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α-Hydroxydimethylacetal Formation From Aminoketones Using Hypervalent Iodine

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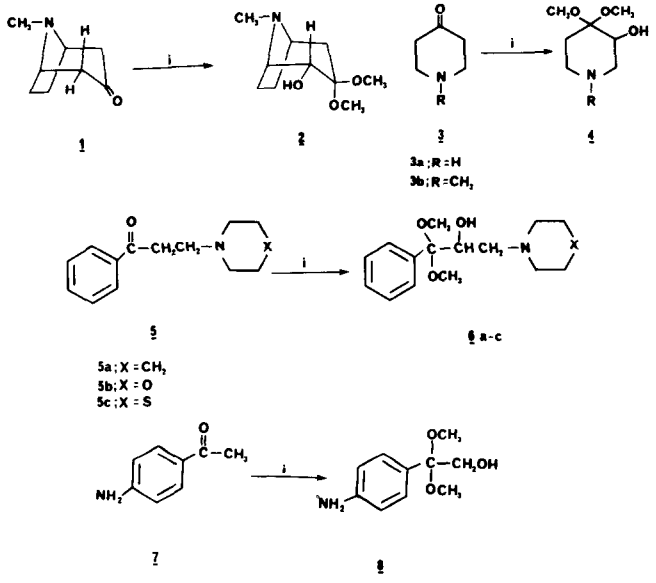
Summary - Various β-aminoketones were converted into the α-hydroxydimethylacetal using either o-iodosylbenzoic acid or (diacetoxy) iodobenzene (KOH/CH_3OH) without oxidation at 1°, 2° or 3°, amino groups or at sulfur in the case of a morpholino group.

We have demonstrated the usefulness of $C_6H_5I(OAc)_2$ in methanolic base for the conversion of enolizable carbonyl compounds into α-hydroxydimethylacetals.[1-5] As with any oxidative procedure in organic synthesis, the compatibility of other potentially oxidizable functionality within a given substrate is an important issue.

The present study addresses the stability of the amino group under the conditions for our α-hydroxylation reaction: $-COCH_2- \longrightarrow -C(OCH_3)_2CHOH-$. The amino group is particularly interesting because it represents an intermediary oxidation level among nitroso, nitro and hydroxylamino. The stability of the amino group to the systems (diacetoxy) iodobenzene/CH_3OH/KOH or o-iodosylbenzoic acid /CH_3OH/KOH[5] is illustrated by the α-hydroxylation of the following disparate aminoketones:

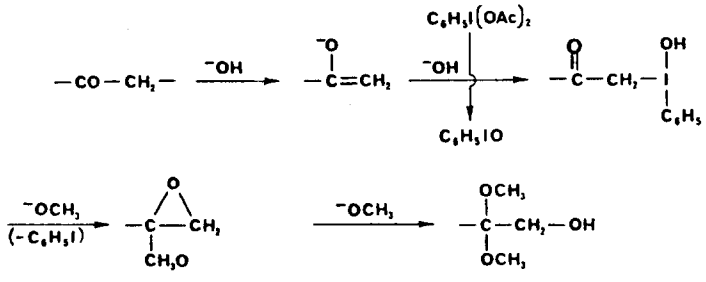


i $C_6H_5I(OAc)_2$-KOH/MeOH

Reference to Table 1 reveals the general usefulness of the oxidative procedure for the range of 1°, 2° and 3° aminoketones. Tropanone (1) yields α-hydroxydimethylacetal derivative 2 with the hydroxyl group in the α-configuration[6]. Oxidation 3b→4b is unremarkable, however 5→6c is unusual because the sulfur atom of the morpholino group is not oxidized. This contrasts with the system $C_6H_5I{=}O/HOAc$ which converts thioethers to sulfoxides. [7-11]

Oxidation 7 → 8 is remarkable in that substituted anilines are easily oxidized by a number of reagents[12], and iodosobenzene has also been reported to oxidize o-nitroaniline to furoxan[13]. m-Aminoacetophenone (9) is likewise transformed to the α-hydroxydimethylacetal in 35% yield but o-aminoacetophenone oxidation proceeded with intramolecular involvement of the amino function to yield a mixture. Similar behavior was observed with o-hydroxyacetophenone.[14] Regarding yields (Table 1) in all cases the n.m.r. spectra of the crude reaction products indicated the absence of substantial amounts of other products. Only in the case of 2 is there another product. Since the yields refer to isolated ones, the rather modest amounts reported in Table 1 may be regarded as reflecting losses in the purification process.

The results of the present study indicate the essential difference between $C_6H_5I{=}O/CH_3OH/\bar{O}H$ and $C_6H_5I{=}O/HOAc$.[15,16] This difference may be understood on a mechanistic basis. The reaction between $C_6H_5I(OAc)_2/CH_3OH/\bar{O}H$ and an enolizable ketone is the nucleophilic addition of the enolate anion to the iodine atom to yield an intermediate which decomposes by intramolecular displacement:



The system $C_6H_5I(OAc)_2/HOAc$ involves $C_6H_5\overset{+}{I}(OAc)$[15,16] formed in a pre-equilibrium as an electrophile which is indiscriminately reactive towards any nucleophilic center such as sulfur or nitrogen. Furthermore, the α-acetoxylation of substituted acetophenones

