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AN EFFICIENT CONVERSION OF KETO GROUPS INTO DIHYDROXYACETONE GROUPS: OXIDATION OF ETHYNYLCARBINOL INTERMEDIATES BY USING HYPERVALENT IODINE REAGENT

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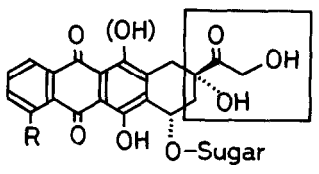
Summary: A short and efficient synthesis of dihydroxyacetone groups from keto groups involving the oxidation of ethynylcarbinol intermediates with [bis(trifluoroacetoxy)iodo]benzene (PIFA), is described.

A short and efficient conversion of keto groups into dihydroxyacetone groups is a quite significant step in the synthetic organic chemistry, since the dihydroxyacetone side chain is the structural component in adriamycin and related antitumor agents (1)[1] and also in cortico steroid antiinflammatory drugs (2).[2]



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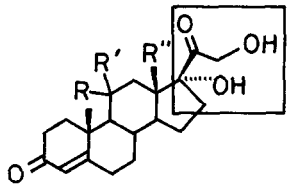

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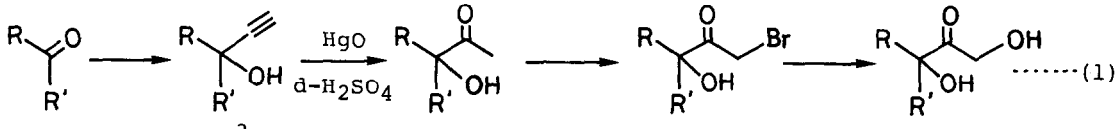
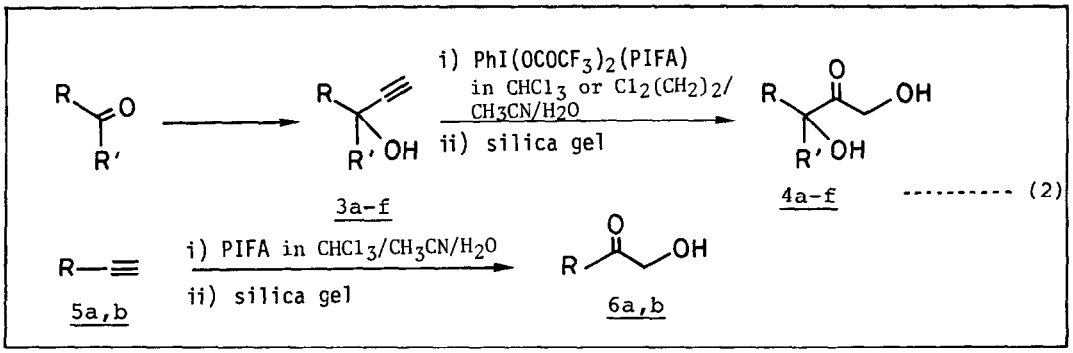
The conversion of keto groups into dihydroxyacetone side chains has been investigated extensively in different ways.[3,4] Among them, the most well-used method is the following route as exemplified in equation 1.[4] Although the



3 4

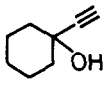
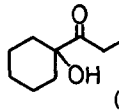
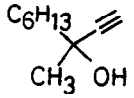
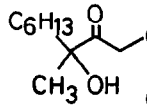
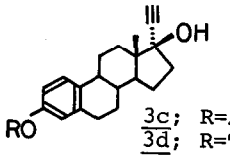
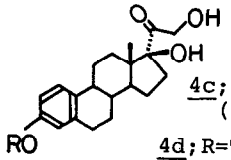
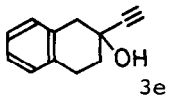
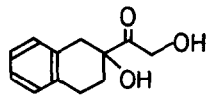
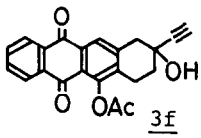
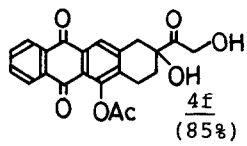
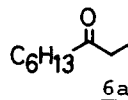
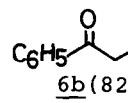
method is satisfactory in overall yield, an unfavorable oxidation-step of the ethynylcarbinol (3) using toxic mercuric(II) oxide and several steps (4 steps) are involved. In connection with our synthetic work in anthracycline area,[5] we required a shorter and useful conversion of the 9-ethynylcarbinol of A ring into dihydroxyacetone side chain, and the use of hypervalent iodine reagent,[6]

