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One-pot synthesis of α-bromoesters and ketones from β-ketoesters and diketones using supported reagents system

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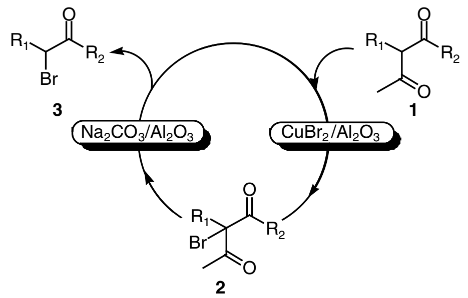
Abstract—A simple and efficient method has been developed for the synthesis of α-bromoesters and ketones from β-ketoesters and diketones in one pot using a supported reagents system, $CuBr_2/Al_2O_3$–Na_2CO_3/Al_2O_3, in which β-ketoester reacts first with $CuBr_2/Al_2O_3$ and the product, α-bromo-β-ketoester, reacts with Na_2CO_3/Al_2O_3 to give the final product, α-bromoesters in good yields.

α-Haloesters and ketones are useful compounds in organic synthesis. For instance, α-haloesters have been employed as precursors of α-amino acid and esters,[1] thiazolidine-2,4-diones,[2] juvenile hormone,[3] and vasopeptidase inhibitors.[4] α-Haloketones are valuable compounds, which are useful in the synthesis of a variety of heterocycles such as thiazoles,[5] imidazoles [6] and pyran-2,5-diones,[7] as well as in other synthetic applications including cross aldol condensations,[8] enaminoketones [9] and Favorskii rearrangements.[10] α-Haloesters are prepared from substitution of corresponding alcohols,[11] halogenation of cyclopropanes,[12] addition of halogens to alkenes.[13] Mignani et al.[14] reported the synthesis of α-haloesters by halogenation–deacylation reactions of β-ketoesters using sodium methoxide and *N*-halosuccinimide. This method is very efficient, but many pre- and after-treatments are necessary to obtain the products. We have developed halogenation–deacylation reactions using a combination of supported reagents. Recently, polymer or inorganic solid-supported reagents have been widely used in organic synthesis. However, there are few examples using a mixture of supported reagents for synthetic purposes in one pot. One-pot synthesis has attracted much interest in recent years because it provides a simple and efficient entry to compounds by including two or more transformations in a single operation to increase the complexity of a product starting from commercially available, relatively simple precursors. Herein we report a simple and efficient bromination–deacylation reactions of β-ketoesters and diketones using supported reagents system $CuBr_2/Al_2O_3$–Na_2CO_3/Al_2O_3 (Scheme 1).



Scheme 1. One-pot reaction system.

β-Ketoesters or β-diketones were added to the suspension of alumina-supported copper(II) bromide ($CuBr_2/Al_2O_3$)[15] and alumina-supported sodium carbonate (Na_2CO_3/Al_2O_3)[16] in benzene, and then the mixture was stirred at 50 °C to give the corresponding α-bromoesters or ketones in good yields. For example, a mixture of 2-benzyl-3-oxobutyric acid ethyl ester (**1a**) (1 mmol), $CuBr_2/Al_2O_3$ (2.4 mmol) and Na_2CO_3/Al_2O_3 (4.5 mmol) was stirred in benzene (10 mL) at 50 °C for 1.5 h, and then the used supported reagents were removed by filtration. The filtrate was evaporated to afford the product, 2-bromo-3-phenylpropionic acid ethyl ester (**3a**), in 79% yield, and the purity was >98%. Toluene also can be used as a solvent for this reaction. When hexane and

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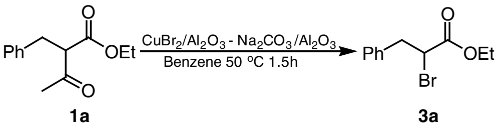
Table 1. Reaction of 2-benzyl-3-oxobutyric acid ethyl ester (**1a**) with various reagents system



Reagents system	Yield (%)	
	2a	**3a**
$CuBr_2$–Na_2CO_3	11[a]	0
$CuBr_2$–Na_2CO_3/Al_2O_3	11[a]	7[a]
$CuBr_2/Al_2O_3$–Na_2CO_3	100[b]	0
$CuBr_2/Al_2O_3$–Na_2CO_3/Al_2O_3	0	79[b]

[a] Yield was determined by GLC.

