Tetrahedron Letters,Vol.29,No.52,pp 6913-6916,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

HYPERVALENT IODINE OXIDATION OF AMINES USING IODOSOBENZENE: SYNTHESIS OF NITRILES, KETONES AND LACTAMS

Robert M. Moriarty,* Radhe K. Vaid and Michael P. Duncan
University of Illinois at Chicago, Department of Chemistry
Chicago, IL 60680

Masahito Ochiai,* Minako Inenaga and Yoshimitsu Nagao*
Institute for Chemical Research, Kyoto University
Uji, Kyoto-Fu 611, Japan

Summary Primary aliphatic amines on oxidation with iodosobenzene in CH_2Cl_2 or H_2O yield the corresponding nitriles, while primary cycloalkylamines give the corresponding cyclic ketones. Lactams are obtained by the oxidation of cyclic amines. (S)(-) Nicotine (15) is oxidized to (±)-cotinine (16). The intermediary imine involved in these processes was trapped in the case of piperidine as the α-aminonitrile.

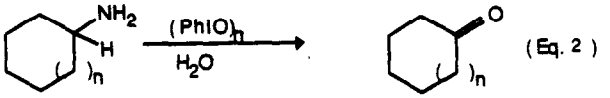
Oxidation of amines can lead to a variety of products depending on the nature of the oxidizing agent and the type of amine (primary, secondary or tertiary). Recently, Butler has compared the oxidation of various amines using lead (IV), thallium (III) and mercury (II) reagents.[1] More recently, Barton et al. have described the oxidation of secondary amines using phenylselenic acid or anhydride and the trapping of the imine with hydrogen cyanide as the α-cyanoamine.[2] Hypervalent iodine and hypervalent organoiodine have had limited use in the oxidation of amines. Varvoglis notes that aliphatic amines are oxidized by diacyloxyiodoarenes to complex mixture of products.[3] In an extension of our work on the oxidative decarboxylation of cyclic amino acids,[4] we report now the oxidation of amines with iodosobenzene in CH_2Cl_2 or in water.

Treatment of benzylamine (1) (1 equiv.) with iodosobenzene (2 equiv.) in CH_2Cl_2 yielded the dehydrogenation product benzonitrile (2).[5] Similarly oxidation of n-hexylamine (3) leads to n-hexanenitrile (4) (Eq. 1 and Table 1).

$$R-CH_2NH_2 \longrightarrow R-C\equiv N \qquad \text{(Eq. 1)}$$

1 R = C_6H_5 2 R = C_6H_5
3 R = n-C_5H_{11} 4 R = n-C_5H_{11}

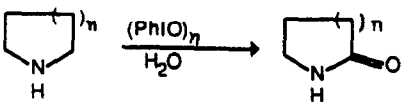
Treatment of cyclohexylamine (5) or cycloheptylamine (7) with equimolar amounts of iodosobenzene in water resulted in formation of cyclohexanone (6) and cycloheptanone (8), respectively, (Eq. 2 and Table1).



(Eq. 2)

5, n = 1 6 n= 1
7, n = 2 8 n= 2

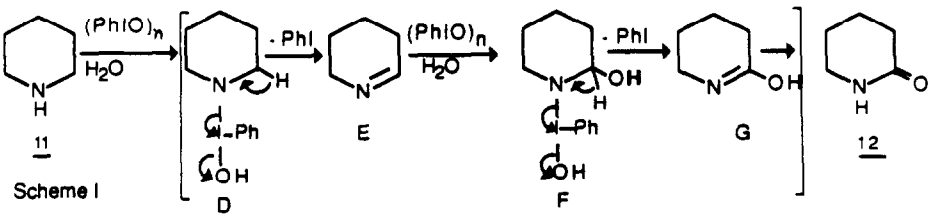
Oxidation of cyclic amines [pyrrolidine (9) and piperidine (11)][6] by iodosobenzene in water led to lactams [2-pyrrolidinone (10) and d-valerolactam (12)], respectively, Eq. 3].



(Eq. 3)

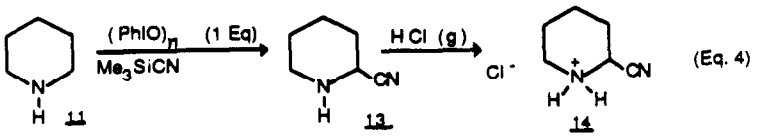
9, n = 1 10, n = 1
11, n = 2 12, n = 2

The α-oxidation of cyclic amines [piperidine (11) for example] probably proceed via (D), an initial nitrogen-iodine type intermediate (Scheme I). The nitrogen-iodine bond dissociates to give iodobenzene and imine (E). The synthesis of phenyliodine (III) bis(phthalimide)[7a] and N-phenyliodonioamide tosylates[7b] support this proposed nitrogen-hypervalent organoiodine structure. As found in the case of the oxidative decarboxylation of L-proline which proceeds *via* initial formation of 1-pyrroline,[4] it is proposed that imine (E) reacts again with a second equivalent of iodosobenzene to give intermediate (F), which then reductively eliminates iodobenzene to give (G), which tautomerizes to δ-valerolactam (12).

