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Catalytic Oxidation of Secondary Amines with Tetra-*n*-propylammonium Perruthenate

Andrea Goti* and Michela Romani

Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, C.N.R.,
Dip. di Chimica Organica "Ugo Schiff", Università degli Studi di Firenze, via G. Capponi 9, I-50121 Firenze, Italy

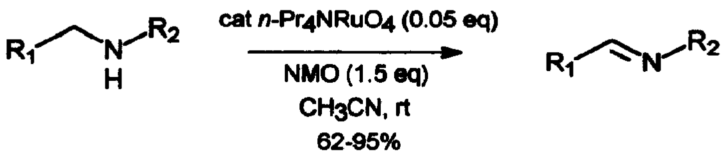
Abstract: *Oxidation of secondary amines by N-methylmorpholine N-oxide and catalytic amounts of tetra-n-propylammonium perruthenate (TPAP) affords straightforwardly the corresponding imines in good yields.*

The direct oxidation of secondary amines to imines is a rarely employed reaction, the known procedures for its application being, with a few exceptions, rather limited in scope.[1] Moreover, almost no procedure employs the simple and selective reagents widely used in the related oxidation of alcohols to carbonyl compounds, the only exception being the Swern oxidation, which is affected by the formation of undesired by-products.[2] Only recently, a few procedures which allow the biologically and synthetically relevant transition-metal catalyzed transformation of amines into imines have been developed.[3]

Being active in the field of nitrogen heterocycles,[4] we investigated the use of tetra-*n*-propylammonium perruthenate (TPAP) as a possible catalyst for the oxidation of nitrogen containing products. This reagent, first synthesized and utilized by Ley and Griffith,[5] has become a commonly used mild catalytic oxidant for the interconversion of alcohols to the corresponding aldehydes or ketones, *N*-methylmorpholine *N*-oxide being the stoichiometric co-oxidant.[5,6] Its mildness and chemoselectivity[6] and commercial availability has made it the reagent of choice in the oxidation of hydroxy groups in very critical and delicate environments,[6,7] where other methods often fail. Very recently, TPAP has been found to be also a good reagent for the oxidation of sulfides to sulfones.[8] In spite of its increasing use in synthesis, no example of use of TPAP in the oxidation of nitrogen containing compounds (except the oxidation of a hydroxyl group in an indole derivative)[5] has been reported so far, at the best of our knowledge.

In this communication we report the use of TPAP for the smooth conversion of secondary amines to the corresponding imines by using 1.5 equivalents of *N*-methylmorpholine *N*-oxide (NMO) and 5% TPAP in acetonitrile in the presence of 4 Å molecular sieves at room temperature for the appropriate time (Scheme).[9]

SCHEME



Amines **1-6** are cleanly oxidized in high conversions and good yields in the conditions reported in the Table. The best reaction conditions have been tuned with amine **1** (see Table) and several other variations not reported in the Table have been also performed. The following generalizations can be stated: *i)* in the absence of TPAP no reaction occurs; *ii)* by increasing the equivalents of oxidant or the reaction temperature, the reaction does not proceed further to more oxidized products; *iii)* acetonitrile is the solvent of choice, the reaction being slowed down by the use of methylene chloride or suppressed by ethereal solvents (in which TPAP does not dissolve); *iv)* the use of molecular sieves is not crucial, but increases the reaction rate and the yields, by limiting the formation of hydrolysis side-products; *v)* NMO is a better co-oxidant than *tert*-butylhydroperoxide; *vi)* an increase in the reaction time or temperature gives less pure products; *vii)* the work-up is extremely simple and rapid, requiring only the removal of acetonitrile and the filtration of the crude mixture on a pad of silica gel with the appropriate solvent (usually ethyl acetate).[9]

Amines **1-4** give almost exclusively the corresponding imines **7-10** (entries 1-4), while indoline (**6**) gives, as expected, the double bond shift to aromatize to indole (**13**) and tetrahydroquinoline (**5**) gives a mixture of the corresponding imine **11** and aromatization product **12**, independently of the reaction conditions and the amount of oxidant used (entries 5), while the isomeric tetrahydroisoquinoline (**4**) aromatize only in minimal part (2-5%) in any experimental condition. Steric encumbering at nitrogen causes the reaction rate to slow down and the yields to decrease for the formation of hydrolysis by-products (entries 3).

