Tetrahedron Letters, Vol. 22, No. 14, pp 1283 - 1286, 1981
Printed in Great Britain

0040-4039/81/141283-04$02.00/0

DIRECT α-HYDROXYLATION OF KETONES USING IODOSOBENZENE

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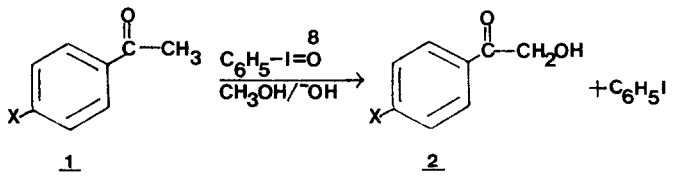
Summary--Ketones are converted smoothly into the corresponding acyloin with a high degree of selectivity upon treatment with iodosobenzene or phenyliodosodiacetate in methanolic sodium hydroxide.

α-Hydroxylation of ketones is commonly accomplished by an indirect method, viz., by the addition of dioxygen ($^3O_2$) to an enolate[2] with subsequent reduction of the α-hydroperoxy ketone by triethyl phosphite.[3] For example, this is a key reaction in the elaboration of the dihydroxyacetone side-chain of cortical steroid from a C_{17}-acetyl precursor. Addition of $^3O_2$ to organometallic enolates is inherently dangerous, and a serious explosion has been encountered in these laboratories.[4]

Direct hydroxylation of enolates is a less common synthetic transformation. Molybdenum peroxide-pyridine-HMPA (MoOPH) oxidation of the enolate yields the corresponding acyloin but the reaction with methyl ketones gives variable results.[5] Epoxidation of enol silanes may be considered a direct route to acyloins.[6]

We report now the high yield conversion of the series of arylmethyl ketones (1a-i) into the corresponding acyloin (2a-i). This reaction is all the more remarkable when applied to 2,6-diacetylpyridine (3), which is converted in 63% yield to 2,6-bis-(hydroxymethylcarbonyl) pyridine (4) without oxidation at nitrogen or further oxidation of the hydroxymethylcarbonyl groups. Similarly, diacetylferrocene (5) is converted to bis-(hydroxymethylcarbonyl) ferrocene (6) again without interference at the iron center. Clearly, alternative routes to these symmetrical systems would present serious difficulties. For example, in the case of 3 or 5, α-halogenation followed by displacement by ^-OH could not succeed because of the intervention of the haloform reaction. Such symmetrically substituted molecules, in the form of their bis-mesylate or bis-tosylates would be of obvious value in the synthesis of macrocycles.[7]



1

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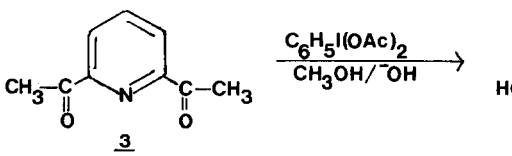
1.	X	Yield %	
a)	H	60	
b)	CH_3	45	(ref.9)
c)	OCH_3	50	
d)	OCH_3	40(3,4-OCH_3)	
e)	F	70	
f)	Cl	63	
g)	Br	70	
h)	I	71	
i)	NO_2	48	



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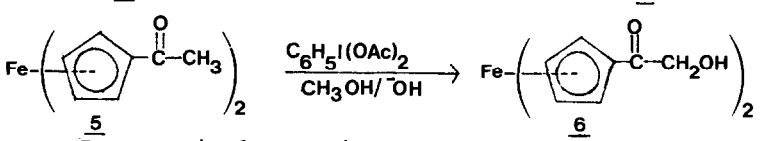
4

(ref. 14)



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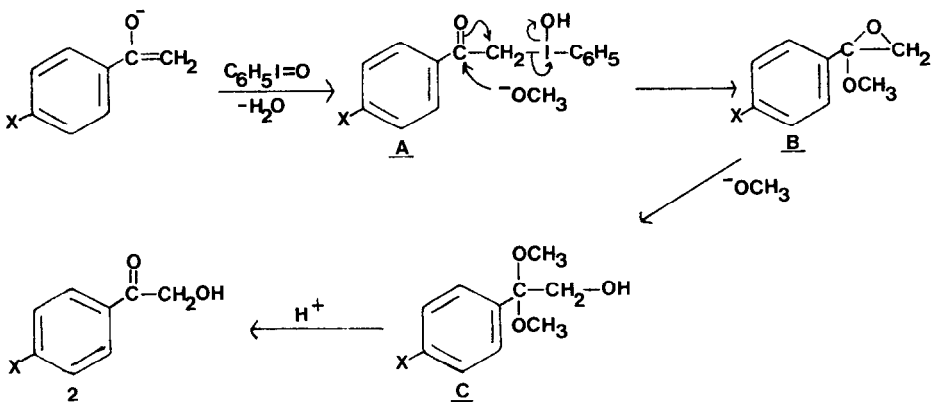
(ref. 14)

In a typical experiment 0.01 mole of the arylmethylketone (1a-i) is dissolved in 15 ml. of CH_3OH and 0.011 mole of $C_6H_5I{=}O$ is added. This mixture is cooled to 10° and 0.01 mole of NaOH in 2 ml. of CH_3OH is added dropwise with stirring. The product is isolated by acidification, extraction with CH_2Cl_2, and separation from iodobenzene by chromatography on silica gel.

