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Novel α-tosyloxylation of ketones catalyzed by the in situ generated hypoiodous acid from alkyl iodide

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ABSTRACT

Using a catalytic amount of 1-iodopropane, a novel and efficient procedure has been developed for direct preparation of α-tosyloxyketones from ketones. In this protocol, 1-iodopropane is first oxidized into iodosylpropane, which decomposes to form the key catalyst hypoiodous acid. With this method, not only α-tosyloxyketones, but also other α-sulfonyloxyketones have been prepared in moderate to good yields, which extends the application of alkyl substituted hypervalent iodine reagents in organic synthesis.

Introduction

The hypervalent iodine compounds, $ArIL_1L_2$, with one aryl and two heteroatom ligands are versatile reagents for the oxidation and functionalization of organic compounds.[1] Due to that hypervalent iodine reagents are nonmetallic oxidants, they avoid the issues of toxicity of many transition metals commonly involved in such processes. Among them, [hydroxyl(tosyloxy)]iodobenzene (Koser's reagent, HTIB) is the most popular and useful reagent for the direct α-tosyloxylation of ketones.[2] The prepared α-tosyloxyketones are important strategic precursors for the construction of various heteroaromatics such as thiazoles, oxazoles, selenazoles, imidazoles, pyrazoles, benzofurans, and lactones.[3] In recent years, the catalytic utilization of hypervalent iodine reagents is increasing in importance, with growing interest in the development of environmentally benign synthetic transformations.[4] With iodobenzene as catalyst, Togo and co-workers have reported several methods for the direct α-tosyloxylation of ketones.[5] They have also investigated new procedures using molecular iodine in place of catalyst iodobenzene.[6] Similarly, on utilization of a catalytic amount of ammonium iodide, we have just successfully synthesized α-tosyloxyketones from ketones.[7]

Derivatives of hypervalent iodine with an alkyl substituent at iodine, RIL_1L_2, generally are highly unstable and can exist only as short-lived reactive intermediates in the oxidations of alkyliodides, which afford either elimination products or the products of oxidatively assisted nucleophilic substitution of iodine.[1a–c] The hypervalent iodine compounds, despite their lack of stability, have found several synthetic applications. Reich and Peake first demonstrated that the elimination proceeds with *syn*-stereochemistry and have also proposed iodosylalkanes as reactive intermediates in the reaction.[8] Knapp et al. applied iodosyl elimination to prepare unsaturated oxazolidinone, the key intermediate in the synthesis of valienamine.[9] Della and Head developed a convenient procedure for the preparation of bridgehead fluorides by the reaction of 1-iodonorbornanes with xenon difluoride.[10] Burton and co-workers utilized the oxidative deiodination reaction to synthesize steroidal products.[11] However, in comparison with aryl substituted hypervalent iodine reagents, these applications are rather limited. Therefore, to extend alkyl substituted hypervalent iodine reagent applications in organic synthesis, and explore their new reactions, especially the catalytic reactions, which is still desired. Asensio et al. reported an oxidation of iodomethane with dimethyldioxirane in 1999, with the in situ generated active hypoiodous acid, they successfully synthesized iodohydrin in good yields.[12] This is an interesting and convenient method for the formation of the active hypoiodous acid, in order to extend its application, we have investigated some novel reactions, and found that when catalytic amounts of alkyl iodides and suitable oxidants are used, the in situ generated active hypoiodous acid can improve some reactions, such as α-tosyloxylation of ketones, sulfonyloxylactonization of alkenoic acid, synthesis of isoxazolines from aldoximes and alkenes, and acetoxyselenenylation of alkenes. Herein, we wish to report a novel and efficient α-tosyloxylation of ketones using a catalytic amount of 1-iodopropane together with a stoichiometric *m*-chloroperbenzoic

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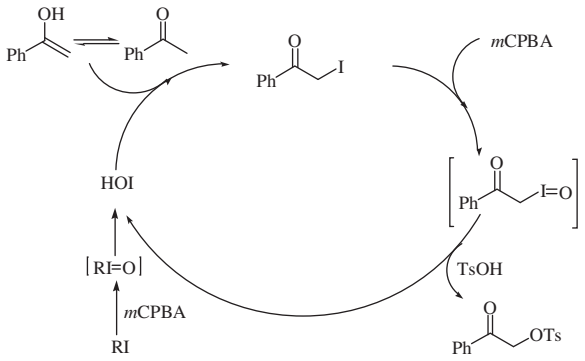
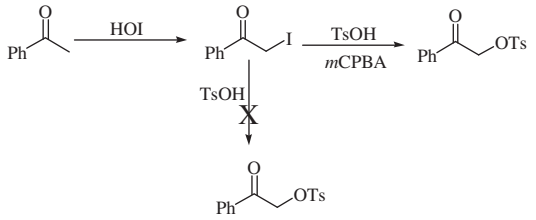
0040-4039/



Scheme 1. Proposed mechanism for the α-tosyloxylation of ketone.



