SELECTIVE OXIDATION OF ALCOHOLS
WITH STABLE ORGANIC POLYRADICALS

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Stable di-, tri- and tetra-radicals of TEMPO or PROXYL type were used as oxygen activators in the selective oxidation of some alcohols, using air as final oxidant. The oxidation process requires also the presence of nitrogen oxides, which convert the nitroxide moiety of the free radicals into the corresponding oxoammonium salt, a strong oxidant able to oxidize selectively the alcohols to aldehydes or ketones. Under these conditions, benzyl alcohol can be oxidized in almost quantitative yields, while 1-octanol cannot be converted into more than 20% 1-octanal.
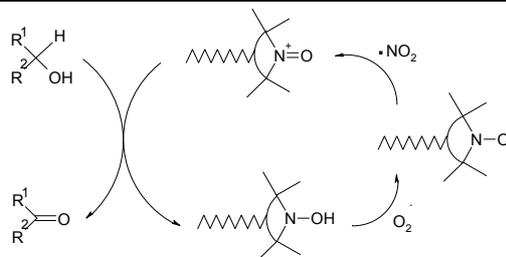
INTRODUCTION

Oxidation reactions are one of the most important in preparative organic chemistry. Many compounds of interest like medicines or other fine chemicals contain an aldehyde or ketone moiety; also, aldehydes and ketones are often key intermediates in chemical industrial processes.[1,2]

Usually, the synthesis of aldehydes or ketones is performed through the oxidation of the corresponding alcohols. These reactions can require transition metal ions as oxidant and frequently cannot be stopped at the carbonyl derivative, the final product being the carboxylic acid; therefore selective oxidation methods are highly attractive.[3-5]

Organic stable free radicals of nitroxide type, like 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) or 2,2,5,5-tetramethyl-1-pyrrolidinyloxy (PROXYL) were proved to work as a redox reagent, meaning that they can be employed in selective or greener oxidation reactions under a broad range of conditions.[6-9] Many derivatives of TEMPO or PROXYL free radicals are known,[10] and nowadays they are even commercially available as free radicals immobilized on organic (polymer) or inorganic materials (silica).

These materials can be easily used as recoverable heterogeneous catalysts in such selective oxidation processes.[10-14] Stable organic polyradicals are also acknowledged as materials of special interest, with high potential as probes, sensors or markers in many physical, biological or chemical processes.[15-17] The molecules bearing two or more paramagnetic moieties (polyradicals) can bring a number of advantages in comparison with monoradicals; their Electron Spin Resonance (ESR) spectra usually have particular features due to the appearance of new lines attributed to intramolecular spin exchange. Polyradicals are also known in literature as high spin compounds, showing interesting magnetic properties; an attractive assets of such compounds is the developing of some co-operative property (i.e. metallic state).[18-20]

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Herein we report the results regarding the investigation of selective oxidation of five alcohols, namely benzylic alcohol, 1-phenyl-ethanol, diphenylmethanol, 1-octanol and furfuryl alcohol, using several stable di-, tri-, and tetra-radicals (Figure 1) in oxidation processes.

RESULTS AND DISCUSSION

The polyradicals synthesized in this work and very similar ones are known [21-26] and they were obtained by related experimental procedures, as shown in literature (see Experimental part).

