

Efficient α -Iodination of Carbonyl Compounds Under Solvent-Free Conditions Using Microwave Irradiation

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Abstract: Direct conversion of carbonyl compounds into α -iodocarbonyl compounds has been successfully achieved under solvent-free microwave irradiation conditions using *N*-iodosuccinimide and *p*-toluenesulfonic acid.

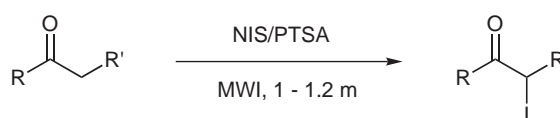
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The preparation of α -iodoketones and their applications as reaction intermediates have attracted considerable attention in various organic transformations.^{1–4} A number of indirect methods are available for the preparation of α -iodoketones, which include the reactions of enol acetates or enol silyl ethers with appropriate iodinating agents such as iodine–copper(II) nitrate⁵ and iodine–silver acetate.⁶ Direct α -iodination of ketones can be achieved by the reaction of ketones with several reagent systems which include iodine–cerium(IV) ammonium nitrate,⁷ potassium iodide–potassium iodate–sulfuric acid,⁸ and iodine–selenium dioxide.⁹ However, the required harsh reaction conditions, long reaction times, or tedious work-up procedures in most of the above-mentioned methods limit their practical utilities in organic synthesis. In addition, far less attention has been given to the conversion of 1,3-dicarbonyl compounds to the corresponding 2-iodo-1,3-dicarbonyl compounds.^{10–12} Among other useful reagents, use of *N*-iodosuccinimide (NIS) for the iodination of various substrates has been received significant attention and the results are reported in a couple of literature.^{13–15} However, application of NIS for the preparation of α -iodoketones has been very sparse. In this context, to our best knowledge, there has been only one report that briefly described the α -iodination of acetophenone using NIS–trifluoromethanesulfonic acid.¹⁴ However, practical application of this method should be limited because of the highly fuming nature of trifluoromethanesulfonic acid.

Recently, organic reactions promoted by microwave irradiation under solvent-free conditions received much attention due to the advantages over conventional methods in terms of rapid reaction rates, improved yields, and environmentally benign reaction conditions.

As part of a program aimed at developing facile method for the preparations α -haloketones, we were interested in

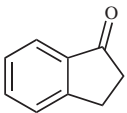
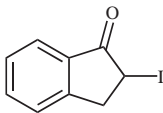
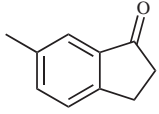
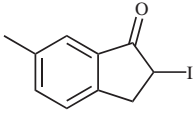
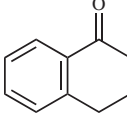
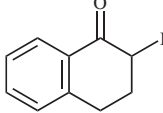
developing a new direct method for α -iodination of ketones promoted by microwave irradiation under solvent-free reaction conditions. Therefore, we report herein a convenient method for the preparation of α -iodocarbonyl compounds from the reaction of carbonyl compounds with NIS in the presence of *p*-toluenesulfonic acid (PTSA) under solvent-free microwave irradiation conditions (Scheme 1).



Scheme 1

Microwave irradiation to the neat mixture of ketone, NIS (1.2 equiv), and PTSA (1.2 equiv) in household microwave oven at its full power (700 W) afforded the corresponding α -iodoketone.¹⁶ All of the reactions studied proceeded smoothly to give the corresponding α -iodoketones with high yields in very short reaction times (1–1.2 min) as shown in the Table 1. Aromatic ring iodination of the aromatic ketones was not detected at all in the reactions investigated. We also examined the iodination of a number of 1,3-dicarbonyl compounds to the corresponding 2-iodo-1,3-dicarbonyl compounds under present reaction conditions and the reactions proved to be highly successful as given in entries 10–13. Preparation of dialkyl iodomalones from dialkyl malonates has been known to be very difficult and there are only a few methods reported to date.^{10,11} When we applied present method for the iodination of dialkyl malonates, the corresponding dialkyl iodomalones were obtained in very high yields (entries 12 and 13). Moreover, synthetically useful 2-iodoindanone and 2-iodotetralone were also obtained in high yields (entries 14–16).⁹ Formation of α,α -diiodinated carbonyl products was not observed in all cases studied in the Table 1. Attempts to react carbonyl compounds with NIS without use of PTSA were unsuccessful to give only unchanged starting materials. Hence, it is reasonable to explain that the enhanced reactivity of NIS came from the increase of enol contents of carbonyl compounds by acid promoted protonation of carbonyl compounds as well as the formation of protonated NIS with PTSA as suggested in analogous acid promoted reaction of carbonyl-conjugated alkynes with NIS.¹⁵

Table 1 Microwave Irradiation Promoted Preparation of α -Iodocarbonyl Compounds

Entry	Substrate	Product	Yield (%) ^a
1	PhCOCH ₃	PhCOCH ₂ I	84
2	<i>p</i> -CH ₃ C ₆ H ₄ COCH ₃	<i>p</i> -CH ₃ C ₆ H ₄ COCH ₂ I	90
3	<i>p</i> -CH ₃ OC ₆ H ₄ COCH ₃	<i>p</i> -CH ₃ OC ₆ H ₄ COCH ₂ I	82
4	<i>p</i> -ClC ₆ H ₄ COCH ₃	<i>p</i> -ClC ₆ H ₄ COCH ₂ I	87
5	<i>p</i> -NO ₂ C ₆ H ₄ COCH ₃	<i>p</i> -NO ₂ C ₆ H ₄ COCH ₂ I	75
6	PhCOCH ₂ CH ₃	PhCOCHICH ₃	78
7	<i>p</i> -CH ₃ C ₆ H ₄ COCH ₂ CH ₃	<i>p</i> -CH ₃ C ₆ H ₄ COCHICH ₃	90
8	<i>p</i> -CH ₃ OC ₆ H ₄ COCH ₂ CH ₃	<i>p</i> -CH ₃ OC ₆ H ₄ COCHICH ₃	82
9	<i>p</i> -ClC ₆ H ₄ COCH ₂ CH ₃	<i>p</i> -ClC ₆ H ₄ COCHICH ₃	83
10	CH ₃ COCH ₂ COOEt	CH ₃ COCHICOOEt	84
11	PhCOCH ₂ COOEt	PhCOCHICOOEt	82
12	MeOCOCH ₂ COOMe	MeOCOCHICOOMe	91
13	EtOCOCH ₂ COOEt	EtOCOCHICOOEt	78
14			76
15			91
16			88

^a Isolated yields.

In conclusion, we have devised a new convenient method for the synthesis of α -iodocarbonyl compounds directly from carbonyl compounds using the combination of NIS and PTSA under solvent free microwave irradiation con-

ditions. The advantages of present method in light of very fast reactions, solvent-free conditions, and high yields should make this protocol as a useful alternative to existing methods.

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- (16) General experimental procedure: A neat mixture of ketone, NIS (1.2 equiv), and *p*-toluenesulfonic acid monohydrate (1.2 equiv) was placed in a glass test tube. The test tube containing reaction mixture was inserted in an alumina bath inside a household microwave oven and irradiated (700 W) three to four times for a period of 20 s with 10 s interval. After cooling down, the reaction mixture was extracted with dichloromethane (2 × 25 mL) and washed with water (40 mL). The dichloromethane layer was separated and dried over MgSO₄. After evaporation of the solvent, the residue was purified by flash column chromatography (SiO₂, dichloromethane) to give pure α -iodoketone.