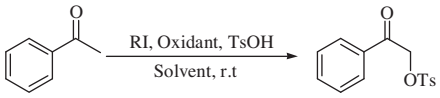
Scheme 2.

acid as the terminal oxidant, and to our knowledge this method has not been reported before.

Discussion and results

At first, 1-iodopentane was selected as representative of alkyl iodides to attempt the novel α-tosyloxylation of ketones. When 1-iodopentane was absent, a mixture of acetophenone with *p*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$) and oxidant *m*-chloroperbenzoic acid (*m*CPBA) was stirred at room temperature for a long time, no desired product was detected, and the substrate acetophenone was recovered quantitatively. After adding a catalytic amount of 1-iodopentane in the mixture, the α-tosyloxylation of ketones occurred smoothly and the desired product α-tosyloxyacetophenone was obtained in good yield. According to the key action of 1-iodopentane in the catalytic reaction, a plausible reaction pathway is hypothesized (Scheme 1). Thus, 1-iodopentane is first oxidized by *m*CPBA into the corresponding iodosylpentane, which is highly unstable and decomposes at once to form hypoiodous acid.[12] Acetophenone then reacts with the in situ generated active hypoiodous acid to afford α-iodoacetophenone,[13] which is easily changed to α-iodosylacetophenone by the continuing oxidation of *m*CPBA. Finally, the reactive hypervalent iodine intermediate α-iodosylacetophenone is rapidly transformed into α-tosyloxyacetophenone by a nucleophilic substitution of $TsOH{\cdot}H_2O$ or attacked by TsOH to form a similar structure of Koser's reagent and subsequent reductive elimination to form the corresponding product.

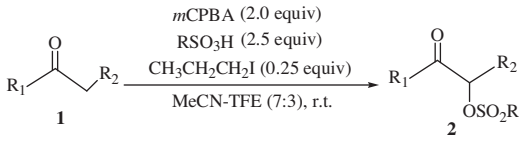
Table 1
Optimization of the α-tosyloxylation of acetophenone

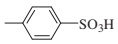
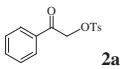
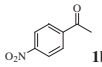
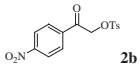
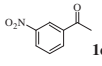
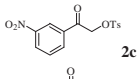
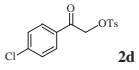
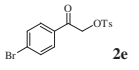
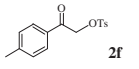
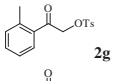
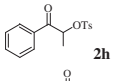
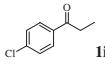
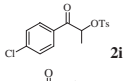
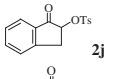
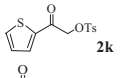
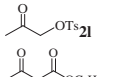
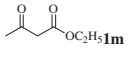
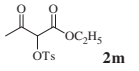
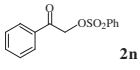
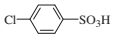
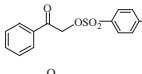
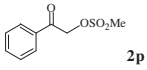
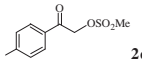
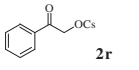


