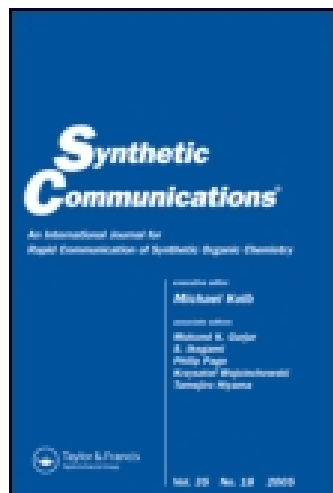


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FACILE SYNTHESIS OF α -KETOCARBONYL COMPOUNDS FROM α -HYDROXYCARBONYL COMPOUNDS¹

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ABSTRACT

Various α -ketocarbonyl compounds were obtained in excellent yields under mild condition from the reaction of the corresponding α -hydroxycarbonyl compounds with sodium hypobromite in the presence of HCl catalyst.

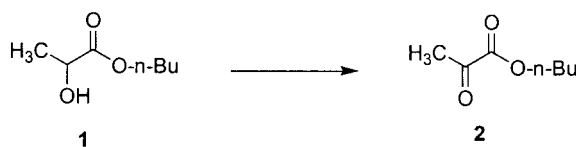
Since α -ketocarbonyl compounds have been used as important intermediates in organic synthesis,² there has been considerable interest in the development of convenient methods for the synthesis of α -ketocarbonyl compounds. Many researchers have published preparation methods for α -ketocarbonyl compounds from various starting material.³ Among them, oxidation of α -hydroxy carbonyl compounds constitutes one of the most

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widely used procedures for α -ketocarbonyl compounds. A number of methods are available for the synthesis of α -ketocarbonyl compounds by oxidation of α -hydroxycarbonyl compounds with KMnO_4 ,⁴ *N*-bromosuccinimide,⁵ CrO_3 ,⁶ lead tetraacetate,⁷ triphenylantimony dibromide,⁸ dimethyl selenide-*N*-bromosuccinimide complex,⁹ oxoaminium salts,¹⁰ perfluoro-*cis*-2-butyl-3-propyloxaziridine,¹¹ and trichloro-oxyvanadium.¹² In this paper, we report a new synthetic method for the synthesis of α -ketocarbonyl compounds from α -hydroxycarbonyl compounds. In order to establish the optimum condition for oxidation of the α -hydroxycarbonyl compounds, we have examined the reaction of *n*-butyl lactate **1** as a model substrate with *N*-bromosuccinimide,⁵ or *N*-chlorosuccinimide, or sodium hypochlorite as an oxidant in CCl_4 or a mixed solvent ($\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$, v/v=1/1). But these reagents did not give satisfactory results (Table 1). On the other hand, as shown in the run 5, the reaction of *n*-butyl lactate **1** with sodium hypobromite in the presence of HCl catalyst afforded the *n*-butyl pyruvate **2** in excellent yield.

To expand general utility of the NaOBr for the transformation of α -hydroxycarbonyl compounds into the corresponding α -ketocarbonyl

Table 1. Optimization Study for Oxidation of *n*-Butyl Lactate



Run	Oxidation Condition	Solvent	Reaction Temp. (°C)	Reaction Time (h)	Yield ^a (%)
1	NBS/ CaCO_3 (1.3 eq/1.3 eq)	CCl_4	78	24	75 ^b
2	NCS/ CaCO_3 (1.3 eq/1.3 eq)	CCl_4	78	24	10 <
3	NaOCl/HCl (1.3 eq/0.3 eq)	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	25	5	23
4	NaOCl/NaBr/HCl (1.3 eq/1.3 eq/0.3 eq)	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	25	5	74
5	NaOBr/HCl (1.3 eq/0.3 eq)	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	25	5	98

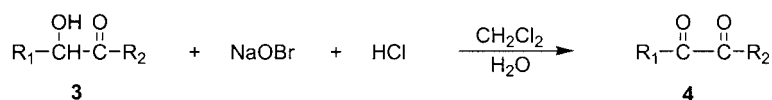
^aYields were determined by GC.

^b*n*-Butyl bromopyruvate was obtained in 10% yield as a side product.



