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DIRECT α -HYDROXYLATION OF KETONES UNDER ACIDIC CONDITIONS USING [BIS (TRIFLUOROACETOXY)] IODOBENZENE

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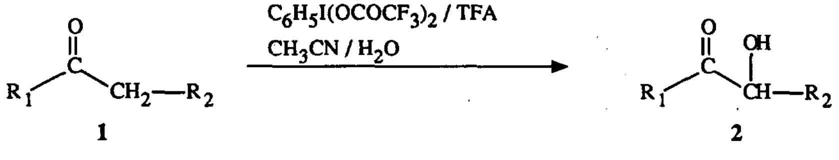
Abstract. [Bis(trifluoroacetoxy)] iodobenzene and trifluoroacetic acid in CH_3CN/H_2O reacts with aromatic, heteroaromatic, and aliphatic ketones to afford α-hydroxyketones in moderate to good yields.

Considerable attention has been directed towards the synthesis of α-hydroxyketones or acyloins. These compounds are important synthetic intermediates and are frequently encountered as structural subunits in many natural products.[1] They have been utilized in the total syntheses of velbanamine,[2a] phytuberin,[2b] periplanone B,[2c] terramycin,[2d] amarolide,[2e] (5S,6S)-aeginetolide,[2f] (5S)-dihydroactinidiolide,[2f] sterpuric acid,[2g] a C/D ring precursor of the taxol skeleton,[2h] vetispirane sesquiterpene glucosides,[2i] olivin,[2j] tirandamycin A,[2k] quassin,[2l] picrotoxinin,[2m] coriamyrtin,[2m] and bulgecinine.[2n]

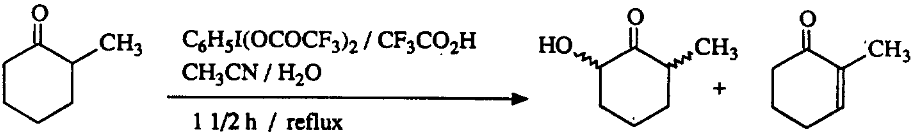
α-Hydroxylation of ketones is commonly accomplished through indirect methods via addition of dioxygen ($^3O_2$) to an enolate with subsequent reduction by triethyl phosphite[3a] or zinc in acetic acid,[3b] or via oxidation of enol silanes with dioxygen,[4a] MCPBA,[4b] osmium tetroxide,[4c] chromyl chloride,[4d] lead tetraacetate,[4e] N-sulfonyloxaziridines,[4f] and iodosobenzene-BF_3/Et_2O.[4g] Direct methods under basic conditions include oxidation by iodosobenzene,[5a] (diacetoxy) iodobenzene,[5b] *o*-iodosylbenzoic acid,[5c] molybdenum peroxide - pyridine - HMPA (MoOPH),[5d] N-sulfonyloxaziridines,[5e] benzeneselenic anhydride[5f] and dimethyldioxirane.[5g] To our knowledge, the only previous example of direct α-hydroxylation of a ketone under acidic conditions was reported by oxidation of cyclohexanone with thallium(III) nitrate.[6] We have found a simple, direct, and general route to acyloins under acidic conditions using hypervalent iodine chemistry.

In continuation of our work on hypervalent iodine chemistry, we now report a new one pot method for conversion of aromatic (**1a-h**), heteroaromatic (**1i-l**), and aliphatic (**1m-r**, **3**) ketones to their corresponding α-hydroxyketones (**2a-r**, **4a**) under acidic conditions using [bis(trifluoroacetoxy)] iodobenzene and trifluoroacetic acid in CH_3CN/H_2O (Schemes 1 and 2).



Scheme 1 - General reaction for α-hydroxylation of ketones.

In order to observe the regiochemistry of the reaction for α-methylene and α-methyne positions 2-methlycyclohexanone was hydroxylated as is shown in scheme 2.

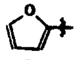
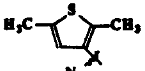
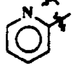
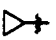
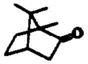


3 4a (23.2%) 4b (55.2%)

Scheme 2 - α-Hydroxylation of 2-methylcyclohexanone.

