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A NEW PROCEDURE FOR α-HYDROXYLATION OF KETONES USING THALLIUM(III) p-NITROBENZENESULFONATE (TNS)

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Abstract: An efficient method for conversion of ketones to α-hydroxyketones by treatment of thallium(III) *p*-nitrobenzenesulfonate with ketones and subsequent hydrolysis using DMSO/H_2O in one pot system is described.

The α-hydroxyketones are widely used synthetic intermediates and are an important constituent of many biologically important natural products.[1] Although there have been numerous methods reported for the preparation of α-hydroxyketones under basic conditions[2], only few reports in the literature account for the direct α-hydroxylation of ketones under acidic conditions. Previous reports describing the direct conversion of ketones to α-hydroxyketones under acidic conditions include oxidative α-hydroxylation of cyclohexanone with thallium(III) nitrate in acetic acid[3] and reaction of ketones with [bis(trifluoroacetoxy)] iodobenzene and trifluoroacetic acid in CH_3CN / H_2O[4]. The latter method offers the general approach for the direct α-hydroxylation of ketones. However, this

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method has the disadvantages to give low yield of aromatic secondary α-hydroxyketones or to require highly acidic conditions. Therefore, an improved method for the conversion of α-methylene ketones to corresponding α-hydroxyketones under mild acidic conditions is required.

Thallium(III) *p*-tolylsulfonate (TTS)[5] or thallium(III) methanesulfonate (TTMS)[6] are known to be excellent reagents for the direct conversion of ketones to corresponding α-sulfonyloxyketones.

We envisioned that application of this strategy to direct α-nosyloxylation of ketones and subsequent hydrolysis of α-nosyloxy ketone intermediates in one pot system would provide an easy access to α-hydroxyketones. This method involves the reaction of thallium(III) *p*-nitrobenzenesulfonate (TNS, obtained by in situ reaction of thallium(III) acetate and *p*-nitrobenzenesulfonic acid) with ketones in acetonitrile, to give intermediate α-nosyloxy ketones, which can then undergo hydrolysis with dimethyl sulfoxide /H_2O (1 : 2) system to give α-hydroxyketones. The results are summarized in Table. Both α-methyl ketones and α-methylene ketones converted equally well to the corresponding α-hydroxyketones in high yields. All reactions were completed in a period of 3 hours without any observable side reactions. Of particular significance is the successful conversion of α-methylene ketones to the secondary α-hydroxyketones in very high yields which could not be achieved under previous conditions[4]. Moreover, this method is proved to be worked well for ketones bearing acid sensitive functionalities (entries

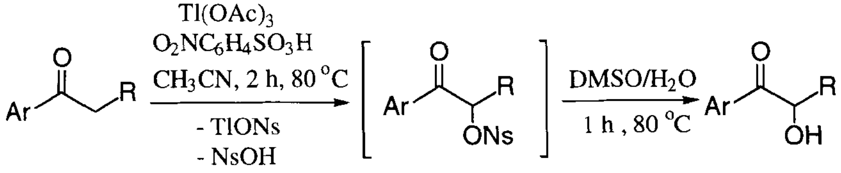
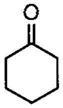
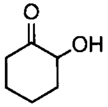


Table. Conversion of ketones to α-hydroxyketones.

Entry	Substrate	Product	Yield (%)[a]
1	$PhCOCH_3$	$PhCOCH_2OH$	90 (69)
2	p-$ClC_6H_4COCH_3$	p-$ClC_6H_4COCH_2OH$	93
3	p-$CH_3C_6H_4COCH_3$	p-$CH_3C_6H_4COCH_2OH$	92 (72)
4	p-$CH_3OC_6H_4COCH_3$	p-$CH_3OC_6H_4COCH_2OH$	87 (58)
5	$PhCOCH_2CH_3$	$PhCOCH(OH)CH_3$	90 (36)
6	p-$EtCO_2C_6H_4COCH_3$	p-$EtCO_2C_6H_4COCH_2OH$	89
7	p-$CH_3C_6H_4COCH_2CH_3$	p-$CH_3C_6H_4COCH(OH)CH_3$	98
8	p-$BrC_6H_4COCH_2CH_3$	p-$BrC_6H_4COCH(OH)CH_3$	91 (21)
9	p-$ClC_6H_4COCH_2CH_3$	p-$ClC_6H_4COCH(OH)CH_3$	97
10	p-$FC_6H_4COCH_2CH_3$	p-$FC_6H_4COCH(OH)CH_3$	90
11	p-$PhCH_2OC_6H_4COCH_2CH_3$	p-$PhCH_2OC_6H_4COCH(OH)CH_3$	85
12			72[b] (47)

[a] Isolated yield. Yields in parenthesis are obtained in ref. 4.

[b] Obtained as a dimer.[7]

6 and 11) which demonstrated the mildness of present reaction conditions. It is of interest to note that the presence of DMSO seems to be essential for the success of hydrolysis reaction. In fact, our initial attempts to conduct hydrolysis in H_2O alone furnished only moderate yields of α-hydroxyketones. The hydrolysis reaction presumably proceed via initial nucleophilic displacement of -ONs group by

sulfoxide oxygen and subsequent hydrolysis of α-dimethylsulfoxonium ion intermediates. This mechanism is analogous to the previous finding in the DMSO assisted bromohydrin formations from bromoniun ion intermediates.[8] Using TTS as a sulfonyloxylation agent, the hydroxylation yields were reduced to 20 % on average presumably due to the poor leaving ability of -OTs group compared to the -ONs group.[9]

In summary, we have described a new one pot synthesis of α-hydroxyketones which has the advantages over the previously described approach to improve yield and to use mild conditions which will provide an added flexibility to the direct α-hydroxylation of ketones.

EXPERIMENTAL SECTION

^{1}H-NMR spectra were obtained on a Varian Gemini 2000 at 300 Mhz. IR spectra were measured on a Jasco FT/IR 5300 spectrophotometer. All reagents and solvents were obtained from commercial sources and used without further purification. All products give spectra in accord with their proposed structures.

General Procedure. To a solution of *p*-nitrobenzenesulfonic acid (1.28 g, 3.35 mmol) in acetonitrile (10 mL), thallium (III) acetate (2.04 g, 10.06 mmol) was added at room temperature. After being stirred for 10 minutes, ketone (2.24 mmol) in acetonitrile (20 mL) was added and the stirring was continued with reflux for 2 h. Then, to the reaction mixture was added 30 mL of dimethyl sulfoxide/H_2O (1 : 2) and the resulting solution was stirred at 80 ^{0}C for an additional 1 h. After removal of acetonitrile under reduced pressure, the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were concentrated under reduced pressure. The resulting residue was then dissolved in Et_2O (80 mL), washed with H_2O (20 mL), and dried over

$MgSO_4$. The solvent was removed *in vacuo* to give a pure α-hydroxyketone. In case of entry 11 the product was further purified by flash column chromatography on silica gel with EtOAc/hexane (1 : 3) as the eluent.

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