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Synthesis of α- and/or γ-benzoyloxy-α,β-enones from α-halo-α,β-enones

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Abstract—Sodium benzoate reacts with α-halo-α,β-enones in the presence of tetrabutylammonium hydrogensulfate or 18-Crown-6 to afford α- and/or γ-benzoyloxy-α,β-enones in good yield. The α/γ and γ/γ′ selectivities are dependent on the substrate and reagent.

The γ-hydroxy-α,β-enone structure is found in many natural products, and its synthesis from α,β-enones is a useful method for the preparation of this class of compound. Allylic bromination and subsequent conversion of bromide into hydroxy group,[1] or allylic oxidation with selenium dioxide are the reported methods.[2]

The preparation of α-alkoxy-α,β-enones from α,β-enones is also a useful synthetic transformation, for which a couple of methods are known. One consists of several successive reactions, bromination of an α,β-unsaturated hydrazone, HBr-elimination, addition of an alcohol, hydrolysis and HBr-elimination.[3] Another is the reaction of a phenol with an α-bromo-α,β-enone in the presence of K_2CO_3.[4] The thermolysis of α-chloro-α,β-epoxy ketones, prepared from the α-chloro-α,β-enone, is a further method.[5] Though there are several methods for the preparation of α and γ-hydroxylated or alkoxylated α,β-enones, more efficient syntheses are desirable. In this letter, we will describe the synthesis of α- and/or γ-benzoyloxy-α,β-enones from α-halo-α,β-enones, which are easily prepared from α,β-enones.[6]

During our investigation of the Heck reaction of 2-iodo-cyclohex-2-en-1-one (**1**) with methyl acrylate using triphenylphosphine, sodium acetate, tetrabutylammonium hydrogensulfate (n-Bu_4NHSO_4), 4 Å molecular sieves and $Pd(OAc)_2$ under Jeffery's conditions,[7] we found that a small amount of 4-acetoxy-cyclohex-2-en-1-one by-product was formed. As 4-acetoxy-cyclohex-2-en-1-one is being generated from 2-iodo-cyclohexenone (**1**), easily prepared from cyclohexeone in one step,[6] this offers a new synthetic method for acetoxylation at the γ-position of α,β-enones, which promoted us to investigate this reaction further. Instead of sodium acetate, sodium benzoate was employed as the nucleophile and reaction conditions were investigated in detail. It was soon discovered that the palladium catalyst is not necessary, and that the ammonium salt is the only necessary additive. When **1** was treated with sodium benzoate and n-Bu_4NHSO_4 at room temperature for 5.5 h, 2-benzoyloxy-cyclohex-2-en-1-one (**2**) and 4-benzoyloxy-cyclohex-2-en-1-one (**3**) were obtained in 43% and 16% yield, respectively, while the starting material **1** was recovered in 19% yield (Table 1, entry 1). As the α- and γ-benzoyloxylated derivatives were obtained in moderate yields, various ammonium salts were screened in order to increase the yield, with the results summarized in Table 1. No reaction proceeds in the case of n-Bu_4NBr with the complete recovery of **1** (entry 2), while the reaction was slow when $BnEt_3NCl$ was employed (entry 3). As n-Bu_4NHSO_4 was found to be a suitable ammonium salt, the solvent was screened next. The total yield of **2** and **3**, and the selectivity between α- and γ-adducts are dependent on the solvent. A good total yield was obtained when acetone or THF were employed as a solvent. In acetone, α- and γ-adducts were obtained in nearly same amount (entry 5), while γ-adduct **3** was predominately generated in THF (entry 9).

When caesium benzoate was employed instead of sodium benzoate under the same reaction conditions as that of entry 5 in Table 1, α- and γ-adducts were

Keywords: Enones; Substitution; Ammonium salt; Crown ether.