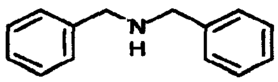
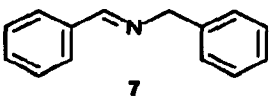
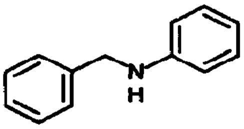
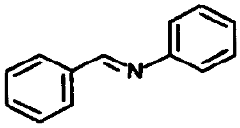
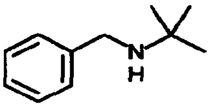
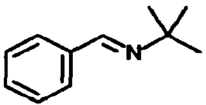
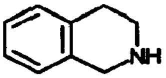
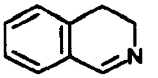
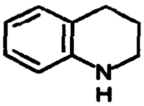
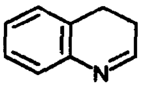
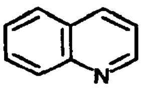
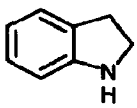
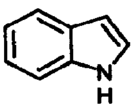
Albeit most of the oxidations have been performed on a 0.5 mmol scale, the reaction can be scaled-up (entry 2b) and the amount of TPAP also reduced, without loss of percent yield.

In summary, this novel oxidation method employs only commercially available and non toxic materials, very mild reaction conditions and no particular technique and compares well in terms of product yields with the other reported transition-metal catalyzed procedures.[3] It is also able, in contrast to other procedures,[3b] to oxidize unactivated positions (see for example compounds **5** and **6**). Indeed, also aliphatic secondary amines can be oxidized, albeit in this case the instability of the resulting imines, which are prone to hydrolysis and oligomerization, complicates the reaction mixtures. In fact, *N*-ethylbenzylamine seems to give oxidation of both the carbon atoms adjacent to nitrogen and dicyclohexylamine also reacts in the experimental conditions.

Due to the broad spectrum of functionalities which tolerate the use of TPAP (silyl ethers, double and triple bonds, cyclopropanes, esters, acetals, epoxides, lactones, halides)[6] the present method should prove its chemoselectivity and usefulness.

Other TPAP catalyzed oxidations of nitrogen containing compounds are currently under investigation in our laboratory.[10]

TABLE. Oxidation of Amines 1-6 Catalyzed by Tetra-*n*-propylammonium Perruthenate

Reagent	Product(s)	Entry	Reaction conditions[a]	Conv.[b]	Yield[b]
 1	 7	1a	3, 24[c]	100	85
		1b	3, 2[c]	83	68
		1c	3, 24	100	88
		1d	3, 2	100	78[d]
		1e	1.5, 2	67	87
		1f	1.5, 6	100	80
 2	 8	2a	1.5, 6	97	95
		2b	2, 20[e]	100	93
 3	 9	3a	1.5, 6	67	46
		3b	1.5, 20	90	62
 4	 10	4a	1.5, 4	69	34
		4b	2, 4	95	53
		4c	3, 72	100	73
		4d	1.5, 24	98	68
 5	 11  12	5a	1.5, 6	85	35, 52[f]
		5b	3, 4	95	52, 18[f]
		5c	3, 24	95	52, 32[f]
 6	 13	6a	1.5, 4	73	66
		6b	1.5, 20	80	51
		6c	3, 6	94	73[g]

[a] Reactions carried out on a 0.5 mmol scale with 5% TPAP in CH_3CN (unless otherwise stated) at room temperature. Equivalents of NMO and time (h) are reported. [b] By ^1H NMR. [c] In CH_2Cl_2. [d] 78% yield after distillation. [e] Reaction carried out on a 5 mmol scale with 2.5% TPAP. [f] Yields refer to 11 and 12, respectively. [g] 53% yield after distillation.

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9. Typical procedure: a 10 mL reaction flask is charged sequentially with dry CH_3CN (2.5 mL), the amine (0.5 mmol), 4 Å powdered molecular sieves (250 mg), NMO (0.75 mmol), and TPAP (0.025 mmol). The reaction mixture is stirred under N_2 at room temperature for the appropriate time (checked by TLC). Acetonitrile is then removed by rotary evaporation and the crude mixture filtered through a pad of Celite and silica gel with ethyl acetate or CH_2Cl_2-CH_3OH in order to remove NMO and ruthenium containing products.
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