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N-IODOSUCCINIMIDE MEDIATED OXIDATIVE CLEAVAGE OF VICINAL, MONOPROTECTED DIOLS[1]

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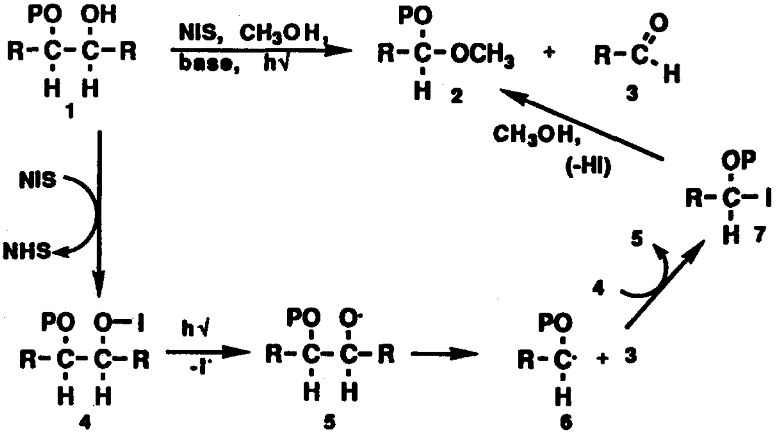
Summary: Vicinal, monoprotected diols are cleaved to mixed acetals and carbonyl compounds upon treatment with N-iodosuccinimide in the presence of light, base, and methanol.

N-Iodosuccinimide (NIS) has been shown to be a versatile oxidant for the alcohol functional group.[2] Initially NIS converts the alcohol to a hypoiodite.[3] The fate of the hypoiodite is dependent on the presence and location of other functionality as well as specific reaction conditions. Beebe has shown that vicinal diols are cleaved to carbonyl compounds upon treatment with NIS and light.[4] Herein we describe an extension of this methodology to the cleavage of vicinal, monoprotected diols (1) to a mixed acetal (2) and a carbonyl compound (3).[5]

A plausible mechanism for this transformation is shown in Scheme 1. Oxidation of vicinal, monoprotected diol 1 with NIS produces hypoiodite 4 and succinimide (NHS). Hypoiodite 4 is homolytically cleaved to produce an alkoxy radical 5 and an iodine radical. Carbon - carbon bond cleavage affords the carbonyl compound and an oxygen-stabilized carbon radical.[6] Iodination of the carbon radical (by hypoiodite 4 , NIS, or the hypoiodite of methanol) followed by nucleophilic displacement with methanol furnishes the observed mixed acetal 2.

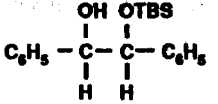
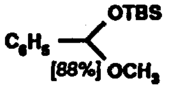
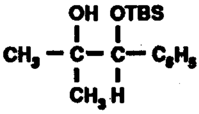
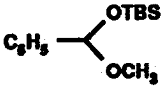
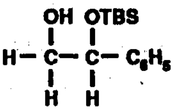
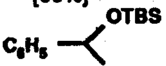
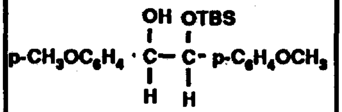
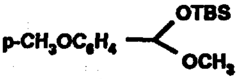
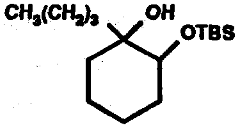
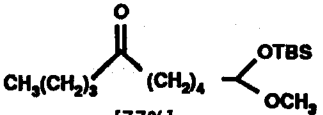
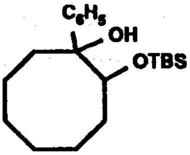
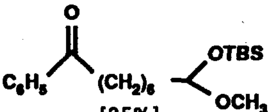
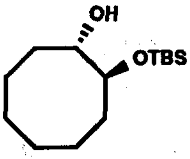
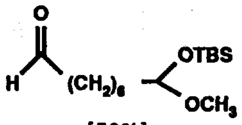
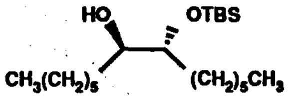
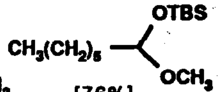
Scheme 1