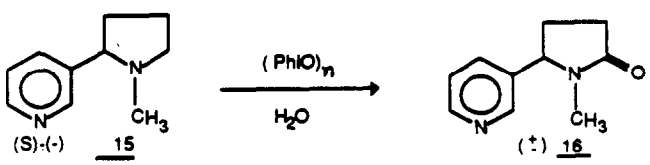


Scheme I

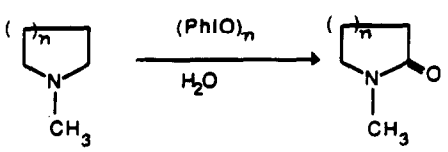
The imine intermediate (E) was trapped by adding trimethylsilyl cyanide to a cooled mixture of iodosobenzene in dichloromethane and piperidine (11). Neutralization and subsequent workup of the reaction mixture yielded α-cyanopiperidine (13), isolated as its crystalline hydrochloride (14, Eq. 4, Table 1).



Cyclic tertiary amines (1 equiv.) are likewise oxidized to the corresponding lactams on treatment with iodosobenzene (2 equiv.) in water. It is interesting that (S) (-) nicotine (15) is oxidized to (±) cotinine(16) on oxidation with iodosobenzene in water. (Table 1)



1-Methylpyrrolidine (17) and 1-methylpiperidine (19) are oxidized to 1-methyl-2-pyrrolidinone (18) and 1-methyl-2-piperidone (20), respectively, with iodosobenzene in water. Other examples are N-(1-phenylcyclohexyl)piperidine (phencyclidine, PCP) (21) ⟶ N-(1-phenylcyclohexyl)piperidone (22), N-(1-cyanocyclohexyl)piperidine (23) ⟶ N-(1-cyanocyclohexyl)piperidone (24) and 1,2,3,4-tetrahydroisoquinoline (25) ⟶ 1,2,3,4-tetrahydroisoquinolinone (26).



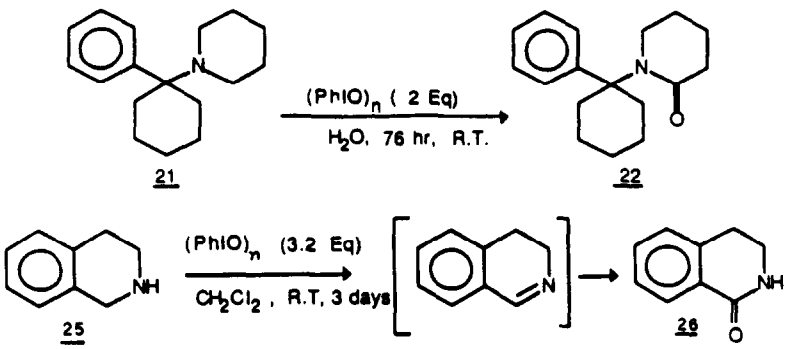


Table 1. Oxidation of Amines

Amines	Conditions	Product(%yield)[a]	mp or bp [Lit. mp or bp]
1	A	2 (48)	35-40°C/0.05mm [188°C][8]
3	A	4 (57)	30-35°C/0.8mm [161-164°C][8]
5	B	6 (49)	38-45°C/5mm [155°C][8]
7	B	8 (52)	59-63°C/5mm [179°C][8]
9	B	10 (49)	22-25°C [23-25°C][8]
11	C	12 (58)	36-40°C [38-40°C][8]
11	D	14 (79)	135-136°C [138°C][9]
15	E	16 (20)	yellow oil [210-211°C][10]
17	F	18 (55)	80-82°C/10mm [81-81°C/10mm][8]
19	F	20 (53)	104-106°C/12mm [105-106°C/12mm][8]
21	E	22 (55)	oil[b]
23	E	24 (55)	oil[c]
25	G	26 (45)	56-58°C [58°C][11]

Conditions A: $(PhIO)_n$, 2 Eq, CH_2Cl_2, 3 days; B: $(PhIO)_n$ 1 Eq, H_2O, 0°, 1 hr, then overnight at RT; C:$(PhIO)_n$, H_2O, 0°, 1 hr, then 4 hr at RT; D:$(PhIO)_n$/TMS-CN, CH_2Cl_2, -78 to 25°, 3 hr, then HCl (gas); E:$(PhIO)_n$, 2 Eq, 96 hr at RT; F:$(PhIO)_n$ 2 Eq, H_2O, 36 hr; G:$(PhIO)_n$/CH_2Cl_2, 3 days.