[b] Isolated yield.

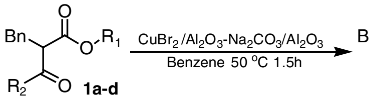
1,2-dichloroethane were used as a solvent, the yield was low. As shown in Table 1, both granular $CuBr_2$ and Na_2CO_3 are inactive in benzene. In a similar reaction in DMF, the α-bromoester was observed only 9% yield along with green precipitate. The reaction using $CuBr_2/Al_2O_3$ and Na_2CO_3 affords only brominated products **2a**, and the deacylation did not occur.

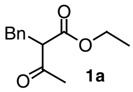
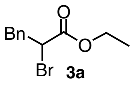
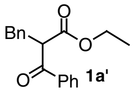
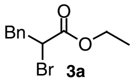
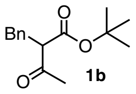
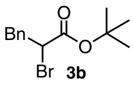
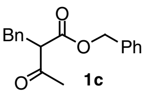
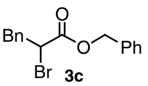
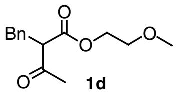
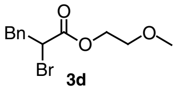
The reaction of a variety of β-ketoesters with $CuBr_2/Al_2O_3$ and Na_2CO_3/Al_2O_3 in benzene gave corresponding α-bromoesters in good yield, except for 2-benzyl-3-oxobutyric acid *tert*-butyl ester (**1b**) (see Table 2). In the reaction with **1b**, 3-bromo-4-phenyl-2-butanone (**3k**) was produced as a main product along with **3b**. This unexpected product **3k** was formed by decarboxylation of the acid, which was yielded by the hydrolysis of 2-benzyl-2-bromo-3-oxobutyric acid *tert*-butyl ester (**2b**). The reactions of benzyl ester (**1c**) and methoxyethyl ester (**1d**) were completed to produce the corresponding bromoesters in 1 h. In the case of 2-benzyl-3-oxo-3-phenylpropionic acid ethyl ester (**1a′**), debenzoylation occurred under similar conditions to afford desired product **3a**, and a small amount of the intermediate, 2-benzyl-2-bromo-3-oxo-3-phenylpropionic acid ethyl ester (**2a′**), was also yielded.

A series of 2-substituted-3-oxobutyric acid ethyl esters (**1e–j**) were converted to the corresponding α-bromoesters under similar conditions. The bromination was not influenced with the steric hindrance of a substituent at α-position in β-ketoesters, whereas the deacylation was affected by the steric hindrance. For instance, 2-acetyl-3-phenylbutyric acid ethyl ester (**1f**) required a larger amount of Na_2CO_3/Al_2O_3 than that of **1a** to give the product **3f**. Bromophenylacetic acid ethyl ester **3e** was produced in good yield only 1 h. In contrast, the reactions of acetoacetic acid ethyl esters having long alkyl groups (**1g–j**) at α-position give corresponding α-bromoesters in moderate yields (see Table 3).

These compounds are brominated by $CuBr_2/Al_2O_3$ first to give the α-bromo-β-ketoesters, which then react with Na_2CO_3/Al_2O_3 to form a mixture of deacylated and debrominated products. For instance, the reaction of 2-acetyl-2-bromodecanoic acid ethyl ester (**2h**) with Na_2 CO_3/Al_2O_3produced deacylated and debrominated products, **3h** and **1h**, in 34% and 37% yields (Scheme 2). The use of large amounts of $CuBr_2/Al_2O_3$ and Na_2CO_3/Al_2O_3 caused a low yield of α-bromoesters because of adsorption of the products on the supported reagents.

Table 2. Preparation of 2-bromo-3-phenylpropionic acid alkyl esters



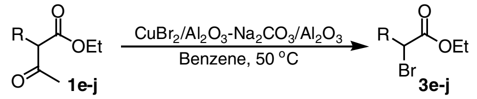
β-Ketoester	Products	Yield (%)
 1a	 3a	79
 1a′	 3a	75
 1b	 3b	24
 1c	 3c	79
 1d	 3d	73