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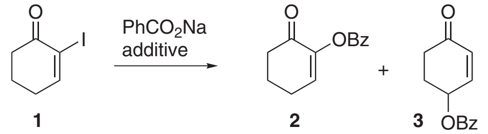
Table 1. α- and γ-Benzoyloxylation under several reaction conditions[a]



Entry	Additive	Equiv	Solvent	Temp. (°C)	Time (h)	Yield **2**/%[b]	Yield **3**/%[b]
1	*n*-Bu_4NHSO_4	1.2	DMF	23	5.5	43	16
2	*n*-Bu_4NBr	1.2	DMF	23	8	0	0
3	$BnEt_3NCl$	1.2	DMF	23	6.5	16	11
4	*n*-Bu_4NHSO_4	2.5	DMF	23	7	47	29
5	*n*-Bu_4NHSO_4	2.5	Acetone	40	1	43	40
6	*n*-Bu_4NHSO_4	2.5	CH_3CN	50	1	50	24
7	*n*-Bu_4NHSO_4	2.5	*t*-BuOH	50	1	21	55
8	*n*-Bu_4NHSO_4	2.5	DMSO	50	1	40	29
9	*n*-Bu_4NHSO_4	2.5	THF	50	2	20	62
10	*n*-Bu_4NHSO_4	2.5	Toluene	Reflux	2	14	51
11[c]	18-Crown-6	2.8	Acetone	Reflux	6	2	63

[a] The reaction was performed with **1** (1.0 equiv), $PhCO_2Na$ (2.5 equiv), additive and MS 4 Å (200 wt %) in solvent (0.2 M).

[b] Isolated yield.

[c] Phenol was isolated in 35% yield.

obtained in 27% and 34% yield, respectively, indicating caesium benzoate is not better nucleophile in this reaction. Instead of *n*-Bu_4NHSO_4, however, crown ether such as 18-Crown-6 was also found to be a suitable additive, affording the γ-adduct **3** predominately. That is, when **1** was treated with sodium benzoate in the presence of 18-Crown-6 in acetone under reflux, the reaction proceeded efficiently, providing the γ-adduct **3** and the α-adduct **2** in 63% and 2% yield, respectively, along with phenol in 35% yield (entry 11).

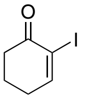
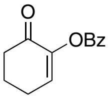
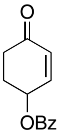
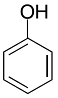
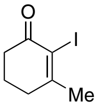
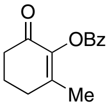
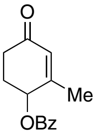
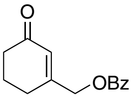
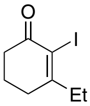
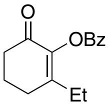
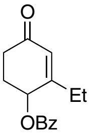
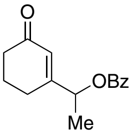
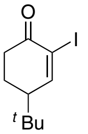
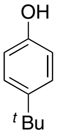
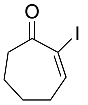
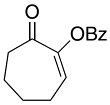
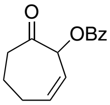
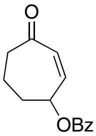
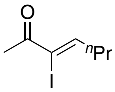
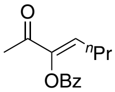
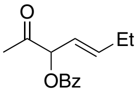
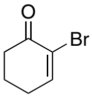
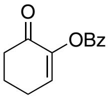
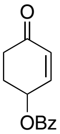
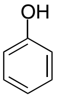
As we had found two suitable additives to sodium benzoate, that is, *n*-Bu_4NHSO_4 (conditions A) and 18-Crown-6 (conditions B), the generality of the reaction under these two reaction conditions was examined with various α-halo-α,β-enones, with the results summarized in Table 2.

