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Highly Efficient and Mild Synthesis of Nitrones by Catalytic Oxidation of Hydroxylamines with Tetra-*n*-propylammonium Perruthenate

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Abstract: *Oxidation of N,N-disubstituted hydroxylamines by N-methylmorpholine N-oxide (NMO) and catalytic amounts of tetra-n-propylammonium perruthenate (TPAP) at room temperature occurs very rapidly to give the corresponding nitrones, which can be trapped by dipolarophiles present in the reaction mixture, in excellent yields. A competitive experiment in the presence of a primary alcohol gave a >50:1 nitrone to aldehyde ratio.*

Among the synthetic methods for the obtainment of nitrones,[1] two procedures are by far the most useful and utilized: *i)* the condensation of a *N*-substituted hydroxylamine with a carbonyl compound and *ii)* the oxidation of secondary amines. The latter can be performed directly from the amine[2] or by a two-step procedure *via* the intermediate *N,N*-disubstituted hydroxylamine.[1] The methods for the direct oxidation of secondary amines suffer of the use of aqueous hydrogen peroxide in water or biphasic systems,[2a-d] of toxic materials,[2d] or of expensive and not commercially available oxidants in stoichiometric (2 equivalents) amounts.[2e-f] On the other hand, highly toxic mercury salts in exceeding amounts are involved in the most successful method for the oxidation of hydroxylamines to nitrones, the use of different oxidants being less universal and satisfactory.[1]

Due to our synthetic interest in the field of *N*-oxides,[3] we were attracted by the development of an alternative oxidation methodology to nitrones and started a research on the use of tetra-*n*-propylammonium perruthenate (TPAP)[4] as a possible catalyst for the oxidation of nitrogen containing products.[5]

In this communication we report on the use of TPAP for the smooth and convenient conversion of hydroxylamines to the corresponding nitrones 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 (Scheme 1).[6]

SCHEME 1

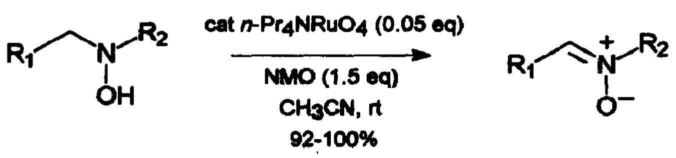
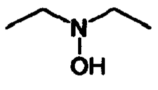
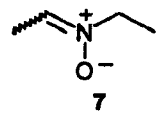
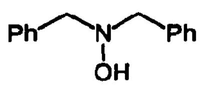
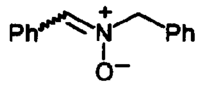
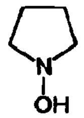
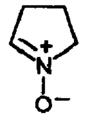
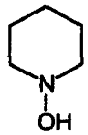
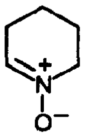
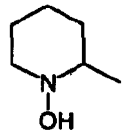
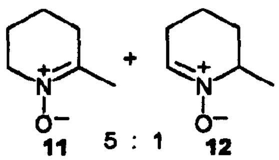
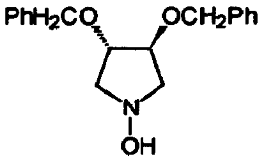
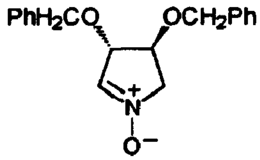


TABLE. Oxidation of Hydroxylamines 1-6 Catalyzed by Tetra-*n*-propylammonium Perruthenate[a]

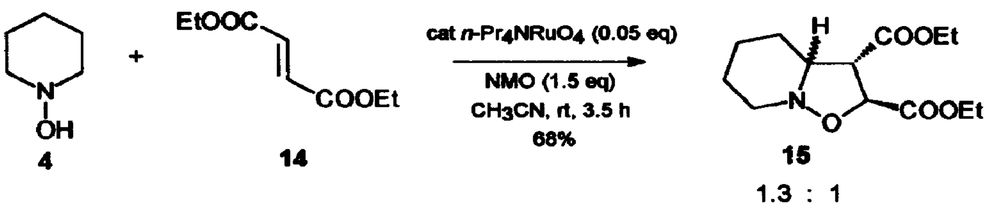
Reagent	Product(s)	Entry	Time (h)	Yield[b]	*Z*:*E* ratio[b]
 1	 7	1a	0.5	100	<1:50
		1b	18	100	1:8
		1c	72	100	1:5
 2	 8	2a	1	92	>50:1
		2b	48	75[c]	>50:1
		2c[d]	3	100[e]	>50:1
 3	 9	3a	0.5	100	
		3b	22	94	
		3c[f]	0.5	98	
 4	 10	4a	3.5	79[g]	
 5	 11 5 : 1 12	5a	0.5	100	
 6	 13	6a[h,i]	72	92	

[a] Reaction conditions (unless otherwise stated): hydroxylamine (0.5 mmol), NMO (0.75 mmol), TPAP (0.025 mmol), dry CH_3CN (2.5 mL), rt. [b] By ^1H NMR. [c] 65% isolated yield by chromatographic separation. [d] On a 5 mmol scale with 1.2 eq of NMO and 1% TPAP; 82% conversion. [e] 100% isolated yield (on the converted hydroxylamine) as a white solid by chromatographic separation. [f] With 1 eq of NMO and 2% TPAP. [g] Nitrone was not isolated; the yield refers to a two-step one-pot reaction by trapping of **10** as adducts with ethyl fumarate (see text). [h] See ref. 3b and 7. [i] On a 0.11 mmol scale.