α-KETOCARBONYL COMPOUNDS

Table 2. Oxidation of α-hydroxycarbonyl Compounds by NaOBr/HCl System in a Mixed Solvent (CH₂Cl₂/H₂O, v/v = 1/1)^{a,b}



Run	R ₁	R ₂	Yield ^c (%)
1	CH ₃	-OCH ₃	90
2	CH ₃	-OCH ₂ CH ₃	92
3	CH ₃	-OCH ₂ CH ₂ CH ₂ CH ₃	96
4	CH ₃	-OCH(CH ₃) ₂	92
5	CH ₃	-OCH ₂ CH(CH ₃) ₂	92 ^d
6	CH ₃	-OCH ₂ CH ₂ CH(CH ₃) ₂	93 ^e
7	CH ₃ CH ₂ CH ₂ CH ₂	-OCH ₂ CH ₂	93
8	Ph	-OH	90
9	Ph	-OCH ₂ CH ₂	93
10	PhCH ₂ CH ₂	-OCH ₂ CH ₂	94
11	Ph	Ph	90
12	2-Pyridine	2-Pyridine	93

^aMolar ratio; substrate: NaOBr : HCl = 1 : 1.3 : 0.3.

^bThe reaction time was 5 h.

^cIsolated yields.

^dCH₃COCO₂CH₂CH(CH₃)₂ : CH₃COCO₂CH₂CBr(CH₃)₂ = 80 : 20, the ratio was determined by ¹H NMR.

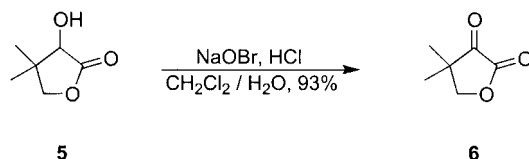
^eCH₃COCO₂CH₂CH₂CH(CH₃)₂ : CH₃COCO₂CH₂CH₂CBr(CH₃)₂ = 75 : 25, the ratio was determined by ¹H NMR.

compounds, we performed the oxidation reaction using α-hydroxycarbonyl compounds **3** such as α-hydroxy esters, α-hydroxyacid, and α-hydroxyketones. The results were summarized in Table 2.

As shown in Table 2, most of the oxidation with sodium hypobromite in the presence of HCl catalyst proceeded smoothly at room temperature. On the other hand, in case of iso-butyl lactate, isoamyl lactate (Run 5, 6), a mixture of the corresponding α-ketoester and bromo-substituted α-ketoester was obtained.

α-Hydroxyketones as well as α-hydroxyesters could be easily transformed into the corresponding α-diketones under mild condition (Run 11, 12). When the same reaction condition was applied to the oxidation of pantolactone **5**, ketopantolactone **6** could be obtained in high yield.





In conclusion, various α -ketocarbonyl compounds could be easily prepared from the α -hydroxycarbonyl compounds by using NaOBr/HCl system under facile and mild conditions in high yields.

EXPERIMENTAL

Synthesis of Pyruvic Acid Butyl Ester: Typical Procedure

700 mL of water and 104 g (2.6 mol) of sodium hydroxide were placed into a 2 L three-necked flask equipped with a cooler, a mechanical stirrer, and a thermometer. The mixture was cooled to -5°C . 67 mL (1.3 mol) of bromine was dropwise added for 2 h, keeping the internal temperature at -5°C to generate sodium hypobromite (NaOBr). 700 mL of cold dichloromethane and 148.12 mL (1 mol) of α -hydroxypropionic acid butyl ester were added slowly to the aqueous sodium hypobromite solution so that the temperature does not exceed 0°C . 26.1 mL (0.3 mol) of concentrated hydrochloric acid was dropwise added for 15 min, keeping the temperature of the reaction mixture at 0°C . After removing the cooler, the reaction mixture was stirred for 5 h at room temperature. After addition of sodium thiosulfonate (100 mL of water and 124 g of $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$), the reaction mixture was stirred for 15 min. The organic layer was separated, and the aqueous layer was extracted twice with dichloromethane. The combined organic layer was dried over magnesium sulfate and filtered. The filtrate was evaporated and distilled under reduced pressure (20 mmHg, b.p. $83\text{--}86^\circ\text{C}$) to give 138.2 g of *n*-butyl pyruvate (96% yield).

$^1\text{H NMR}$ (CDCl_3): δ 4.25 (t, 2H), 2.46 (s, 3H), 1.72 (m, 2H), 1.43 (m, 2H), 0.95 (t, 3H)

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