If acid is omitted, the dimethylketal of the acyloin is obtained.[10] A reasonable mechanism is the following:

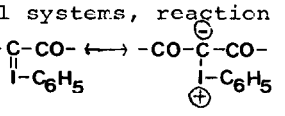


A

B

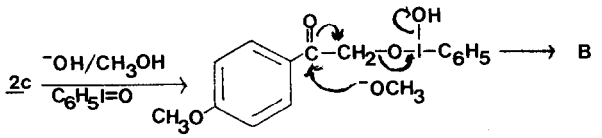
C

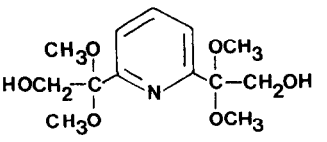
2

The essential features of this mechanism are the addition of the enolate of the ketone to $C_6H_5I{=}O$ to yield intermediate A. Interestingly, in the case of 1,3-dicarbonyl systems, reaction under the above conditions yields a stable ylid:[11]  formed conceivably

via dehydration of an intermediate analogous to A. Step A→ B involves nucleophilic attack of methoxide at the carbonyl group A with the thus formed alkoxide anion acting as an intramolecular nucleophile. Analogy for this reaction course exists.[12] Hypervalent iodine as is present in A is a reasonable leaving group. For example, m-chloroperbenzoic acid treatment of alkyl iodides leads to alcohols possibly via iodose intermediates.[13]

This mechanism accounts for the feature that the initially formed primary alcohol does not undergo further oxidation under the reaction conditions. For example, 2c in methanol upon addition of one equivalent of $C_6H_5I{=}O$ undergoes no change. However, addition of base yields B, which subsequently converts to C. The acyloin is protected from further oxidation by being captured as its dimethyl ketal.





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Likewise, the intermediary ketal 7 was isolated and characterized.[14]

Other α-hydroxylations using $C_6H_5I{=}O/^{-}OH/CH_3OH$ are the conversion to the acyloin of deoxybenzoin [15], acetylferrocene[16], 2-acetylpyridine[17], ethylphenylketone[18], and dibenzylketone (which yields 1,3-diphenyl-2-hydroxy-1-propanone)[19]. Purely aliphatic ketones also undergo the above reaction and will be discussed in a future publication.

Acknowledgement. Generous support by the National Science Foundation under grant CHE-77-06617 enabled us to do this research.

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14. Potassium hydroxide (5.6 g.; 0.1 mole) was dissolved in 50 ml. of CH_3OH at 0° and 2,6-diacetyl pyridine (1.63 g.; 0.01 mole) was added over a 10 min. period. The $C_6H_5I(OAc)_2$ (6.44 g.; 0.02 mole) was added during 10 mins.. The reaction mixture was stirred at room temperature overnight. Work-up followed by crystallization yielded 2.0 g. of 7 (72%), m.p. 153-4°; ^{1}H NMR ($CDCl_3$) δ3.2 (12 H, s, $-OCH_3$) 3.5 (2H, s, -OH) 3.9 (4H, s, $-CH_2$) 7.7 (2H, s, -3,5-pyridinium protons) 7.95 (1H, s, 4-pyridinium proton). Anal. Calcd. for C, 54.36, H, 7.32, N, 4.88; found: C, 53.83, H, 7.29, N, 4.79. Hydrolysis was carried out in acetone-p-TsOH to yield 4 in 90%, m.p.120-122°, ^{1}H NMR ($CDCl_3$) δ1.25 (2H, s, -OH) 5.25 (4H, s, $-CH_2-$) 8.10~8.25 (3H, pyridinium) IR 3500-3300, OH, 1710, C=O. Anal. Calcd. for C, 55.38, H, 4.62 N, 7.18; found: C, 55.30, H, 4.40, N, 7.10. Compound 6 was obtained in 34% and had m.p. 170° (dec) ^{1}HNMR ($CDCl_3$) δ4.2 (2H, s -OH) 4.65 (8H, m.), 4.85 (4H, m.). IR (KBr) 3440, 3100, 1675, 1625 cm^{-1}.
15. Deoxybenzoin yields 1,2-diphenyl-1-methoxyethylene oxide (53% yield). C. L. Stevens, M. L. Weiner, and R. C. Freeman, J. Am. Chem. Soc., 75, 3977 (1953).
16. α-Hydroxyacetylferrocene, m.p. 129-131°, ^{1}HNMR ($CDCl_3$) δ3.5 (1H,-OH), 4.25 (5H, s), 4.6 (4H, m), 4.85 (2H, m) IR (KBr) 3370, 3100, 1660 cm^{-1}.
17. Dimethylketal, liquid, ^{1}HNMR δ2.15 (1H, s, -OH), 3.25 (6H, s, OCH_3), 4.00 (2H, s, $-CH_2-$), 7.25 (1H, m, C_4-H), 7.75 (2H, m, $C_{3,5}$-H), 8.6 (1H, m, C_6-H), IR (neat film) 3400, 2950, 1700 cm^{-1}.
18. α-Hydroxypropiophenone was obtained in 75% yield (K. Auwers, Ber., 50, 1179 (1917)).
19. 1,3-Diphenyl-2-hydroxy-1-propanone was obtained in 80% yield (P. L. Julian, E. W. Meyer, A. Magnani and W. Cole, J. Am. Chem. Soc., 67, 1203 (1945)). This is formally a rearrangement product in relationship to the expected 1,3-diphenyl-1-hydroxy-2-propanone. Base equilibration between these isomers is discussed by Julian et al. vide infra..

(Received in USA 28 July 1980)