Summarizing, the synthesis consists either in a simple coupling reaction (such is an amide bond formation), which was achieved by linking together an acid and an amine derivative (commercially available) in the presence of the coupling agent *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), or using a similar single-step reaction, coupling the amine with an isocyanate derivative, as showed in Figure 1. Althought such reactions proceed usually with high yields, in our cases these were around 20-30% (except for DI-T, ~100%); a possible explanation consists in the difficulty to obtain the fully functionalized polyradicals (*i.e.* tri- and tetra-radicals).
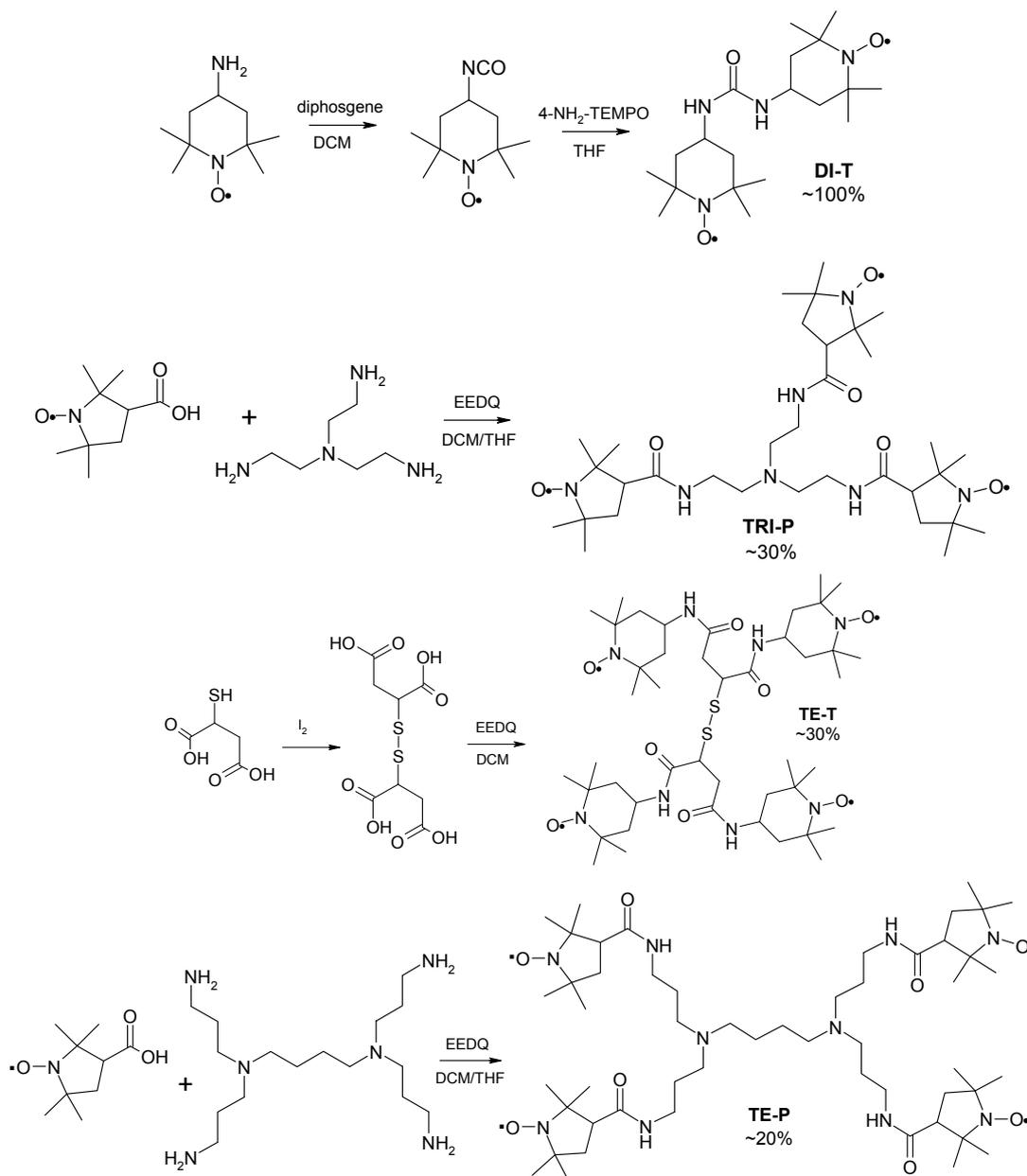