Entry	Solvent	Oxidant (equiv)	RI (equiv)	TsOH (equiv)	Time (h)	Yield[a] (%)
1	CH_3OH	*m*CPBA (1.2)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	12
2	EtOAc	*m*CPBA (1.2)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	29
3	THF	*m*CPBA (1.2)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	34
4	EtOH	*m*CPBA (1.2)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	19
5	MeCN	*m*CPBA (1.2)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	44
6	CH_2Cl_2	*m*CPBA (1.2)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	43
7	DMF	*m*CPBA (1.2)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	17
8	CF_3CH_2OH	*m*CPBA (1.2)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	45
9	MeCN–CF_3CH_2OH (1:1)	*m*CPBA (1.2)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	54
10	MeCN–CF_3CH_2OH (6:4)	*m*CPBA (1.2)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	54
11	MeCN–CF_3CH_2OH (7:3)	*m*CPBA (1.2)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	57
12	MeCN–CF_3CH_2OH (8:2)	*m*CPBA (1.2)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	54
13	MeCN–CF_3CH_2OH (9:1)	*m*CPBA (1.2)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	53
14	MeCN–CF_3CH_2OH (2:8)	*m*CPBA (1.2)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	49
15	MeCN–CF_3CH_2OH (7:3)	Oxone (1.2)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	22
16	MeCN–CF_3CH_2OH (7:3)	$NaBO_3{\cdot}4H_2O$ (1.2)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	24
17	MeCN–CF_3CH_2OH (7:3)	*m*CPBA (1.5)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	63
18	MeCN–CF_3CH_2OH (7:3)	*m*CPBA (2.0)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	66
19	MeCN–CF_3CH_2OH (7:3)	*m*CPBA (2.5)	$CH_3(CH_2)_4I$ (0.2)	2.0	12	61
20	MeCN–CF_3CH_2OH (7:3)	*m*CPBA (2.0)	$CH_3(CH_2)_4I$ (0.2)	2.5	12	72
21	MeCN–CF_3CH_2OH (7:3)	*m*CPBA (2.0)	$CH_3(CH_2)_4I$ (0.2)	3.0	12	72
22	MeCN–CF_3CH_2OH (7:3)	*m*CPBA (2.0)	$CH_3(CH_2)_5I$ (0.2)	2.5	12	70
23	MeCN–CF_3CH_2OH (7:3)	*m*CPBA (2.0)	$CH_3(CH_2)_3I$ (0.2)	2.5	12	72
24	MeCN–CF_3CH_2OH (7:3)	*m*CPBA (2.0)	CH_3CHICH_3 (0.2)	2.5	12	76
25	MeCN–CF_3CH_2OH (7:3)	*m*CPBA (2.0)	$CH_3(CH_2)_2I$ (0.2)	2.5	12	79
26	MeCN–CF_3CH_2OH (7:3)	*m*CPBA (2.0)	$CH_3(CH_2)_9I$ (0.2)	2.5	12	63
27	MeCN–CF_3CH_2OH (7:3)	*m*CPBA (2.0)	$CH_3(CH_2)_2I$ (0.1)	2.5	12	72
28	MeCN–CF_3CH_2OH (7:3)	*m*CPBA (2.0)	$CH_3(CH_2)_2I$ (0.25)	2.5	12	82
29	MeCN–CF_3CH_2OH (7:3)	*m*CPBA (2.0)	$CH_3(CH_2)_2I$ (0.3)	2.5	12	83
30	MeCN–CF_3CH_2OH (7:3)	*m*CPBA (2.0)	—	2.5	12	0
31	MeCN–CF_3CH_2OH (7:3)	*m*CPBA (2.0)	$CH_3(CH_2)_2I$ (0.25)	2.5	6	77
32	MeCN–CF_3CH_2OH (7:3)	*m*CPBA (2.0)	$CH_3(CH_2)_2I$ (0.25)	2.5	24	84

[a] Isolated yields.

Table 2
Preparation of α-sulfonyloxyketones **2**



Entry	Substrate	RSO_3H[a]	Product	Time (h)	Yield[b] (%)
1	 **1a**	 (TsOH)	 **2a**	12	82
2	 **1b**	TsOH	 **2b**	8	90
3	 **1c**	TsOH	 **2c**	8	88
4	 **1d**	TsOH	 **2d**	8	81
5	 **1e**	TsOH	 **2e**	8	80
6	 **1f**	TsOH	 **2f**	10	80
7	 **1g**	TsOH	 **2g**	8	81
8	 **1h**	TsOH	 **2h**	12	72
9	 **1i**	TsOH	 **2i**	8	69
10	 **1j**	TsOH	 **2j**	14	68
11	 **1k**	TsOH	 **2k**	16	27
12	 **1l**	TsOH	 **2l**	12	93
13	 **1m**	TsOH	 **2m**	12	73
14	**1a**		 **2n**	8	65
15	**1a**		 **2o**	8	56
16	**1a**	$MeSO_3H$	 **2p**	8	51
17	**1e**	$MeSO_3H$	 **2q**	8	52
18	**1a**	(+)-Camphorsulfonic acid (CsOH)	 **2r**	10	47

[a] Ts, *p*-Me–$C_6H_4SO_2$; Cs, (+)-10-camphorylsulfonyl.
[b] Isolated yield.

To identify above mechanism, we have focused our attention on the key intermediate α-iodoacetophenone due to that other intermediates iodosylpentane and α-iodosylacetophenone are highly unstable[1a–c] and difficult to be determined by NMR and normal physical methods. Firstly, α-iodosylacetophenone was prepared by the reaction of acetophenone with hypoiodous acid.[13] Then the prepared α-iodoacetophenone was treated with $TsOH{\cdot}H_2O$ and *m*CPBA for several hours, the desired α-tosyloxyacetophenone was obtained in a good yield (86%); however, in the absence of *m*CPBA, no product was detected (Scheme 2). Therefore, the in situ generated hypervalent iodine intermediate α-iodosylacetophenone may be responsible for the reaction.