P = protecting group

The results of our initial cleavage studies are shown in Table 1.[7] Several aspects of this oxidation are worthy of note. It was observed that there was a significant rate enhancement when large excesses of methanol were used. When the cleavage shown in entry 1 was performed with 16 eq of methanol the reaction went to completion in 1.25 h producing an 89% GC yield of

Table 1[a]

Entry	Monoprotected, vicinal diol	Cleavage product(s) [yield][b]	Reaction time (h)
1	 $C_6H_5-\underset{H}{\overset{OH}{C}}-\underset{H}{\overset{OTBS}{C}}-C_6H_5$	C_6H_5-CHO [89%][c]  [88%]	1.25
2	 $CH_3-\underset{CH_3}{\overset{OH}{C}}-\underset{H}{\overset{OTBS}{C}}-C_6H_5$	 [69%][d]	8.00
3	 $H-\underset{H}{\overset{OH}{C}}-\underset{H}{\overset{OTBS}{C}}-C_6H_5$	 [85%][d]	1.50
4	 $p\text{-}CH_3OC_6H_4\cdot\underset{H}{\overset{OH}{C}}-\underset{H}{\overset{OTBS}{C}}\text{-}p\text{-}C_6H_4OCH_3$	$p\text{-}CH_3OC_6H_4\text{-}CHO$ [75%]  [64%]	0.25
5		 [77%]	4.00
6		 [85%]	2.00
7		 [50%]	5.00
8		$CH_3(CH_2)_5-CHO$ [52%][c] $CH_3(CH_2)_5-CO_2CH_3$ [17][c]  [76%]	0.50

a. Reaction conditions: 3NIS, $3Li_2CO_3$, $16CH_3OH$, C_6H_6 (0.1M), hν (Sylvania 150 W infrared lamp), 35°C.

b. Isolated yield except where noted.

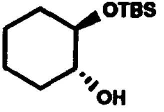
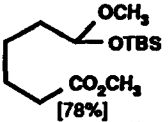
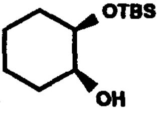
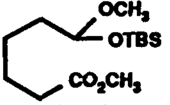
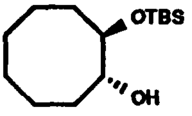
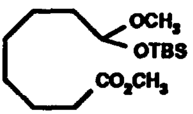
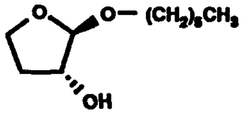
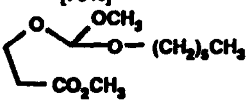
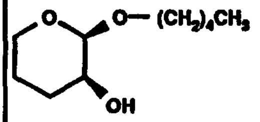
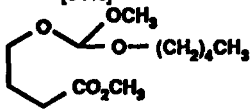
c. Yield determined by GC.

d. The acetone and formaldehyde cleavage products generated in entries 2 and 3 were not quantitated.

benzaldehyde. When 2 eq of methanol were used under otherwise identical conditions the GC yield of benzaldehyde was only 40% after 1.25 h. We postulate that the rate enhancement is due to the ability of methanol to function as an iodonium ion carrier.[8,9] Substituents that stabilize both carbon radicals and carbonyls also enhance the rate of the reaction as can be seen by comparing entries 1 and 4 as well as 6 and 7. Presumably the cleavage shown in entry 2 is slow (relative to entries 1 and 3) due to steric congestion around the hydroxyl moiety. Entries 5 - 7 demonstrate the behavior of monoprotected, vicinal cycloalkanediols. These transformations are of interest since terminally differentiated products (one carbonyl, one protected carbonyl) are produced. This reaction exhibits excellent chemoselectivity. N-Iodosuccinimide is known to oxidize alcohols directly to carbonyl compounds in the presence of carbonate.[10] The ketones and aldehydes corresponding to the starting monoprotected diols were not observed. Alkoxy radicals with alkyl chains longer than three carbons are known to undergo intramolecular cyclization.[2b, 3] Entry 8 demonstrates that carbon - carbon bond cleavage is apparently more facile than cyclization for alkoxy radicals with the general structure of 5.

