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Synthesis of α-acetoxy and formyloxy ketones by thallium(III) promoted α-oxidation

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Treatment of ketones with thallium(III) triflate in amide solvents at 60 °C for 30 min followed by addition of small amounts of H_2O cleanly provided the corresponding α-acyloxy ketones.

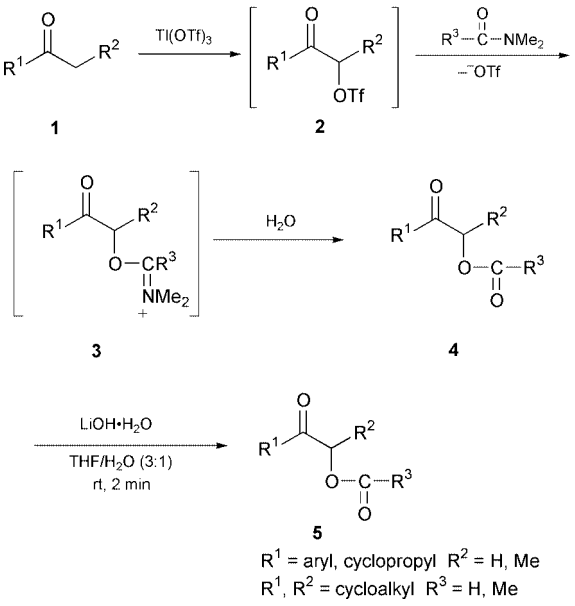
The α-hydroxy ketone subunit is found in a variety of biologically interesting natural products.[1] The formate and acetate groups can serve as useful protective groups for the hydroxy functions in α-hydroxy ketones.[2,3] The α-acetoxy ketones can be prepared *via* various ways which include the reaction of α-bromo ketones with carboxylate ions,[4] the oxidation of morpholine enamine with thallium(III) triacetate,[5] anodic oxidation of enol acetates in acetic acid,[6] and $Cu(acac)_2$ catalyzed insertion reactions of α-diazo ketones with carboxylic acids.[7] In addition, it has been reported that the solvolytic reaction of α-keto triflate in acetic acid or formic acid can provide corresponding α-acyloxy ketones,[8] but potential difficulties in preparing α-triflyloxy ketone precursors (*e.g.* α-triflyloxy propiophenone) limits their further synthetic applications. There exist only a few methods that deal with the direct preparation of α-acetoxy ketones from ketones. These involve the oxidation of ketones with lead tetraacetate,[9] the oxidation of ketones with manganese(III) acetate in acetic acid,[10] and the oxidation of aromatic ketones with hypervalent iodine reagent followed by solvolysis in acetic acid in the presence of silver carbonate.[11] Although many procedures have been reported for the preparation of α-acetoxy ketones, relatively little is known for the preparation of α-formyloxy ketones. The only reported method involves anodic oxidation of enol carbonate in DMF–$LiClO_4$.[12] To the best of our knowledge, no general method for the one-pot conversion of ketones to their corresponding α-formyloxy ketones has been reported.†

We now report a new and highly efficient preparation method for the α-formyloxy ketones and α-acetoxy ketones. This methodology is based on the hydrolysis of iminium salt intermediates **3** formed by the reaction of α-triflyloxy ketone with amide solvent. Initial treatment of ketones with thallium(III) triflate, formed *in situ* by the reaction of thallium(III) acetate with trifluoromethanesulfonic acid, in DMF at 60 °C followed by addition of small amounts of H_2O cleanly provided the α-formyloxy ketones in excellent yields. The probable mechanism is shown in Scheme 1. The thallium(III) organosulfonate mediated α-sulfonyloxylation of ketones is well established.[13] Therefore, the reaction of ketones with thallium(III) triflate at room temperature for 10 min should provide α-triflyloxy ketone intermediates **2** which undergoes rapid solvolytic reaction with DMF at 60 °C for 20 min to give iminium salts **3**. These intermediates are instantaneously hydrolysed to give desired α-formyloxy ketones in the presence of H_2O. Although the utility of DMF as a formate anion equivalent for the preparation of alkyl formates has been reported,[14] application of this method for the α-formyloxylation of ketones is unprecedented. Among the ketones examined, aliphatic ketones such as acetone and pentan-3-one gave complex product mixtures under the present reaction conditions. In the case of cyclopentanone, α-formyloxy cyclopentanone was detected in 98% yield as judged by GC analysis but a number of attempts to isolate pure α-formyloxy cyclopentanone by column chromatographic separation failed owing to the decomposition of the compounds. When the present reaction conditions were applied to cyclohexanone, a mixture of α-hydroxy cyclohexanone and α-formyloxy cyclohexanone was obtained in a ratio of 84 : 16 as indicated by GC, probably due to the highly unstable preformed α-formyloxy cyclohexanone undergoing further hydrolysis.