Hydroxylamines 1-6 are very rapidly and efficiently oxidized in less than one hour and high yields (>90% for the single oxidation step) to give the corresponding nitrones (Table). The reaction occurs also in absence of catalysis by TPAP, but very slowly, the conversion of hydroxylamine 1 to nitrone 7 being less than 10% after 3 d. The regio- and stereochemical features of the process are quite similar to those observed in other oxidation procedures. Hydroxylamine 1 affords nitrone 7 as a *Z*:*E* mixture, the less stable *E* isomer being the predominant (>50:1 after 30 min, entry 1a)[8] and isomerizing to the more stable *Z* isomer at longer reaction times (entries 1b-c), as already observed for a different nitrone.[9] Nitrone 8 is formed only as the more stable *Z* isomer (entries 2), as normally observed for *C*-phenyl substituted nitrones. About the regiochemical outcome, hydroxylamine 5 furnished a 5:1 mixture of the ketonitrone 11 to the aldonitrone 12 (entry 5) vs. a 3:1 ratio obtained in the oxidation with yellow mercuric oxide.[10] Most of the oxidations have been performed on a 0.5 mmol scale by using 1.5 eq of NMO and 5% TPAP, but the reaction can be carried out with just 1 eq of NMO and 1-2% TPAP (entry 3c) and scaled-up (entry 2c) maintaining the same efficiency.

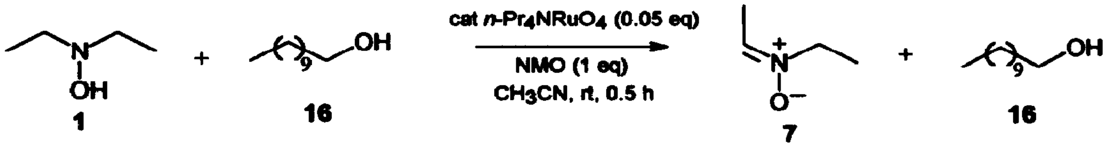
Since the oxidation conditions are extremely mild and tolerate the presence of even very delicate functional groups,[4b] the reaction can be carried out in the presence of dipolarophiles, in order to directly obtain valuable isoxazolidine adducts, suitable substrates for other useful transformations.[1a,11] This concept is exemplified by the direct obtainment of isoxazolidines 15 (68% isolated yield by column chromatography, 1.3:1 diastereomeric ratio) from hydroxylamine 4 and ethyl fumarate (14, 1.5 eq) in the oxidation conditions (Scheme 2).[12]

SCHEME 2



The very high rate of the oxidation to nitrones prompted us to verify the chemoselectivity affordable in a competitive experiment with a primary alcohol, which are also known to be oxidized very quickly.[4b] We then subjected a 1:1 mixture of hydroxylamine 1 and 1-undecanol (16) to the standard oxidative conditions employing 1 eq of NMO. After 30 min we recovered a 1:1 mixture of the nitrone 7 and the starting alcohol 16, thus assessing a >50:1 rate reaction of hydroxylamine to alcohol, since undecanal could not be detected even in trace in the reaction mixture by ^{1}H NMR (Scheme 3).

SCHEME 3



In summary, this novel oxidation method employs only commercially available and non toxic materials, very mild reaction conditions and quick and simple work-up procedures and gives excellent yields of nitrones, so that it can be expected to meet high popularity among researchers involved in this field. Since TPAP tolerates a large number of functionalities (silyl ethers, double and triple bonds, cyclopropanes, esters, acetals, epoxides, lactones, halides),[4b] including hydroxyl groups in this peculiar case, it is expected to be extremely useful for in situ generation of nitrones in the presence of dipolarophiles able to capture them to give useful isoxazolidine intermediates and particularly in intramolecular cycloadditions of complex molecules.

The scope and usefulness of this reaction is furtherly under investigation in our research group.

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6. Typical procedure: a 10 mL reaction flask is charged sequentially with dry CH_3CN (2.5 mL), the hydroxylamine (0.5 mmol), 4 Å powdered molecular sieves (250 mg), NMO (0.5-0.75 mmol), and TPAP (0.01-0.025 mmol). The reaction mixture is stirred under N_2 at room temperature for 0.5-1 h. The crude reaction mixture is then filtered through a pad of Celite and silica gel with CH_2Cl_2-CH_3OH or CH_3OH in order to remove the excess of NMO and ruthenium containing products.
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