OXIDATION OF AMINES TO IMINES WITH HYPERVALENT IODINE

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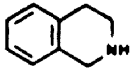
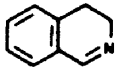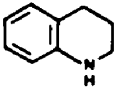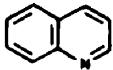Département de Chimie Organique, Université de Genève,
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Abstract - PhIO, either alone or in conjunction with $RuCl_2(PPh_3)_3$ is efficient for dehydrogenation of secondary, activated amines to imines. PhIO also effects oxidative decarboxylation of phenylalanine ethyl ester **6a** to benzyl cyanide **6d**. The mechanistic significance of this latter transformation, which does not occur with other hypervalent iodine oxidants is discussed.

The oxidation of amines to imines is not a very frequently encountered reaction, and the scope of the known procedures is rather limited.[1] Notable recent exceptions are based on oxidants such as the di-*t*-butyliminoxyl radical[2] and diphenylselenium bis (trifluoroacetate).[3] A particularly interesting procedure was reported by *Murahashi et al.*[4] which allows high yield conversion of secondary amines with *t*-butyl hydroperoxide in presence of a ruthenium catalyst. Since we had in previous work observed some parallel behaviour between Ru catalyzed alcohol and hydroquinone oxidations with *t*-butyl hydroperoxide[5] and iodosyl benzene (PhIO),[6] we extended our investigations towards a series of amines. We found that PhIO alone or, better, in presence of $RuCl_2(PPh_3)_3$ and molecular sieves effects clean conversion of secondary, activated amines to imines in 70-98% yield. The principal results are summarized in Table 1.

The structural requirement for the reaction is the presence of an activating phenyl ring or double bond in α position of the C-H bond undergoing oxidation (entries 1, 2, 4, 10). In the absence of such activation the reaction does not proceed. Typically, tetrahydroquinoline (**8a**, entry 12) affords only a 5% yield of quinoline (**8b**) in 12 h, and 3,4-dihydroisoquinoline (**7b**) does not further react with excess PhIO, although a small amount of isoquinoline always accompanies oxidation of tetrahydroisoquinoline (**7a**). Primary amines are also reactive; however in this case the intermediate imines are hydrolyzed *in situ*, and only the corresponding ketones and aldehydes are isolated in moderate to poor yields (entries 6, 7). The presence of the Ru catalyst accelerates the reactions, but oxidation proceeds also in its absence, albeit at slower rate (entries 3, 5, 11). In this respect PhIO differs from *t*-butyl hydroperoxide which converts secondary amines only in the presence of Ru.[4] On the other hand *t*-butyl hydroperoxide/Ru is a more powerful oxidant than PhIO/Ru, since it also oxidizes tetrahydroquinoline (**8a**) and 3,4-dihydroisoquinoline (**7a**) to the fully aromatized quinoline (**8b**) and isoquinoline, respectively.[4]
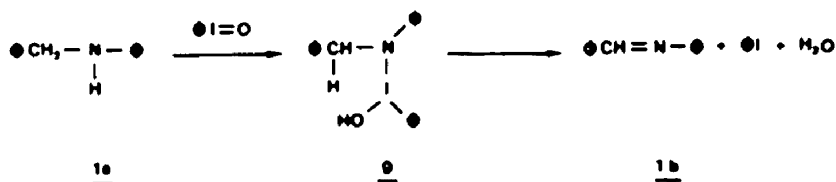
The Ru-catalyzed amine oxidation with PhIO could proceed in analogy to that with *t*-butyl hydroperoxide, i.e. *via* a ruthenium-amine complex undergoing β-hydride elimination to a imine-hydridoruthenium species which, in turn, is oxidized by PhIO.[4,7] Alternatively, a Ru-oxo complex[8] could be involved which, after dehydrogenation of the amine, is regenerated by PhIO. Our experiments provide no evidence in favor of one or the other of these mechanisms.

