TPAP/NMO System as a Novel Method for the Synthesis of Nitronyl Nitroxide Radicals

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Abstract: An easy oxidation of dihydroxyimidazolidine derivatives to nitronyl nitroxide radicals (NNRs) can be achieved using the tetra-*N*-propylamonium perruthenate/*N*-methylmorpholine *N*-oxide (TPAP/NMO) system. The procedure offers several advantages in terms of simplicity, yield, cost and 'green' chemistry.

Key words: radicals, oxidations, nitronyl nitroxide, green chemistry, TPAP/NMO

Since the end of the 20th century, purely organic compounds have been investigated as electrical conductors and superconductors.[1] In this field several efforts were dedicated to the preparation of organic magnets. From their first preparation in 1968,[2] nitronyl nitroxide radicals (NNRs, Figure 1) had a vigorous expansion starting from the nineties[3] in the field of physics, chemistry and nanotechnology and found application for the study of surfaces properties,[4] the development of organic magnets[5] and the achievement of single-chain magnets.[6]

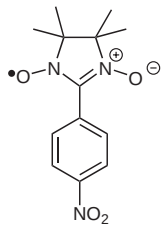


Figure 1 First example of nitronyl nitroxide radical used as molecular magnet

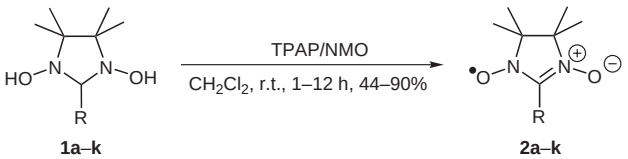
Classical methods available for the preparation of NNRs foresee the controlled oxidation of a suitable dihydroxyimidazolidine precursor. However, several of these procedures suffer of a number of drawbacks; for example the general use of $NaIO_4$ often requires the use of an excess of oxidizing agent and to carry out the reaction in a two-phase system, a condition obviously unsuitable for water-sensitive organic compounds.[2] In addition, NNRs can be prepared using toxic species like SeO_2,[7] or harmful and pollutant compounds like PbO_2,[8,2a,c] MnO_2,[9,2c] AgO_2,[10] as oxidants in stoichiometric or, sometimes, in overstoichiometric amounts. Costs of the oxidizing species and formation of overoxidized by-products are among the other problems to face for NNR synthesis.

TPAP/NMO is a well-known oxidizing system working with catalytic amount of the actual oxidant Ru(VII) species, continuously regenerated by a stoichiometric amount of NMO. The reaction can be easily accomplished in organic solvents like CH_2Cl_2 or AcCN and it has been successfully utilized for the oxidation of alcohol to carbonyl compounds[11] as well as for the synthesis of imines and nitrones from secondary amines[12] and hydroxylamines,[13] respectively.

In this light, we decided to verify whether TPAP/NMO could be exploited for the preparation of NNR starting from dihydroxyimidazolidines.

To our satisfaction, the reaction of compound **1a** [prepared from the corresponding aromatic aldehyde and 2,3-di(hydroxyamino)-2,3-dimethylbutane][2] with 5% TPAP and one equivalent of NMO, in CH_2Cl_2 at room temperature for three hours, allowed the isolation of NNR **2a** as a blue solid in 81% yield (Scheme 1, Table 1).[14]

To verify the generality and applicability of this new procedure, we prepared dihydroxyimidazolidines **1a**–**k**, which were reacted with TPAP/NMO under the above reported conditions to obtain NNRs as summarized in Table 1. The reaction allowed the preparation of electron-poor (entries 1–3) and electron-rich aromatic (entries 4–6), heteroaromatic (entry 11) as well as aliphatic (entry 10) NNRs that were isolated as deep colored powders (blue for **2a**,**c**–**i**, green for **2b**, red-purple for **2j** and purple in the case of **2k**). Yields are usually good and in any case comparable to those previously reported.[2,7–10] Moreover, due to the short reaction time required to complete the transformation and the mild reaction conditions required, no formation of overoxidized by-products was ever detected.



Scheme 1 General scheme of synthesis of nitronyl nitroxide radicals with TPAP/NMO system

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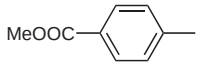
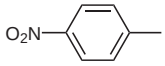
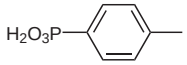
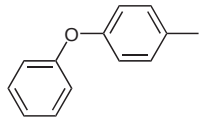
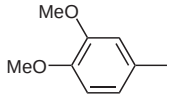
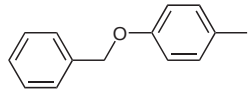
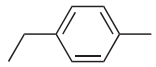
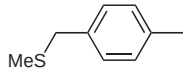
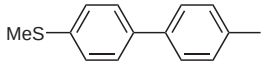
Table 1 Synthesis of Aromatic and Aliphatic NNRs **2** with TPAP/NMO System

Entry	R	Time (h)	Product[a]	Yield (%)[b]
1		3	**2a**[15]	81
2		1	**2b**[3]	79
3		12	**2c**[c]	49
4		2.5	**2d**	87
5		1.5	**2e**	90
6		2	**2f**[16]	80
7		1.5	**2g**	64
8		1.5	**2h**	60
9		1.5	**2i**	72
10	CH_3–$(CH_2)_{13}$–	3.5	**2j**	44
11		1	**2k**	72

[a] All compounds gave satisfactory elemental analysis (C, H, N ± 0.4%). EPR signals: $g_{iso} = 2.006$, $a_{iso} = 7.59 \pm 0.1$ G.
[b] Yields of a single run without optimization.
[c] Reaction carried out in methanol.

Operatively, after mixing of the reagents in CH_2Cl_2 at room temperature the reactions were monitored by TLC until complete consumption of dihydroxyimidazolidine (1–12 h), the organic phase washed with water and evaporated to give the crude NNRs which were purified by silica gel column chromatography.[14] Reagents and solvents were used without any previous purification and any other work up manipulations are required before chromatography. Dichloromethane revealed to be the solvent of choice for this procedure, however, derivative **1c**, due to its poor solubility in such solvent, was successfully oxidized to NNR **2c** in MeOH. In addition, to confirm the versatility of this novel method, TPAP/NMO oxidation was effectively used also in the case of derivatives **1h** and **1i** without affecting the oxidation sensitive sulfide sulfur functionality (i.e. no evidence of the corresponding sulfoxides or sulfones was pointed out in the crude reaction mixture).

In conclusion, a reliable preparation of aromatic, heteroaromatic and aliphatic NNRs bringing also redox-sensitive groups has been developed by means of the TPAP/NMO system. This new procedure is competitive in term of generality, simplicity cost and eco-compatibility with the oxidation procedures known so far.

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