[bis(trifluoroacetoxy)iodo]benzene (PIFA) dissolved these problems. The hypervalent iodine reagents have been shown to react with some alkynes to give alkyliodonium salts,[7] but the reactivities are not fully clarified: i) The reaction of (perfluoroalkyl)phenyliodonium salt with terminal alkynes is complicated, since a mixture of substitution and addition products has been obtained,[8] ii) Non-terminal alkynes react with two equivalents of PIFA to form tetra-trifluoroacetoxy derivatives leading to α-diketones, while phenylalkynes react with one equivalent of PIFA to form alkylphenyliodonium salts leading to α-hydroxyacetophenones,[9] and iii) Non-terminal alkynes are converted into α-diketones by oxidation with iodosobenzene in the presence of Ru-catalyst, while terminal alkynes afford carboxylic acids.[10] We report here a novel, general, and efficient conversion of ethynylcarbinols (3)[11] into structurally important dihydroxyacetones (4) by using PIFA in $CHCl_3$ or $ClCH_2CH_2Cl/CH_3CN/H_2O$. The reagent is, of course, useful for conversion of terminal alkyl- and arylalkynes (5) into α-hydroxyketo compounds (6) (equation 2).



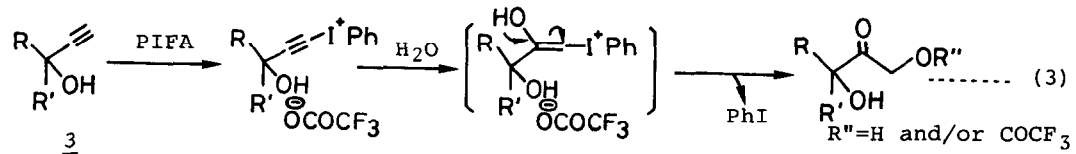
The following is a typical experimental procedure. To a solution of PIFA (2.2 mmol) in a solution of $CHCl_3/CH_3CN/H_2O$ (4 ml, 80:10:1) was added the ethynylcarbinol (3a, 1 mmol) dropwise. The mixture was stirred at reflux for 10 h, cooled to room temperature, and partitioned between water and CH_2Cl_2. The organic layer was dried and concentrated to give a mixture of the dihydroxyacetone (4a) and its O-trifluoroacetate. The mixture was passed through a dry silica gel column with ethyl acetate to hydrolyze the trifluoroacetate. The eluate was concentrated and purified by column chromatography on silica gel with benzene:ethyl acetate=5:1 as the eluting solvent to give pure 4a in 77% yield from 3a. Similarly, other ethynylcarbinols (3b-f) and terminal alkynes (5a,b) were also readily converted into the corresponding dihydroxyacetones (4b-f) and α-hydroxyketones (6a,b), respectively in good yields. All known products were identified by comparison with authentic samples and new compounds were characterized by microanalyses and IR and ^{1}H-NMR spectral data. The reaction conditions, yields, and the data of structural importance are summarized in the Table.

Table Oxidation of Ethynylcarbinols with [Bis(trifluoroacetoxy)iodo]benzene

Starting Materials	Conditions[a]	Product (Yield)[b]	[M.p] or B.p (Reported)	$\nu_{max}^{CHCl_3}$ cm^{-1}	^{1}H-NMR ($CDCl_3$) δ $-COCH_2OH$
 3a	80°, 10h	 4a (77%)	[90°]	3550-3400, 1710	4.49
 3b	80°, 10h	 4b (77%)	105-115°/5 (bath temp)	3550-3400, 1710	4.43
 3c; R=Ac 3d; R=Ts	80°, 19h	 4c; R=Ac (53%)	[111-112°]	3550-3400, 1750, 1710	4.54
		4d; R=Ts (60%)	[75-76°]	3550-3400, 1710	4.47
 3e	80°, 12h	 4e (76%)	[103-104°] (lit.[12] 105-106°)	3550-3400, 1725	4.63
 3f	5eq PIFA in $ClCH_2CH_2Cl$/ CH_3CN/H_2O, 100°, 4h	 4f (85%)	[198-199°]	(in KCl disc) 3500-3400, 1760, 1720, 1670	4.67
C_6H_{13}-≡ 5a	80°, 5h	 6a (78%)	71-74°/7 (lit.[13] 70-76°/6)	3550-3400, 1715	4.23
C_6H_5-≡ 5b	80°, 6h	 6b (82%)	[82.5-83.5°] (lit.[14] 82-84°) (lit.[15] 86-87°)	3550-3400, 1690	4.84

a The reaction was carried out with 1.1-2.2 equiv of PIFA in $CHCl_3/CH_3CN/H_2O$ except for the case of 3f.
b Yields of products isolated by column chromatography are given.

The reaction presumably proceeds with an initial formation of the alkynyliodonium salts and subsequent hydrolysis to dihydroxyacetones (equation 3). The formation of the iodonium salt from alkynes with some hypervalent iodine reagents is well documented by recent studies.[7]



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