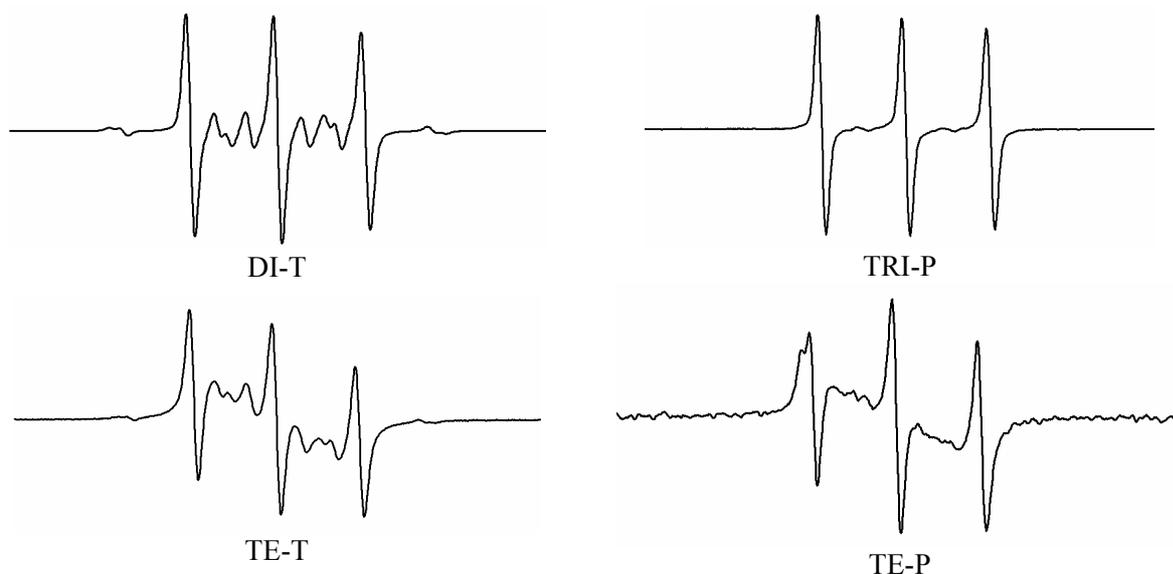Fig. 1 – Synthesis of the polyradicals employed in this work.

Fig. 2 – ESR spectra of the polyradicals (solvent DCM).

The ESR spectra of the polyradicals thus synthesized showed the expected triplet with additional features due to the spin-spin coupling. The presence of two or more nitroxide moieties in a molecular structure usually is accompanied by the appearance in the ESR spectra of additional lines attributed to spin-spin coupling. The intensity and number of lines depend on the ratio between coupling constant (J) and the hyperfine constant (a_N), and probability of collision with solvent molecules (the solvent nature).[26]

As a consequence, the polyradicals used in this study show the expected triplet attributed to interaction of the unpaired electron with the N nucleus and additional lines attributed to spin-spin interactions. The values of line-width of the central line increase in the case of polyradicals compared with those observed for TEMPO and PROXYL monoradicals as an effect of spin-spin interactions, as well. HR-MS spectra confirmed also the structure of the compounds.

The investigation on catalytic activity of these polyradicals in oxidation processes has been performed aiming to evidence the influence of structural features of the paramagnetic moiety and if there is any synergic effect of the presence of two or more paramagnetic groups in the molecular structure.
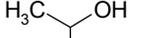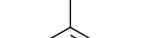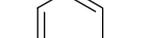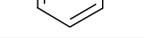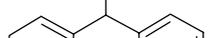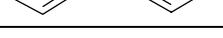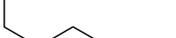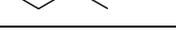
For testing as substrates in the oxidation procedure, we took into consideration five alcohols, with different reactivity, namely benzyl alcohol, 1-phenyl-ethanol, diphenyl-methanol, 1-octanol and furfurol alcohol (Table 1). The oxidation reactions were performed under air, using DCM as solvent; as nitrogen oxides source has been used a mixture of sodium nitrite and acetic acid, as literature data showed.[27,28] The results are compiled into Table 1.