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Table 1. Oxidation of Amines with PhIO/RuCl₂(PPh₃)₃[a]

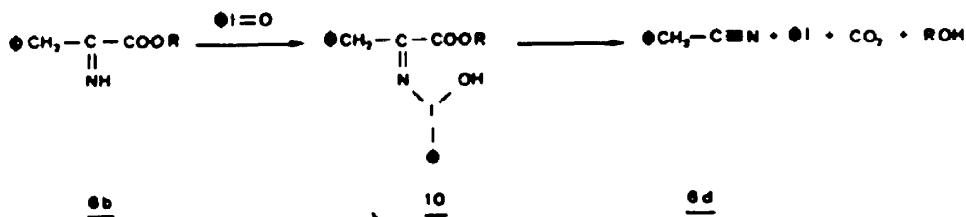| Entry	Amine	No	PhIO, eq	RuCl₂(PPh₃)₃[b]	t(h)	Product	No	Yield(%)[c]
1	●CH₂—NH—●	1a	2	1	1	●CH=N—●	1b	77[d]
2	●CH₂—NH—CH₂●	2a	1.1	1	.5	●CH=N—CH₂●	2b	83[d]
3	"	2a	1.1	0	.8	"	2b	98[d]
4	●CH=CHCH₂—NH●	3a	2	1	12	●CH≡CHCH≡N●	3b	86[d]
5	"	3a	2	0	12	"	3b	40[e]
6	●₂CH—NH₂	4a	2	1	2	●₂C=O	4c	30
7	●CH₂—NH₂	5a	2	1	.6	●CH=O	5c	14
8	●CH₂CH(NH₂)COOEt	6a	2	0	.5	●CH₂—C≡N	6d	80
9	"	6a	2	0[f]	.8	●CH₂CCOOEt (+6d) ‖ O	6c	13 (23)
10	<structure: tetrahydroisoquinoline NH>	7a	2	1	.6	<structure: dihydroisoquinoline N>	7b	72[g]
11	"	7a	2	0	.5	"	7b	78[h]
12	<structure: tetrahydroquinoline N-H>	8a	2	1	12	<structure: quinoline N>	8b	6

[a]Conditions: see text. [b]mol-% with respect to substrate. [c]Isolated yield. [d]Yield determined by G.C. Isolated yields are 20 to 30% less. [e]Ca. 60% of unreacted 3a recovered. [f]No molecular sieves. [g]Other product isoquinoline (8.5%). [h]Other product isoquinoline (15%).

The oxidation of amines to imines by PhIO in absence of catalyst may be formulated in analogy to that of hydrazides to azo compounds with PhI(OAc)₂[9] (Scheme 1). Nucleophilic addition of the amine 1a to the iodosyl function leads to 9 which breaks down via β-hydride elimination to imine 1b, iodobenzene and H₂O. This mechanism is consistent with that proposed for amine oxidation with diphenylselenium bis(trifluoromethylacetate).[8]

$$●CH_2-\underset{\underset{H}{|}}{N}-● \xrightarrow{\;●I=O\;} ●\underset{\underset{H}{|}}{CH}-\underset{\underset{HO{\diagdown}●}{|}}{N}{\diagup}^{●} \longrightarrow ●CH=N-● \;+\; ●I \;+\; H_2O$$
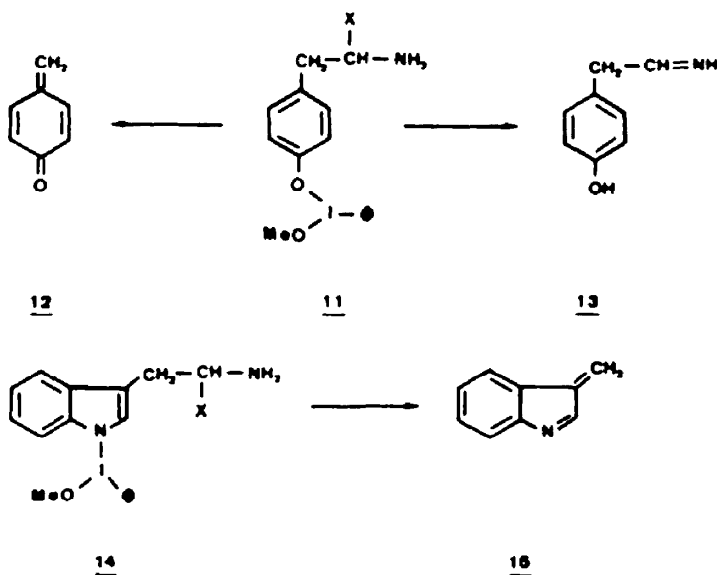
1a   9   1b