a. Purified by column chromatography (neutral alumina) using hexane; dichloromethane (5:1).

b. IR(neat) cm^{-1}: 1659 cm^{-1}(sharp C=O stretching); ^{1}H-NMR($CDCl_3$) δ:1.2-2.9(m,16H,8xCH_2), 3.4(m, 2H, N-CH_2-), 7.45 (m,5H, aromatic protons). Showed satisfactory C, H and N analysis.

c. IR(neat) cm^{-1}: 2212 (sharp C≡N stretching), 1660 (sharp C=O stretching); ^{1}H-NMR($CDCl_3$) δ: 1.3-2.1(m,12H,6xCH_2), 2.2(m,4H,2xCH_2), 3.3(m,2H,CH_2). Showed satisfactory C, H and N analysis.

Acknowledgement:
The American authors thank the U.S. Army for support of this work under contract DMAD 85-C-5190 and the Petroleum Research Fund PRF 17962.

References:
1. R. N. Butler, *Chem. Rev.*, **84**, 249 (1984).
2. D.H.R. Barton, A. Billion and J. Boinin, *Tetrahedron Lett.*,**26**, 1229 (1985).
3. A. Varvoglis, *Chem. Soc. Rev.*, **10**, 377 (1981).
4. M.Ochiai, M. Inenauga, Y. Nagao, R.M. Moriarty, R.K. Vaid and M.P. Duncan, *Tetrahedron Lett.*, Accepted(1988).
5. Iodosobenzene (8.22 g, 37.36 mmol) and dry dichloromethane (100 ml) were placed in a 250 ml round bottom flask equipped with a reflux condenser, a magnetic stirring bar and a drying tube (drierite). To the stirred mixture, benzylamine (1, 2.00 g, 18.67 mmol) was added. The reaction mixture was stirred for 3 days, after which time the solid iodosobenzene disappeared. The solvent was removed in vacuo, yielding crude product. The crude product was subjected to GC analysis, and analysis showed that benzonitrile was the major product (80-90%) along with 5-10% of benzaldehyde. These yields are based upon the comparison with iodobenzene, the reduced form of the oxidizing agent. The crude product was subjected to flash chromatography (neutral alumina; hexane; dichloromethane, 20:1) to remove iodobenzene. The product which resulted was distilled under vacuum to yield pure benzonitrile (2), bp 35-40°C/0.05 mm (lit[7] bp 188°C), 0.92 g (48%). IR (neat) 2228 cm^{-1}.
6. Iodosobenzene (18.00 g, 81.82 mmol) and tap water (400 ml) were placed in a 1L round bottom flask equipped with a magnetic stirring bar. The mixture was stirred for 15 min at which time a well mixed slurry resulted. The slurry was cooled in ice and pyrrolidine (9, 3.00 g, 42.18 mmol) added in one portion via pipette. The mixture was stirred at 9°C for 1 h then stirred at room temperature until a clear solution developed (4-5 hr). The solution was then transferred to a separatory funnel and extracted with dichloromethane (3 X 100 ml). The organic extracts were combined, dried ($MgSO_4$) and concentrated in vacuo to yield the crude product. Addition of petroleum ether to this and cooling in the freezer resulted in crystallization of the product. The cooled crystals were washed twice with ice cold petroleum ether to yield pure product (10), m.p. 22-25°C (lit[8] 23-25°C), which is extremely hygroscopic. (1.79g, 49%). IR (Neat) cm^{-1}; 3380 (br, N-H), 1660 (sh, C=O) ^{1}H-NMR ($CDCl_3$) d:2.25 (m, 4H,2 X CH_2); 4.41 (t,2H, CH_2N), 7.50 (m, 1H, NH).
7. (a) L. Hajiarapoglou, S. Spyroudis and A. Varvoglis, *Synthesis*, **207** (1983); (b) I.M. Lazbin and G. F. Koser, *J. Org. Chem.*, **52**, 746 (1987)
8. Aldrich Catalog, 1987.
9. H. Bohme, H. Ellenberg, O. E. Herboth and W. Lehners, *Chem. Ber.*, **92**, 1608 (1959).
10. W. G. Frankenburg and A. A. Vaitekunas, *J. Am. Chem. Soc.*, **79**, 149 (1957). The ^{1}H-NMR of our synthetic (±) was essentially identical to that of an authentic sample of (-)-cotinine (Sigma Chem. Co.).
11. R.V. Davis, B. Iddon, H. Suschitzky and M.W. Gittos, *J. Chem. Soc. Perkin Trans. 1*, 180 (1978).

(Received in USA 28 July 1988)