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Efficient microwave induced direct α-halogenation of carbonyl compounds

Jong Chan Lee,* Jin Young Park, So Young Yoon, Yong Hun Bae and Seung Jun Lee

Department of Chemistry, Chung-Ang University, Seoul 156-756, South Korea

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Abstract—A novel and direct method for the synthesis of α-halocarbonyl compounds using sequential treatment of carbonyl compounds with [hydroxy(tosyloxy)iodo]benzene followed by magnesium halides under solvent-free microwave irradiation conditions is described.

α-Haloketones are among the most versatile intermediates in organic synthesis and their high reactivity makes them prone to react with large number of nucleophiles to provide a variety of useful compounds.[1] Direct conversion of carbonyl compounds into α-halocarbonyl compounds is very important synthetic transformation that has been received considerable attention. Generally the direct conversion to α-chloroketones from ketones can be accomplished by using chlorination agents such as copper(II) chloride,[2] sulfuryl chloride,[3] *p*-toluenesulfonyl chloride,[4] *N*-chlorosuccinimide,[5] and tetraethylammonium trichloride.[6] α-Bromination of ketones can be achieved using various reagents which include bromine,[7] copper(II) bromide,[8] *N*-bromosuccinimide,[5] and tetrabutylammonium tribromide.[9] In addition, α-iodination of ketones is commonly achieved using iodine–cerium(IV) ammonium nitrate,[10] iodine–mercury(II) chloride,[11] and iodine–selenium dioxide.[12] However, these methods suffer from drawbacks such as long reaction times, use of hazardous chemicals, and cumbersome workup procedures. Furthermore, most of these methods generally employed strongly acidic or basic conditions, which accompanied by undesirable formation of α,α-dihalogenated products in significant amount. Recently a lot of effort has been made to the development of new efficient reaction conditions on the α-halogenation reactions of 1,3-dicarbonyl compounds. For example, combination of magnesium perchlorate with *N*-halosuccinimide has been recently demonstrated to be as effective for α-halogenation of 1,3-dicarbonyl compounds.[13]

In the last decade, microwave promoted reactions under solvent-free conditions have received considerable attention as a powerful technique to effect various organic transformations.[14] Very recently, microwave induced α-bromination of ketones achieved under solvent-free conditions by use of dioxane–dibromide in combination with silica gel.[15] In addition, we recently reported the use of *N*-iodosuccinimide and *p*-toluenesulfonic acid for facile microwave induced α-iodination of ketones.[16] However, to the best of our knowledge, method for α-chlorination of carbonyl compounds under solvent-free microwave irradiation conditions has been unprecedented to date.

Hypervalent iodine compounds received continuous attention in organic synthesis and amongst these, [hydroxy(tosyloxy)iodo]benzene (Koser's reagent, HTIB) has been most commonly employed in numerous organic transformations.[17] In continuation of our research on application of hypervalent iodine(III) sulfonates to microwave promoted solvent-free reactions, we now wish to report the first method that can be generally applicable to α-chlorination as well as α-bromination and α-iodination of carbonyl compounds under solvent-free microwave irradiation conditions, which involves sequential reaction of the carbonyl compounds with

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* Corresponding author. Tel.: +82-2-820-5202; fax: +82-2-825-4736; e-mail: jclee@cau.ac.kr

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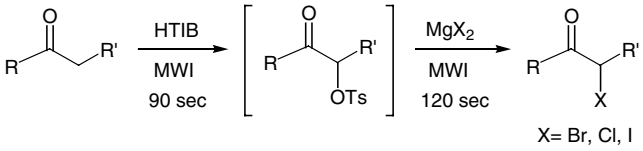
Table 1. Preparation of α-halocarbonyl compounds under microwave irradiation