In the reaction of 2-iodo-3-methyl-cyclohex-2-en-1-one, three products, that is, 2-benzoyloxy-cyclohex-2-en-1-one, 4-benzoyloxy-cyclohex-2-en-1-one and 3-benzoyloxy-methyl-cyclohex-2-en-1-one were obtained in 30%, 20% and 19% yield, respectively, under conditions A (entry 3), while the γ- and γ′-isomers were obtained selectively without the α-isomer under conditions B. Namely, 3-benzoyloxymethyl-cyclohex-2-en-1-one, the γ′-isomer, and 4-benzoyloxy-3-methyl-cyclohex-2-en-1-one, the γ-isomer, were obtained in 68% and 17% yield (entry 4). When the 3-ethyl derivative was examined, the α/γ-selectivity under conditions A was similar to that of the 3-methyl derivative, giving three products (entry 5). Reaction is slow under conditions B, affording the γ- and γ′-benzoyloxylated product in 46% and 27% yield, respectively, with a small amount of α-benzoyloxylated product (6%, entry 6). When there is a substituent at the 4-position, the phenol was obtained in good yield. That is, 4-*tert*-butyl-2-iodo-cyclohex-2-en-1-one was converted into 4-*tert*-butylphenol in good yield irrespective of the reaction conditions (entries 7 and 8). In the case of a cycloheptene derivative, the β,γ-unsaturated derivative was obtained in substantial amounts. The expected products, 2-benzoyloxy-cyclohept-2-en-1-one and 4-benzoyloxy-cyclohept-2-en-1-one, were obtained in 20% and 15% yield, respectively, with 2-benzoyloxy-cyclohept-3-ene-1-one being formed in 41% yield under conditions A (entry 9). Predominant formation of the γ-benzoyloxylated product was observed under conditions B: 4-benzoyloxy-cyclohept-2-en-1-one was formed in 58% yield (entry 10). An acyclic α,β-enone showed a different profile. α-Benzoyloxylated products were obtained selectively under both reaction conditions. Under conditions A, 3-benzoyloxy-hept-3-en-2-one was obtained in 72% yield without γ-benzoyloxylated product (entry 11). Under conditions B, 3-benzoyloxy-hept-3-en-2-one was obtained in 40% yield along with the α-benzoyloxylated β,γ-unsaturated derivative in 21% yield (entry 12).

Not only α-iodoenones, but also α-bromoenone can be employed, reacting with sodium benzoate under both reaction conditions (A and B) to afford α- and γ-benzoylated cyclohexenone, though longer reaction time is necessary compared with that of α-iodoenones (entries 13 and 14).

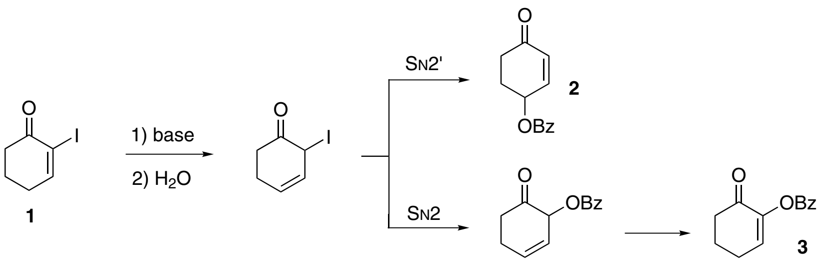
3-Bromo-pent-3-ene-2-one is reported to react with phenol in the presence of K_2CO_3 to afford 3-phenoxy-pent-3-en-2-one, a reaction for which the $\mathrm{Ad_{SN}E}$ mechanism[8] has been proposed.[4] The present reaction does not proceed via an $\mathrm{Ad_{SN}E}$ process, because β,γ-unsaturated derivatives are isolated. The mechanism is shown in Scheme 1 for the reaction of 2-iodo-cyclohex-2-en-1-one (**1**). Sulfate anion (conditions A) and benzoate anion (conditions B) act as a base to generate the dienolate, which reacts with some kind of proton source such as another cyclohexenone molecule, the acetone solvent, or the hydrogensulfate anion, affording 2-iodo-cyclohex-3-en-1-one. 4-Benzoyloxy-cyclohex-2-en-1-one (**2**) was obtained by an S_N2' benzoyloxylation, while S_N2 benzoyloxylation and isomerization afford 2-benzoyloxy-cyclohex-2-en-1-one (**3**). In spite of the