Scheme 1

In view of recently reported[10,11] oxidations of certain amino acid derivatives with PhI(OAc)₃, the reaction between PhIO and phenyl alanine ethyl ester (6a) was also investigated. In presence of molecular sieves (entry 8) benzyl cyanide (6d) was formed (80%). Without molecular sieves the yield of benzylcyanide dropped to 23%, and in addition a 12.5% yield of phenylpyruvate (6c) was isolated. The formation of 6c suggests that the reaction of 6a should proceed first according to Scheme 1 to the imine 6b, which is hydrolysed or, in presence of molecular sieves, undergoes oxidative fragmentation, presumably via the adduct 10. (Scheme 2); the latter is expected to decarboxylate to benzyl cyanide (6d), CO₂ and iodobenzene.

Scheme 2

The formation of benzyl cyanide (6d) from 6a and PhIO is unexpected. Recently Moriarty et al.[10,11] reported specific oxidative cleavage reactions of NH₂ terminal tyrosine and tryptophane derivatives with PhI(OAc)₃ in MeOH. In this system the presence of the free OH of the tyrosine or the free NH groups of the indole moieties are a prerequisite for the reaction. Derivatives of phenylalanine are unreactive. Accordingly, a mechanism was formulated via adducts 11 and 14 formed by attack of PhI(OMe)₃ on these functionalities (Scheme 3). The reaction then proceeds to

Scheme 3

the methylene derivatives 12 and 15 or, in some cases (X = COOH or CONH₂) to imine 13 which is further oxidized to a nitrile. In the case of phenylalanine ethyl ester (6a) this mechanism cannot occur, and the reaction with PhIO must involve attack on the NH₂ group. It follows, therefore, that the pathway shown in Scheme 2 is not general for all hypervalent iodine derivatives. Although it accounts nicely for the specificity of the cleavage reaction, it is not definitely established even for PhI(OAc)₃. In fact no evidence rules out a pathway leading to a methylene derivative via attack on the NH₂ groups of tyrosine and tryptophane; the presence of electron-donating substituents in adducts of type 9 could favor fragmentation to 12 or 15 rather than dehydrogenation to imines. The specificity observed with PhI(OAc)₃ can be ascribed to the more efficient electron release by the free OH or NH groups of the tyrosine and tryptophane, respectively, in comparison to that of unfunctionalized analogues, such as phenyl alanine. PhIO is a more

powerful, but less selective reagent than PhI(OAc)$_2$,[13] and does not require the presence of electron-releasing groups in the substrate.

The oxidation of p-nitroaniline to p,p'-dinitroazobenzene (40%) by PhIO has been reported some years ago.[13] We expected to extend the scope of this transformation by use of PhIO/Ru. However, the reaction is not general for aromatic primary amines. Under our conditions (PhIO) an almost intractable mixture was obtained from which azobenzene (16%) and azoxybenzene (28%) were isolated. Azobenzene itself was unreactive towards PhIO. In the presence of Ru the yields of azobenzene and azoxybenzene dropped to 8 and 7% respectively. Under the same conditions, some conversion of azobenzene to azoxybenzene occurred (30%, 38% of starting material recovered) and nitrosobenzene was partially (31%) converted to nitrobenzene, but these transformations are of no preparative interest. The oxidation of amines to azo compounds proceeds however well with PhI(OAc)$_2$.[14]

ACKNOWLEDGMENTS

EXPERIMENTAL PART'

General: ^{1}H-NMR spectra were measured at 60 MHz on a Varian 360A or T-60A spectrometer or at 220 (Varian XL-200) and 360 MHz (Bruker WH360). IR spectra were obtained with CHCl$_3$ solutions or KBr pellets on Perkin Elmer 257 or 681 instruments. Mass spectra were measured on Varian SM-1 and EM-600 as well as Flanigan 4000 at 70 eV. Columns of 2.5 m length and 3 mm diameter were used for the GC analyses, which were carried out either with a Carlo Erba 2300AC instrument connected to a Hewlett-Packard 3380A integrator, or to a Hewlett-Packard 5830 instrument. In both cases, nitrogen was used as carrier gas and flame ionization for detection.