When the same reaction protocol used in α-formyloxylation of ketones was conducted in *N*,*N*-dimethylacetamide instead of DMF, α-acetoxylation of ketones took place remarkably well to give uniformly high yields of α-acetoxy ketones with all of the ketones examined. The representative results are summarized in Table 1. It is important to note that the solvolytic reaction of iminium salts in DMF was carried out at 60 °C to obtain the best results. Elevated temperature gave a number of side products. The intermediates iminium salts **3** were not stable enough to be isolated.

We have also studied the cleavage reactions of α-formyloxy and α-acetoxy ketones to their corresponding α-hydroxy ketones. We found the lithium hydroxide in aqueous solution to be suitable for the cleavage of the formyl and acetyl groups. Treatment of isolated α-formyloxy ketones or α-acetoxy ketones in THF–H_2O (3 : 1, v/v) solution of lithium hydroxide at room temperature for 2 min afforded the corresponding α-hydroxy ketones **5** in excellent yields ranging from 95 to 98%.

In conclusion, the facile conversion of ketones to the α-formyloxy ketones and α-acetoxy ketones has been accomplished in excellent yield. The present approach provides efficient entry for installation of α-acyloxy moieties into ketones and their clean deprotection should find wide applica-



Scheme 1

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Table 1 Conversion of ketones to α-formyloxy ketones

Entry	Ketones	% Yield[a] of α-formyloxy ketones	% Yield[a] of α-acetoxy ketones
1	$PhCOCH_3$	94	96
2	p-$CH_3C_6H_4COCH_3$	92	92
3	p-$CH_3OC_6H_4COCH_3$	97	98
4	p-$ClC_6H_4COCH_3$	90	90
5	$PhCOCH_2CH_3$	96	97
6	p-$CH_3C_6H_4COCH_2CH_3$	91	93
7	p-$CH_3OC_6H_4COCH_2CH_3$	97	98
8	p-$PhCH_2OC_6H_4COCH_2CH_3$	99	99
9	Cyclopropyl methyl ketone	99[b]	99[b]
10	Cyclopentanone	99[c]	99
11	Cyclohexanone	—[d]	99
12	Indan-1-one	98	99
13	2-Acetylthiophene	97	98

[a] Isolated yields. [b] The acyloxylation occurred at methyl position. [c] GC yield. [d] α-Hydroxy ketone was obtained as a major product.

tions in the construction of α-hydroxy ketone subunit in natural product synthesis.

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Notes and references

† **Caution**: *Thallium compounds are highly toxic; they should therefore be handled with extreme caution and all operations must be carried out in an efficient fume hood.* The experimental procedure for the preparation of α-formyloxy acetophenone is representative. To thallium(III) acetate (0.572 g, 1.5 mmol) in DMF (5 mL) was added trifluoromethanesulfonic acid (0.675 g, 4.5 mmol) at rt under nitrogen with stirring for 10 min. To the reaction mixture acetophenone (0.120 g, 1.0 mmol) was added and stirred at 60 °C for 20 min. After reaction, the temperature was brought down to rt, H_2O (1 mL) was added and stirred for an additional 10 min. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with saturated $NaHCO_3$ aqueous solution, water, and dried over $MgSO_4$. Evaporation of solvent, followed by short column chromatography on silica gel (ethyl acetate–hexane 1:2) yielded the α-formyloxy acetophenone.

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