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

Compound	m.p.	Yield[a]	nmr(δ)[b] CH-OH	nmr(δ)[b] CH_3O-	Mass spectrum (20ev or 70 ev). m/e M+	Base Peak	Others[c]
2	85-86°	33%	3.90-3.88m	3.29s 3.24s	201 (58)	82[d]	M-31 (84);[c] 97, 96
4a (R=H)	88-89°	42%	3.96-3.82m	3.40s 3.29s	161 (8)	45	M-31 (35)[c]
4b (R=CH_3)	109-110°	54%	3.90-3.82m	3.28s 3.24s	175 (22)	86	M-31 (45),[c] 126 (55), 112 (43)
6a (X=CH_2)	80°-81°	50%	4.15,3.95 d,d (J=3Hz)	3.38s 3.23s	279 (6)	98[e]	151 (46),[f] 128 (52)
6b (X=O)	75-77°	60%	4.20-4.02 d,d (J=3Hz	3.40s 3.25s	281 (1)	100[e]	151 (48),[b] 130 (18)
6c (X=S)	129-30°	65%	4.16-3.98 d,d (J=3Hz)	3.38s 3.22s	297 (1)	116[e]	151 (40)[f]
8	159-62°	29%	3.75s	3.18s	197 (3)	166(M-31), 120, 92	
10	oil	35%	3.8s	3.3s	197 (1)	166(M-31), 120, 92, 84	

a. Isolated yields. Using o-iodobenzoic acid the oxidation product is isolated by direct extraction. Using $C_6H_5I(OAc)_2$, the crude reaction product is chromatographed.

b. At 60 MHz using $CDCl_3$ as solvent relative to TMS.

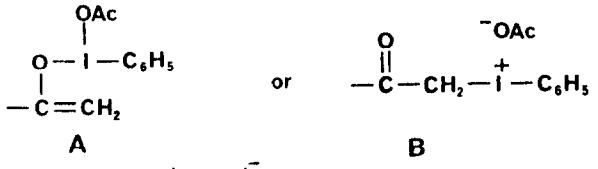
c. M-31 corresponds to loss of OCH_3

d. Base peak at m/e 82 indicates 6 and 7 positions of the tropane system are unsubstituted.

e. Base peak is $CH_2=\overset{+}{N}(CH_2CH_2)$ X

f. Peak at m/e 151 corresponds to $C_6H_5\overset{+}{C}(OCH_3)_2$

with $C_6H_5I(OAc)_2$/HOAc is known.[17] However in this case the reaction leads directly to the α-acetoxyketone possibly via attack of AcOH on A or B.



A or B

Obviously the system $C_6H_5I{=}O/CH_3OH/\bar{O}H$ is essentially more selective and synthetically superior.

Finally several of α-hydroxydimethylacetals reported in Table I were converted via the ketone to the oxime and these were studied as reactivator agents for diisopropylfluorophosphonate inhibited acetylcholinesterase. These results will be reported elsewhere.

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References

1. R. M. Moriarty, H. Hu and S. C. Gupta, Tetrahedron Lett. 22, 1283 (1981).
2. R. M. Moriarty, L. S. Jahn and P. C. Du, J. Chem. Soc. Chem. Commun., 641 (1981).
3. R. M. Moriarty, S. C. Gupta, H. Hu, D. R. Berenschot and K. B. White, J. Am. Chem. Soc., 103, 686 (1981).
4. R. M. Moriarty and H. Hu, Tetrahedron Lett. 22, 2747 (1981).
5. R. M. Moriarty and K. C. Hou Tetrahedron Lett., 25, 691 (1984) In this paper the advantage of using o-iodosylbenzoic acid in this oxidation reaction is described.
6. The structure of 2 is based upon an X-ray crystallographic study of the derived oximino methiodide (with W. A. Freeman of this Department).
7. L. K. Dyall, Aust. J. Chem., 26, 2665 (1973).
8. H. H. Szmant and R. L. Lapinski, J. Am. Chem. Soc., 78, 3400 (1956); K. C. Schreiber and V. Fernandez, J. Org. Chem., 26, 2478, 2910 (1961); J. P. A. Castrillon and H. H. Szmant, J. Org. Chem., 32, 976 (1967).
9. C. Srininasan, A. Chellamani and P. Kuthalingam, J. Org. Chem., 47, 428 (1982).
10. W. D. Johnson and N. V. Riggs, Aust. J. Chem., 17, 787 (1964); W. D. Johnson and J. E. Sherwood, ibid, 25, 1213 (1972).
11. A. A. Humffray and H. E. Imberger, J. Chem. Soc. Perkin II. 382 (1981).
12. K. H. Pausacker, J. Chem. Soc., 1989 (1953), G. B. Barlin, K. H. Pausacker, J. Chem. Soc., 3122 (1954) J. Mitchell and K. H. Pausacker, J. Chem. Soc., 4502 (1954). G. B. Barlin and N. V. Riggs, J. Chem. Soc., 3125 (1954) H. H. Szmant and R. L. Lapinski, J. Am. Chem. Soc., 78, 458 (1956).
13. A. J. Boulton and D. Middleton, J. Org. Chem., 39, 2956 (1974).
14. As might be anticipated neighboring participation is important in these processes. In the case of o-hydroxyacetophenone this is a synthetically useful reaction and a complete report will be published.
15. K. Swaminathan and N. Venkatasubramanian, J. Chem. Soc., Perkin Trans., 2, 1161 (1975).
16. Most published examples of $C_6H_5I(OAc)_2$ as an oxidant use HOAc as solvent.
17. F. Mizukami, M. Ando, T. Tanaka, and J. Imamura, Bull. Chem. Soc. Jpn, 51, 335 (1978).

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