The chemicals and solvents used are from commercial sources unless otherwise indicated. They were purified and dried when necessary according to established methods.

Iodosylbenzene. This oxidant was synthesized from iodobenzene dichloride:[15] A mixture of iodobenzene dichloride (60 g; 0.22 mol), Na$_2$CO$_3$ (50 g) and 100 g of crushed ice were mixed until obtainment of a paste. NaOH (140 ml, 5N) was added in portions of 20 ml and with mixing after each addition. Finally, the reaction mixture was diluted with water (100 ml) and allowed to stand overnight. The precipitate was filtered, washed with water and, subsequently, with CHCl$_3$. After drying in a desiccator over P$_2$O$_5$ (12 Torr) 28.0 g (59%) of iodosylbenzene was obtained as yellow powder, m.p. 210°(d).

Iodometric titration.[16] 250 mg of iodosylbenzene were added to an Erlenmeyer flask containing H$_2$SO$_4$ (10.0 ml, 6N), KI (2.0 g), CHCl$_3$ (10 ml) and water (100 ml). After stirring for 15 min the mixture was titrated with 0.1N Na$_2$S$_2$O$_3$. The end-point, indicated by decolorization of the two phases, was reached after addition of 22.7 ml, which corresponds to a purity of 98.4% of the iodosylbenzene.

Amines and imines. The following compounds, used as substrates for oxidation of for reference purposes, were prepared by literature procedures: Cinnamyl aniline (**3a**)[17] via reduction of the imine **3b** with NaBH$_4$[18] and 3,4-dihydro-iso-quinoline (**7b**) by oxidation of commercial **7a** with Fremy's salt.[19] The imines were independently synthesized via condensation: **1b** from aniline and benzaldehyde,[20] **2b** from benzylamine and benzaldehyde[21] and **3b** from aniline and cinnamic aldehyde.[22]

Oxidation of amines to imines, general procedure: To the amine (1.0 mmol) dissolved in 25 ml of CH$_2$Cl$_2$ was added at RT and under nitrogen, 0.5 g of molecular sieves (4 Å) and ~0.25 mmol of internal standard. RuCl$_2$(PPh$_3$)$_3$ (9.6 mg, 0.01 mol) was added when desired, followed by 1-4 eq. of PhIO and 25 ml of CH$_2$Cl$_2$. Oxidation started upon vigorous magnetic stirring and was monitored by TLC and GC. At the end-point all of the suspended PhIO was dissolved and the reaction mixture transparent. The solution was filtered and yields were analyzed by GC using mixtures of known compositions of independently prepared reference compounds for determination of the response factors.[23]

The imines were isolated by column chromatography and identified by comparison of their physical and spectroscopic data with those of independently prepared samples. The conditions used for analysis and isolation are summarized in Table 2.

Table 2. Analysis and Isolation of Imines

Imine	Column	Temp.	Standard	Isolation
1b	Carbowax 20 M, 20% KOH 2%, Chromosorb G	208°	Tetracosane	-
2b	id.	190°	Tricosane	Alox neutral/CH_2Cl_2
3b	DEGS 5%, Chromosorb G	198°	Octacosane	Alox neutral/hexane
7b	- -	-		Silica gel/ethyl acetate (flash chromatography)

Oxidation of 6a (absence of molecular sieves). Phenyl alanine ethyl ester (6a) (400 mg, 2 mmol) was oxidized in 40 ml of CH_2Cl_2 with 1 eq. of PhIO. Reaction was complete after 30 min at RT. Iodobenzene was separated from the oxidation products by column chromatography (SiO_2, CH_2Cl_2). After evaporation of the solvent, 100 mg of a mixture of benzyl cyanide (6d) and ethyl phenyl pyruvate (6c) in a ratio of 6d/6c = 0.54 was obtained. 6c was isolated via its 2,4-dinitrophenylhydrazone derivative,[24] m.p. 133° (Lit. 132.5-133°).[25] ¹H-NMR ($CHCl_3$) of 6c (keto form): 7.25 (5H, s); 4.30 (2H, q), 1.4 (3H, t). MS of 2,4-dinitrophenylhydrazone derivative ($C_{18}H_{16}N_4O_6$): 372 (M⁺, 2), 337 (3), 117 (20), 91 (100), 77 (17).

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