Entry 8 also demonstrates that aliphatic aldehydes tend to be further oxidized to the corresponding methyl esters under these reaction conditions. Good yields of methyl esters could be obtained by increasing the amounts of methanol, carbonate, and NIS as shown in Table 2. In

Table 2[a]

Entry	Monoprotected, vicinal diol	Cleavage product [yield][b]	Reaction time (h)
1		 [78%]	10.0
2		 [60%]	12.0
3		 [73%]	22.0
4		 [64%]	10.0
5		 [70%]	11.0

a. Reaction conditions: 7NIS, 7Li_2CO_3, 32CH_3OH, C_6H_6 (0.1M), hν (Sylvania 150 W infrared lamp), 35°C.

b. All yields are isolated.

these cases gas chromatographic reaction monitoring revealed that the reaction did indeed proceed by initial cleavage to the aldehyde followed by slower oxidation to the methyl ester. The NIS mediated oxidation of aldehydes to methyl esters has been reported previously.[10,11] It should be noted that the protected portions of the diols in entries 1 and 2 of Table 2 are actually acetals so that cleavage results in the formation of mixed ortho esters. In the future we plan to investigate the effect of varying both the protecting group and the carbon radical stabilizing group(s).

Acknowledgements

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References and notes

1. Portions of this work were presented at the 199th American Chemical Society Meeting in Boston, MA, April 26, 1990.
2. a) McDonald C.; Beebe, T.; Beard, M.; McMillen, D.; Selski, D. *Tetrahedron Lett.*, **1989**, 30, 4791. b) Beebe,T.; Adkins, R.; Bogardus, C.; Champney, B.; Hii, P.; Reinking, P.; Shadday, J.; Weathorford, W.; Webb, M.; Yates, S. *J. Org. Chem.*, **1983**, 48, 3126. c) Beebe, T.; Adkins, R.; Belcher, A.; Choy, T.; Fuller, A.; Morgan, V.; Sencherey, K.; Russell, L.; Yates, S. *J. Org. Chem.*, **1982**, 47, 3006.
3. Heusler, K.; Kalvoda, J. *Angew. Chem. Int. Ed.*, **1964**, 3, 525.
4. Beebe, T.; Hii, P.; Reinking, P. *J. Org. Chem.*, **1981**, 46, 1927.
5. A related electro-oxidative cleavage of vicinal hydroxyacetals has been reported, see: Shono, T.; Matsumura, Y.; Inoue, K.; Iwasaki, F. *J. Chem. Soc. Perkin Trans. I*, **1986**, 73.
6. For a concise description of how carbon radicals can be stabilized by various substituents, see Viehe, H.; Merenyi, R.; Stella, L.; Janousek, Z. *Angew. Chem. Int. Ed.*, **1979**, 18, 917.
7. Starting materials and products were characterized by IR, ^{1}H-NMR, and GC/CIMS.
8. We have observed that NIS has very limited solubility in the reaction mixture. Presumably the hypoiodite of methanol would be much more soluble and could produce the requisite hypoiodite of the monoprotected diol by hypoiodite exchange.

$$CH_3OH + NIS \rightleftharpoons CH_3OI + NHS$$

$$CH_3OI + \mathbf{1} \rightleftharpoons CH_3OH + \mathbf{4}$$

9. A reviewer suggested an alternative possibility involving formation of $CH_3O\cdot$ via photolytic decomposition of methanol hypoiodite. Hydrogen abstraction from **1** by $CH_3O\cdot$ would then generate **5**.
10. McDonald, C.; Holcomb, H.; Kennedy, K., Kirkpatrick, E.; Leathers, T.; Vanemon, P. *J. Org. Chem.*, **1989**, 54, 1213.
11. Swartwood, P.; McDonald, C. *Proc. Second Nat. Conf. Undergraduate Res.*, **1988**, 283.

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