Entry	Substrate	Product	Yield (%)[a]		
			X = Br	Cl	I
1	$PhCOCH_3$	$PhCOCH_2X$	85 (75)[b]	86	70 (84)[c]
2	p-$CH_3OC_6H_4COCH_3$	p-$CH_3OC_6H_4COCH_2X$	91 (73)[b]	90	75 (82)[c]
3	p-$BrC_6H_4COCH_3$	p-$BrC_6H_4COCH_2X$	83 (76)[b]	83	72
4	p-$NO_2C_6H_4COCH_3$	p-$NO_2C_6H_4COCH_2X$	82 (80)[b]	80	65 (75)[c]
5	$PhCOCH_2CH_3$	$PhCOCHXCH_3$	95	92	85 (78)[c]
6	p-$CH_3OC_6H_4COCH_2CH_3$	p-$CH_3OC_6H_4COCHXCH_3$	94	90	77 (82)[c]
7	p-$BrC_6H_4COCH_2CH_3$	p-$BrC_6H_4COCHXCH_3$	85	88	75
8	$PhCOCH_2CH_2CH_3$	$PhCOCHXCH_2CH_3$	88	83	80
9	CH_3COCH_2COOEt	$CH_3COCHXCOOEt$	76	80	65 (84)[c]
10	$CH_3COCH_2COO^tBu$	$CH_3COCHXCOO^tBu$	92	90	65
11	$PhCOCH_2COOEt$	$PhCOCHXCOOEt$	85	83	67 (82)[c]
12	$EtOOCCH_2COOEt$	$EtOOCCHXCOOEt$	83	81	67 (78)[c]
13	2-Acetylthiophene	α-Halo-2-acetylthiophene	83	75	73
14	Cyclopentanone	α-Halocyclopentanone	61	60	63
15	Cyclohexanone	α-Halocyclohexanone	67	62	66
16	1-Indanone	2-Halo-1-indanone	85	83	73 (76)[c]

[a] Isolated yield.
[b] Yields obtained from Ref. 15.
[c] Yields obtained from Ref. 16.



Scheme 1.

HTIB and followed by MgX_2 (X = Br, Cl, and I). The reactions were carried out by treating neat ketones with 1.2 equiv of HTIB under microwave irradiation and subsequent microwave irradiated reaction of preformed α-tosyloxyketone intermediates with 2.0 equiv of magnesium halides (Scheme 1). When the reactions were performed using sodium, potassium, and zinc halides in place of magnesium halides, the yields of reactions were significantly reduced with increased impurities. Presumably this result can be explained by superior coordinating ability of magnesium toward both carbonyl oxygen and sulfonate oxygen. A variety of arylmethylketones, arylmethyleneketones, and cyclic ketones were reacted well under the present reaction conditions to give the corresponding α-halogenated ketones in good to excellent yields. The results of our studies are shown in Table 1. All of the reactions studied were completed in less than 4 min. Both α-chlorination and α-bromination reactions were accomplished equally well along with somewhat reduced yields in cases of α-iodination as demonstrated in Table 1. We next explored the scope of the present method by treating 1,3-dicarbonyl compounds at present reaction conditions. As shown in Table 1 (entries 9–12), the reactions were highly successful to give α-halogenated 1,3-dicarbonyl compounds with high yields in short reaction times. Therefore, we have developed the first method for the microwave promoted efficient preparation of α-chlorocarbonyl compounds under solvent-free conditions. In addition, the yields of α-brominated and α-iodinated compounds obtained in this study are superior or comparable to those obtained from the other previously reported microwave induced α-bromination and α-iodination methods.[15,16] General experimental procedure is as follows: A carbonyl compound (1.0 mmol) and HTIB (0.470 g, 1.2 mmol) were mixed and placed in a 50 mL of glass tube. The reaction mixture was inserted in an alumina bath inside household microwave oven and irradiated at the power of 700 W three times for a period of 30 s with 20 s intervals. After cooled down the reaction mixture to room temperature, a magnesium halide (2.0 mmol) was added and additionally irradiated for two times for a period of 60 s with 20 s interval. The reaction mixture was extracted with dichloromethane (2 × 25 mL) and washed with water (40 mL). The dichloromethane layer was separated and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (SiO_2, methylene chloride) to give pure α-halocarbonyl compound.

In conclusion, we have developed a new and efficient method for the α-halogenation of carbonyl compounds using commercially available reagents under solvent-free microwave irradiation conditions. The advantages of the present method in terms of ease of manipulation, fast reaction rates, and formation of cleaner products under neutral reaction conditions should make this protocol as a valuable alternative to the existing methods.

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