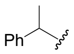
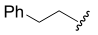
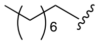
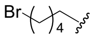
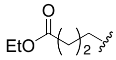
α-Bromoketones were also obtained from the corresponding β-diketones (**1k–p**) by using supported reagents system $CuBr_2/Al_2O_3$–Na_2CO_3/Al_2O_3 (see Table 4). These reactions proceeded with a smaller amount of Na_2CO_3/Al_2O_3 and shorter reaction time than that of β-ketoesters. 3-(1-Phenylethyl)-2,4-pentanedione (**1l**) required a larger amount of Na_2CO_3/Al_2O_3 and longer reaction time than that of the other β-diketones. When using β-diketones having a long alkyl chain at α-position, brominated intermediates were not debrominated with Na_2CO_3/Al_2O_3. Therefore α-bromoketones were obtained in excellent yields at 50 °C for 1 h.

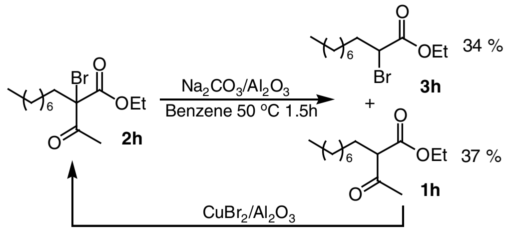
In addition, we tried to carry out three step reaction in one pot. That is, an ester having acetylthio group at α-position was prepared from β-ketoester using three components of supported reagents in one pot. Compound **1a** was added to a suspension of $CuBr_2/Al_2O_3$, Na_2CO_3/Al_2O_3 and $AcOSK/SiO_2$ in benzene, and the mixture was stirred at 50 °C for 2 h to give **4a** in 34% yield (Scheme 3).

In conclusion, we have developed a simple and efficient procedure for synthesis α-bromoesters and ketones in

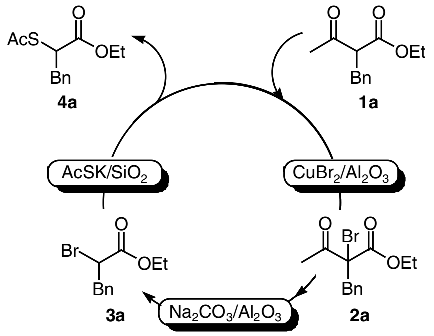
Table 3. Preparation of α-bromo esters



Products	R—	$CuBr_2/Al_2O_3$ (mmol)	Na_2CO_3/Al_2O_3 (mmol)	Time (h)	Yield (%)
3e	Ph—	2.4	3.75	1.0	74
3f		2.4	7.5	2.5	82
3g		4.5	7.5	1.5	66
3h		4.5	7.5	22.0	46
3i		4.5	7.5	6.0	59
3j		4.5	7.5	2.0	46



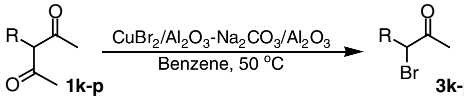
Scheme 2.

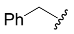
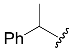
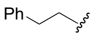
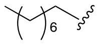
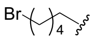
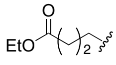


Scheme 3. One-pot three step reaction.

one pot from readily available starting materials. These experimental results demonstrate that two reagents reacting with each other in homogeneous solution are rendered mutually inactive by supporting them onto separate inorganic supports, and two step reactions are possible in one pot by using a couple of supported reagents. Moreover, these α-bromoesters and ketones, which have been produced by this method, would be able to undergo further transformations in the same vessel, because more reaction stages could be supplied

Table 4. Preparation of α-bromo ketones



Products	R—	$CuBr_2/Al_2O_3$ (mmol)	Na_2CO_3/Al_2O_3 (mmol)	Time (h)	Yield (%)
3k		2.4	3.0	1.0	84
3l		2.4	6.0	2.0	81
3m		2.4	3.0	1.0	88
3n		2.4	3.0	1.0	90
3o		2.4	3.0	1.0	90
3p		2.4	3.0	1.0	77

by using supported reagents. These efforts are now under investigation.

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16. Alumina supported sodium carbonate was prepared as follows. Alumina (ICN Biomedical N-Super 1, 18.41 g) was added to a solution of sodium carbonate (15 mmol, 1.59 g) in distilled water, and the mixture was stirred at room temperature for 0.5 h. The water was removed by rotary evaporator under reduced pressure below 60 °C, and the resulting reagent was dried in vacuo (10 mmHg) at room temperature for 5 h.