As a general rule, it is noticed that activated alcohols gave higher yields of oxidation, reaching 96-100% for benzyl alcohol and furfurol (Entries 1, 3 and 17, Table 1), while 1-octanol cannot overpass 20% (Entry 13). PROXL derived poly-radicals (TRI-P and TE-P) generally gave lower results than TEMPO derived poly-radicals (DI-T and TE-T); however, in the case of diphenylmethanol the tendency is reversed (Entry 10 and 12 compared with Entry 9 and 11). Comparison of the yields obtained for alcohol oxidation in the presence of TEMPO monoradicals with those obtained in the present study leads to conclusion that using of polyradicals does not improve the oxidative process, comparatively with the use of monoradicals;[28,29] moreover, we were unable to recover it in order to recycle them (however, the un-reacted alcohols can be recovered, as no other decomposition or oxidation products of them were noticed). Another explanation of the different reactivities regarding the benzyl alcohol derivatives may consists in the steric hindrance; also, the stability of the disulphide group towards NOx should not be disregarded.

Table 1

Yields of oxidation (measured by NMR) of the employed alcohols to the corresponding aldehydes
or ketone using the synthesized polyradicals

Entry	Alcohol	Polyradical	Yield %
1		DI-T	96
2		TRI-P	55
3		TE-T	100
4		TE-P	38
5		DI-T	56
6		TRI-P	25
7		TE-T	45
8		TE-P	21
9		DI-T	29
10		TRI-P	44
11		TE-T	34
12		TE-P	60
13		DI-T	20
14		TRI-P	18
15		TE-T	1
16		TE-P	8
17		DI-T	100
18		TRI-P	66
19		TE-T	2
20		TE-P	10

$$NaNO_2 + CH_3COOH \longrightarrow CH_3COONa + HNO_2$$

$$2\ HNO_2 \longrightarrow H_2O + NO + NO_2$$

$$2\ NO + O_2 \longrightarrow 2\ NO_2$$
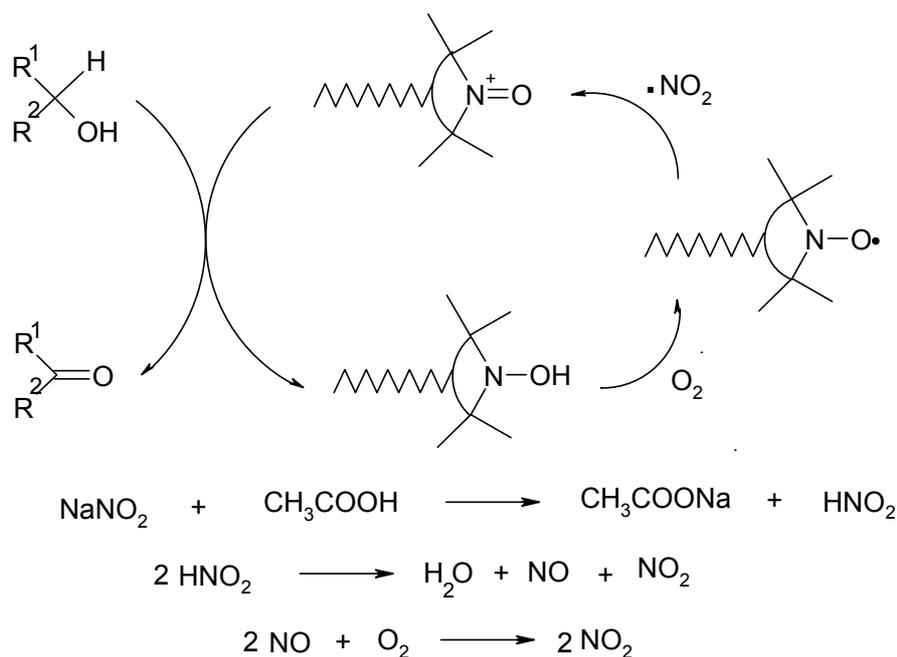
Fig. 3 – Proposed mechanism for selective oxidation of alcohols.

Regarding the mechanism of reaction, Figure 3 shows an overview of the reactions that took place; this is well known in literature.[31-35] Nitrogen oxides are generated from the reaction of sodium nitrite with acetic acid, which are mostly converted into nitrogen dioxide due to the presence of air (oxygen). Nitrogen dioxide oxidizes the nitroxide moieties from TEMPO or PROXYL into the corresponding oxoammonium salts, which oxidize further the alcohol. The stable free radical is regenerated by the oxidation of the hydroxylamine, thus closing the catalytic cycle.

