Direct α -Oxytosylation of Ketones by Using Pentavalent Organobismuth Reagents

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A new method for the preparation of α -tosyloxy ketones by a direct oxytosylation of ketones using a combination of heterocyclic pentavalent organobismuth compounds and *p*-toluenesulfonic acid monohydrate is described.

 α -Tosyloxy ketones are known as very useful reagents for the synthesis of heterocyclic compounds such as thiazoles, imidazoles, oxazoles, pyrazoles, etc., and they excel in stability and toxicity in comparison with the frequently used α -halo ketones.¹

Preparation of α -tosyloxy ketones via a direct oxytosylation of ketones is generally carried out by employing hypervalent iodine such as [hydroxy(tosyloxy)iodo]benzene (Koser's reagent).² Although several efficient methods by using catalytic amounts of PhI were recently reported,³ examples that applied this iodine system to electron-rich aromatic ketones such as methoxyphenyl ketones were only a few because sometimes undesirable side reactions proceeded at the same time.⁴ In a very recent report on α -oxytosylation of ketones by using *N*-methyl-*O*-tosylhydroxylamine, there were no examples of methoxyphenyl ketones.⁵

In organic transformation, pentavalent organobismuth compounds are often used as mild oxidants and arylation reagents.⁶ It was recently reported from our laboratory that the reactivity of pentavalent heterocyclic bismuth compounds was quite different from the noncyclic ones: for example, oxidative coupling reactions of carbonyl compounds using pentavalent bismuth



Figure 1.

Table 1. Effects of organobismuth(V) reagents

	O + Ph 5a +	Bi ^v reagent (1.1 equiv)	0	
		(2.5 equiv) CH_3CN , rt, 24 h	Ph 6a	
_	Entry	Bi ^v reagent	Yield/% ^a	
	1	1	ND ^b	
	2	2	trace	
	3	3	17	
	4	4a	35 ^c	

^aIsolated yield. ^bNot detected. ^cPhOTs was obtained in 42% yield as by-product.

ditriflates,⁷ and the ligand coupling reactions of pentavalent bismuth disulfonates.⁸ In this communication, we would like to report a new direct α -oxytosylation of ketones by utilizing unique oxidation behavior of heterocyclic organobismuth compounds.

In the first place, reactivities of pentavalent bismuth dicarboxylates (1–3 and 4a, Figure 1) were examined in the α -oxytosylation of acetophenone in CH₃CN at room temperature (see Table 1).⁹ Those bismuth compounds were easily prepared from the corresponding trivalent bismuth ones^{8a,8b} on treatment with a combination of *m*-chloroperoxybenzoic acid (MCPBA) and *m*-chlorobenzoic acid. While the use of triphenylbismuth compound 1 did not give the desired α -tosyloxyketone 6a (Entry 1), heterocyclic bismuth compounds 2, 3, and 4a provided 6a (Entries 2–4), and the best result was obtained in the case of using 4a. However, PhOTs was formed in 42% yield as by-product due to the ligand coupling reaction of in situ generated pentavalent bismuth ditosylate (Entry 4).

In order to inhibit this side reaction caused by the ligand coupling reaction, effects of aryl group on the reactivity of the bismuth compounds **4b–4f** were next examined, and reaction conditions were optimized (see Table 2). When 2-methoxyphenyl group was introduced, the yield of **6a** was poor because of the decrease in solubility of the corresponding bismuth ditosylate to CH₃CN (Entry 1). In the case of 4-methoxyphenyl group, **6a** was obtained in 57% yield along with the by-product, 4-methoxyphenyl tosylate, in less than 10% (Entry 2). After screening various halophenyl groups, 4-fluorophenyl group turned out to

Table 2	 Effects 	of ary	l group	and	reaction	condition
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C) + TsOH•H ₂ O ·	Ar 4		O OTs		
Pn 5a	`	013010, 11, 2	Pn	6a		
Entry	Ar	Bi ^V /equiv	TsOH•H ₂ O /equiv	Yield/% ^a		
1	2-MeOC ₆ H ₄	4b /1.1	2.5	6		
2	4-MeOC ₆ H ₄	4c /1.1	2.5	57		
3	4-BrC ₆ H ₄	4d /1.1	2.5	49		
4	4-CIC ₆ H ₄	4e /1.1	2.5	56		
5	$4-FC_6H_4$	4f /1.1	2.5	62		
6	$4-FC_6H_4$	4f /1.1	1.1	4		
7 ^b	4-FC ₆ H ₄	4f /1.5	3.3	75		
8 ^b	4-FC ₆ H ₄	4f /1.5	5.0	82		
9 ^c	4-FC ₆ H ₄	4f /1.5	5.0	75		

^aIsolated yield. ^bThe reaction was carried out at rt for 72 h. ^cThe reaction was carried out at $45 \degree$ C for 20 h.

Table 3. α -Oxytosylation of various ketones



^aIsolated yield. ^bThe reaction was carried out at 45 °C for 20 h using 2 equiv of **4f** and 4.2 equiv of TsOH•H₂O. ^cYields of **6k** and **6l** were determined by the integrated ratio of ¹H-NMR from the mixture of two compounds.

be the most potential aryl group (Entries 3–5). In addition, it retarded the side reaction and the formation of 4-fluorophenyl tosylate was less than 10%. The yield of **6a** decreased considerably to 4% when the amount of TsOH•H₂O was reduced to 1 equiv for **4f** (Entry 6). Concerning effects of the amounts of TsOH• H₂O, more than 2 equiv were then needed for bismuth compounds to exchange the two carboxylate ligands. Then, it was found that the combined use of 1.5 equiv of **4f** and 5 equiv of TsOH•H₂O gave **6a** in 82% yield (Entry 8). Although the desired reaction proceeded faster at the elevated temperatures, it became slightly complicated because of side reactions, and thus **6a** was obtained in 75% yield (Entry 9). Finally, various ketones were examined under the optimized conditions (see Table 3). Then, electron-rich aromatic ketones, methylacetophenones or methoxyacetophenones, gave the corresponding α -tosyloxy ketones **6b–6e** in moderate to good yields (Entries 1–4). While the yields of electron-poor aromatic and heteroaromatic ketones were also acceptable (**6f–6i**, Entries 5–8). Acetone, a typical aliphatic ketone, is also applied to this reaction (Entry 9). Concerning regioselectivity of nonsymmetrical ketones, it was noteworthy that the primary center was more favorable than the secondary one (5.5:1) as shown in the reaction of 2-butanone (Entry 10). This tendency of regioselectivity is opposite to that of 1:1.57 obtained by using hypervalent iodine system,^{2c} and that this bismuth system showed higher selectivity in comparison with 2.6:1 observed in the case of *N*-methyl-*O*-tosylhydroxyamine.⁵

It is noted that a new direct α -oxytosylation of ketones using heterocyclic organobismuth compound **4f** was established. To the best of our knowledge, this is the first report on α -oxytosylation of ketones by utilizing oxidizing ability of pentavalent organobismuth compound, and various ketones including methoxyacetophenones were successfully applied to the present reaction. It is interesting to note that reverse regioselectivity was observed different from that of using hypervalent iodine system when the nonsymmetrical keotone such as 2-butanone was examined in this bismuth system. Further investigation including the reaction mechanism is currently under way in our laboratory.

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- 9 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/ index.html.