Table 2. Benzoyloxylation reaction of various α-iodo- or α-bromo-α,β-alkenones

Entry	Starting material	Reaction conditions[a]	Products and yield/%[b]					
1 2		A 40 °C, 1 h B reflux, 6 h		43 2		40 63		<5 35
3 4		A 40 °C, 5 h B reflux, 4 h		30 0		20 17		19 68
5 6		A 50 °C, 5 h B reflux, 16 h		47 6		25 46		20 27
7 8		A reflux, 4 h B reflux, 16 h		95 65				
9 10		A 23 °C, 2 h B 50 °C, 6 h		20 2		41 9		15 58
11 12		A 50 °C, 6 h B reflux, 18 h		72 40		10 21		
13 14		A 40 °C, 2 h B reflux, 10 h		65 11		12 67		7 20

[a] n-Bu_4NHSO_4 was employed in conditions A and 18-Crown-6 was used in conditions B.

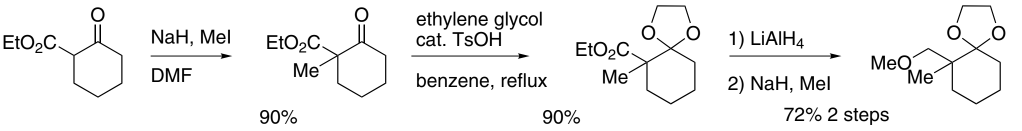
[b] Isolated yield.



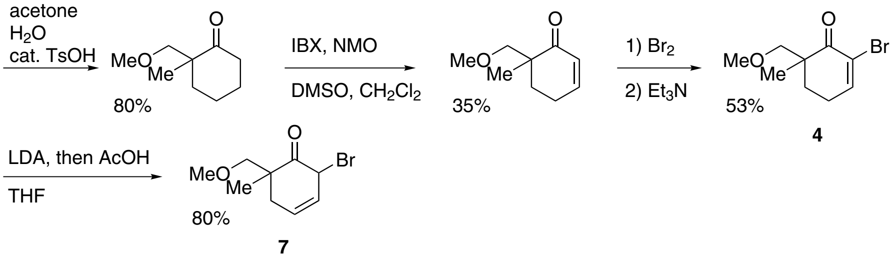
Scheme 1. The reaction mechanism of α and/or γ benzoyloxylation of α-iodo-α,β-enone.

several attempts, the preparation of 2-iodo-cyclohex-3-en-1-one, proposed intermediate, was unsuccessful owing to its instability. The corresponding bromocyclohexenone, however, can be prepared and isolated, and its reactivity was investigated. Both 2-bromocyclohex-2-ene-1-one derivative **4**[9] and 2-bromocyclohex-3-en-1-one derivative **7**[9,10] were treated with sodium benzoate and n-Bu_4NHSO_4 in the presence of MS 4 Å in acetone, and their reactions were compared. The reaction of **7**, completing within 1 h at room temperature, is faster than that of **4**, requiring 10 h at the same temperature. α-Benzoylated adduct **5** and γ-adduct **6**[11] were obtained in 75%, 5% yield and 48%, 4% yield, respectively, in the reactions of **4** and **7**. In the reaction of **7**, however, 2-benzoyloxycyclohex-3-one derivative **8**[12] were isolated in 7% yield. As **8** is easily isomerized into more stable **5**,

8 is regarded as a precursor of **5**. The results that the tendency of the formation of **5** and **6** is same in both reactions of **4** and **7**, and that **8** was isolated strongly support that a β,γ-unsaturated α-halo ketone such as **7** is a reaction intermediate.



(1)



