **23** 96%
9	 **24**	 **25** 63%
10	 **26**	 **27** 33%
11[b]	 **10**	 **29** 23%
12[c]	 **15**	 **30** 35%

[a] All reactions were carried out with 1.3 equiv of methyl α-bromoacrylate and 1.3 equiv. of DBU at room temperature in THF. Yield are based on 1,3-dicarbonyl compounds.

[b] Methyl α-bromocrotonate was used.



Scheme 3

In summary, we have shown that tandem nucleophilic reactions of both carbon and oxygen ends of enolates of 1,3-dicarbonyl compounds **1** to methyl α-bromoacrylate **2** furnished a variety of substituted hydrofuran derivatives **3** or **4** in satisfactory yields. Simplicity of operation as well as synthetic utility of hydrofuran derivatives **3** or **4** encourage further application of our methods to natural product synthesis.

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