In light of successful formation of α-tosyloxyacetophenone, the reaction conditions were optimized, the results are summarized in Table 1. When acetophenone was treated with 2.0 equiv of $TsOH{\cdot}H_2O$ and 1.2 equiv of *m*CPBA in the presence of 0.2 equiv of 1-iodopentane in several organic solvents at room temperature for 12 h, the reaction usually gave poor yields (entries 1–8). Utilization of a mixture solvent of acetonitrile and 2,2,2-trifluoroethanol ($MeCN–CF_3CH_2OH$), the yield increased and the mixture

solvent MeCN–CF_3CH_2OH (7:3) was proved to be the favorable solvent system for the reaction (entries 9–14). Other oxidants, such as Oxone® and $NaBO_3{\cdot}4H_2O$ normally led to rather poor yields (entries 15 and 16). The amounts of *m*CPBA and TsOH were also checked, the results showed that 2.0 equiv of *m*CPBA and 2.5 equiv of $TsOH{\cdot}H_2O$ were suitable for the reaction (entries 17–21). A series of alkyl iodides were active in the reaction, in which 1-iodopropane was the most effective one, and 0.25 equiv of it was the best choice for the reaction (entries 22–29). However, in the absence of alkyl iodide, no product was observed (entry 30). The suitable reaction time should be 12 h (entries 28, 31, and 32).

With the optimal conditions in hand, in order to assess the scope of this method, a series of ketones were investigated to react with *m*CPBA and $TsOH{\cdot}H_2O$ in the presence of 1-iodopropane in MeCN–CF_3CH_2OH (7:3), a good result was obtained (Table 2).[14]

As shown in Table 2, the reaction was compatible with most of the studied alkyl aryl ketones except 2-acetylthiophene (**1k**) and provided the corresponding α-tosyloxyketones in good yields (entries 1–11). It was also found that the groups on the benzene ring, no matter whether they were electron-donating or electron-withdrawing groups, did not influence on the yield. Due to the hinder effect of the methyl group, propiophenone (**1h**) and *p*-chloropropiophenone (**1i**) furnished the respective products in somewhat lower yields compared with **1a** and **1d**. Acetone, an aliphatic ketone, when treated under the same conditions, the desired product was afforded with an excellent yield of 93% (entry 12). Ethyl acetoacetate, a β-dicarbonyl compound, was also active in the reaction, and it gave the corresponding product in 73% yield (entry 13). Other aromatic sulfonic acids, such as benzenesulfonic acid and *p*-chlorobenzenesulfonic acid, can react with acetophenone and result in the corresponding products in moderate yields (entries 14 and 15). Methanesulfonic acid and (+)-camphorsulfonic acid, both aliphatic sulfonic acids were also active in the reaction and the corresponding α-sulfonyloxyketones were obtained in moderate yields (entries 16–18). This result has extended its application compared with previous reports in which the α-sulfonyloxylation of ketones using iodobenzene and molecular iodine as catalysts was only suitable for aromatic sulfonic acids, and when an aliphatic sulfonic acid was used, the reaction usually got trace amount of product.[5,6]

Conclusion

We have developed a novel and efficient process for the synthesis of various α-tosyloxyketones in moderate to good yields by the reaction of ketones with *m*CPBA and $TsOH{\cdot}H_2O$ in the presence of a catalytic amount of 1-iodopropane in MeCN–CF_3CH_2OH (7:3) at room temperature for several hours. This method has some advantages such as mild reaction conditions and simple procedure, which suits to prepare not only α-tosyloxyketones, but also other α-sulfonyloxyketones. Furthermore, the use of alkyl iodide in the catalytic reactions will extend the scope of alkyl substituted hypervalent iodine reagents in organic synthesis.

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14. *A typical procedure for α-tosyloxylation of ketones:* To a mixture solvent of MeCN–CF_3CH_2OH (7:3) (5 mL), ketone **1** (0.5 mmol), *m*CPBA (1.0 mmol), 1-iodopropane (0.125 mmol) and $TsOH{\cdot}H_2O$ (1.25 mmol) were added. The resulting solution was stirred at rt for several hours. After the reaction completed, H_2O (10 mL), satd aq $Na_2S_2O_3$ (5 mL) and satd aq Na_2CO_3 (5 mL) were added to the mixture, then it was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and the filtration was concentrated under reduced pressure. The residue was then purified on a silica gel plate (4:1 hexane–ethyl acetate) to furnish α-tosyloxyketones **2**.