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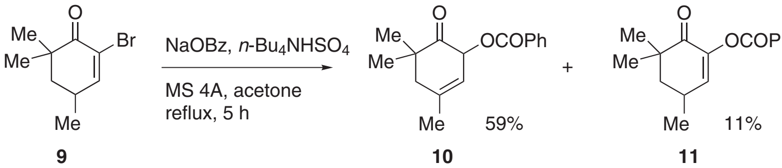
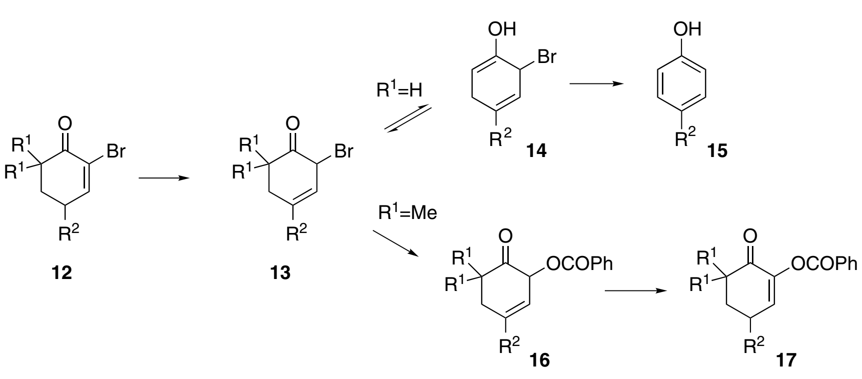


9 **10** **11**

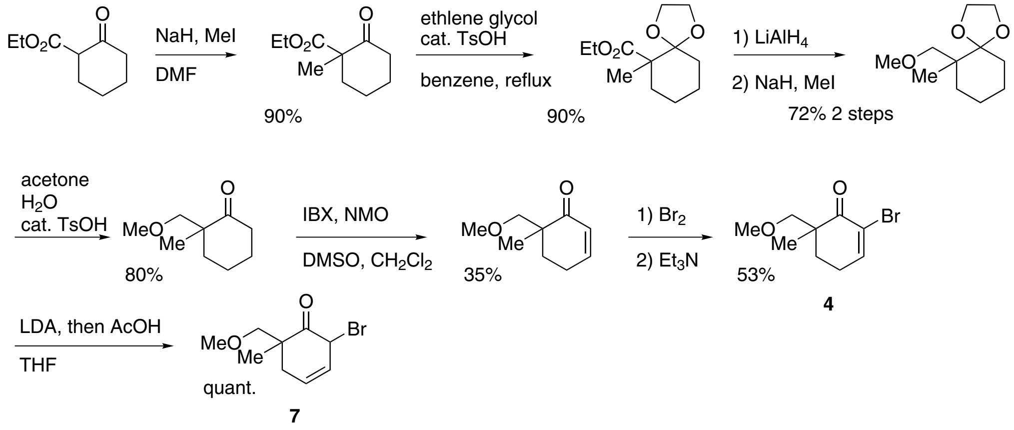
(3)

In order to shed light on the mechanism for the generation of phenol (Table 1, entries 7 and 8) having the substituent at the 4-position, 4,6,6-trimethyl-2-bromocyclohex-2-en-1-one (**9**) was treated with $PhCO_2Na$ under conditions A, affording **10** and **11** in 59% and 11% yield, respectively (Eq. 3). This result suggests the mechanism with a substituent at the 4-position as follows: first, isomerization occurred to generate β,γ-unsaturated **13**. S_N2' reaction is slow owing to the steric hindrance at the 4-position. When R^1 is H, phenol was generated via enol ether **14**, while S_N2 reaction proceeded to afford **16** and **17** when R^1 is methyl (Scheme 2).

In summary, α and/or γ-benzoyloxylated α,β-enones are synthesized from α-iodo- or α-bromo-α,β-enones, which are easily prepared from α,β-enones, in good yield by reaction with sodium benzoate in the presence of *n*-Bu_4NHSO_4 or 18-Crown-6. The α/γ and γ/γ′ selectivities are dependent on the reagent and substrate. The present reaction would be a useful synthetic method for the



Scheme 2. The reaction mechanism for the formation of **15** and **17**.



preparation of α and/or γ-benzoyloxylated α,β-enones from α,β-enones.

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9. Compounds **4** and **7** were prepared by the above route.
10. Compound **7** was obtained as a 1.0:1.0 diastereomer mixture and the stereochemistry is not determined.
11. Compound **6** was obtained as a 1.8:1.0 diastereomer mixture and the stereochemistry is not determined.
12. Compound **8** was obtained as a 1.6:1.0 diastereomer mixture and the stereochemistry is not determined.