The method works well for α-methylketones (**1a-d,f,i-k,n,o**). In contrast, α-methylene (acyclic and cyclic) ketones (**1g,h,p,q**) are hydroxylated in moderate yields. The lower yields for hydroxylation at α-methylene positions probably results from steric interactions between the bulky hypervalent iodine reagent and the substrates and/or the relative ease of enolization of the ketones. In the reaction of (±)-camphor, where steric

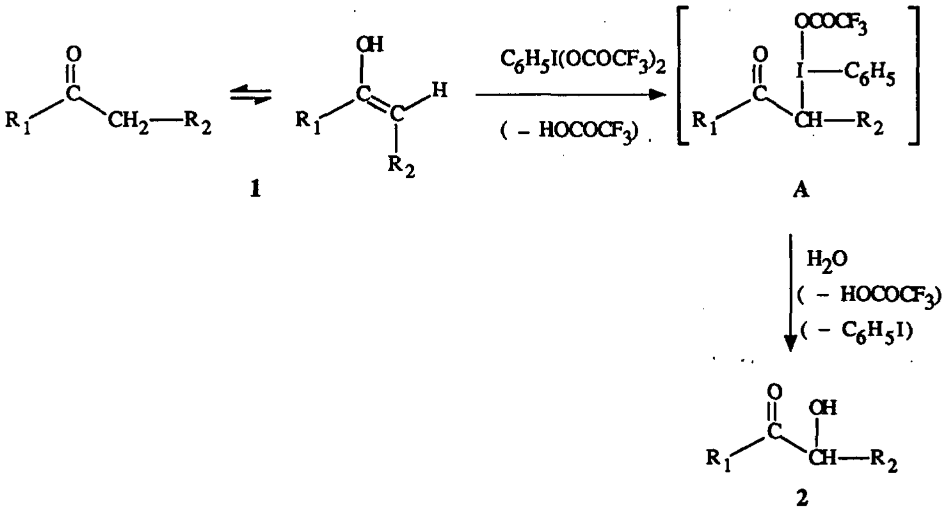
Table 1. α-Hydroxyketones Formed by I(III) Oxidation

Ketone	R_1	R_2	Time(h)	Product	Yield%[a]
1a	C_6H_5	H	3	**2a**	69
1b	p-$CH_3C_6H_4$	H	3	**2b**	72
1c	p-$CH_3OC_6H_4$	H	3	**2c**	58
1d	p-FC_6H_4	H	3	**2d**	67
1e	p-$NO_2C_6H_4$	H	3	**2e**[b]	29
1f	o-$CH_3C_6H_4$	H	3	**2f**	70
1g	C_6H_5	CH_3	3	**2g**	36
1h	p-BrC_6H_4	CH_3	4	**2h**	21
1i		H	3	**2i**	69
1j		H	4	**2j**	73
1k		H	3	**2k**	84
1l		H	3	**2l**	0
1m	$(CH_3)_3C$	H	3	**2m**	41
1n		H	3	**2n**	70
1o		H	3	**2o**	74
1p	$-(CH_2)_4-$		2	**2p**[c]	47
1q	$-(CH_2)_5-$		3	**2q**	94
1r			228	**2r**	0

a) Yield of isolated pure product. *b*) *p*-nitrobenzoic acid was also obtained in 29% yield. *c*) Isolated as the dimer.

effects are comparatively large, no reaction was observed after 9 1/2 days. An exception to this trend was cycloheptanone (**1q**) which was α-hydroxylated in high yield. The only isolated product from the reaction with cyclopropylmethyl ketone was hydroxymethylcyclopropyl ketone. *p*-Nitrobenzoic acid (29%) was obtained as a byproduct of overoxidation in the α-hydroxylation of *p*-nitroacetophenone due to the substrates greater reactivity under the reaction conditions. Although the method works well for heteroaromatic compounds containing oxygen and sulfur, it failed for 2-acetylpyridine (**1l**).

A reasonable pathway (Scheme 3) for the α-hydroxylation involves an initial ligand exchange by the enolic form of the ketone (**1**) with a trifluoroacetoxy ligand of [bis(trifluoroacetoxy)] iodobenzene to give intermediate **A**. Step **A** to **2** can occur through displacement of the hypervalent iodine moiety by water to yield the α-hydroxyketone (**2**). Water is a stronger nucleophile than trifluoroacetic acid[7] so α-hydroxylated products would be expected under these conditions -- not α-trifluoroacetoxy ketones.



Scheme 3 - Mechanism for a-hydroxylation of ketones.

In a typical experiment, acetophenone (**1a**)(0.60g, 5.0mmol) was added to a stirred solution of CF_3CO_2H (0.77ml, 10.0mmol), water (5ml), and CH_3CN (25ml). $PhI(OCOCF_3)_2$ (4.30g, 10.0mmol) was added and the solution was heated to reflux for 3 hrs. The reaction was monitored by thin layer chromatography. When the reaction was completed the reaction mixture was concentrated in vacuo to remove CH_3CN. The residue was partitioned between CH_2Cl_2 (125ml) and water (50ml). The aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were then washed with a saturated aqueous solution of $NaHCO_3$ (3 x 25ml), dried over MgSO4, filtered, and concentrated in vacuo . Final purification was accomplished by triturating the crude product with cold hexanes to yield 2-hydroxyacetophenone (**2a**) (O.471g, 3.46mmol, 69%). In some cases the products were isolated by column chromatography.

In conclusion, the present method provides a direct route to α-hydroxyketones under acidic conditions. It consists of very simple experimentation and is successful for a variety of ketones.

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