Out attempts to collect the polyradical (for afterward reuse) by different means (precipitation or even chromatographic separation) failed. A closer look by TLC analysis indicated that a part of the polyradical is destroyed in the oxidative process, one of the possible explanation being probably due to the labile disulphide groups. No further experiments for improving the recyclability were made. In these conditions, the grafting of polyradical to a solid support remains as a solution to assuring their re-use in a catalytic cycle.

EXPERIMENTAL

All chemicals, materials and solvents were purchased from Sigma-Aldrich, Merck or Chimopar. NMR spectra were recorded on a Bruker Fourier apparatus at 300 MHz using $CDCl_3$ as solvent (isotopic purity 99.9%) and TMS as internal standard. ESR spectra were recorded on a Jeol JES FA100 apparatus using the following typical settings: frequency 8.99 GHz, field 3330 G, sweep width 100-200 G, sweep time 60-120 s, time constant 30 ms, gain 50-500, modulation frequency 100 kHz, modulation width 1 G. HR-MS were recorded on a ThermoScientific (LTQ XL Orbitrap) apparatus.

4-Isocyanato-TEMPO was obtained in a similar way as literature data [30] showed; 2 g of 4-amino-TEMPO were dissolved in 15 mL of cold DCM and 0.25 mL of diphosgen (also dissolved in 15 mL of cold DCM) were added under vigorous stirring; the mixture was maintained below 0° C with an external cooling (ice and salt); after few minutes, 70 mL DCM were added, and the final solution was extracted twice with 100 mL aqueous hydrochloric acid (1 M) and once with 100 mL sodium hydroxide (1 M); the organic layer was dried over anhydrous magnesium sulfate, filtered off and the solvent removed under vacuum (below 30° C). Yield ~50%.

2,2'-succinic acid disulphide was obtained by oxidation of 2-mercapto-succcinic acid;[21] to 300 mg of the acid dissolved in 30 mL of methanol were added under stirring 300 mg of iodine; after 2 hours, a solution of sodium thiosulfate was added drop-by-drop until the colour of iodine disappear. To the mixture was added 150 mL of DCM and 100 mL of water, and the organic layer was separated, dried over anhydrous magnesium sulfate, filtered off and the solvent removed. Yield is quantitative.

DI-T radical was prepared by adding an equal amount of 4-isocyanato-TEMPO and of 4-amino-TEMPO in THF and leaving the mixture at room temperature overnight; removal of the solvent affords the pure material in almost quantitative yield. HR-MS: *m/z* calculated for $C_{19}H_{36}N_4O_3$ M^+ 368.2782; found 368.2807.

TRI-P radical was prepared by adding 75 mg of tris(2-aminoethyl)amine, 625 mg of EEDQ and 372 mg of 3-carboxy-PROXYL free radical to a mixture 50 mL DCM and THF (9/1 v/v) as solvent. After five days, the solution was extracted with 50 mL aqueous hydrochloric acid (1 M) and with 50 mL of sodium hydrogen carbonate (1 M); the organic layer was separated and dried over anhydrous magnesium sulfate, filtered off and the solvent removed under vacuum. The crude mixture was purified by column chromatography using silica as stationary phase and ethyl acetate as eluent. Yield ~30%. HR-MS: *m/z* calculated for $C_{33}H_{61}N_7O_6$ $M+H^+$ 651.4678; found 651.5704.

TE-T radical was obtained reacting 150 mg of the disulphide with 400 mg of 4-amino-TEMPO in the presence of 500 mg EEDQ dissolved in 100 mL DCM. After 3 days, the solution was extracted with 100 mL aqueous hydrochloric acid (1 M) and with 100 mL of sodium hydrogen carbonate (1 M); the organic layer was separated and dried over anhydrous magnesium sulfate, filtered off and the solvent removed under vacuum. The crude mixture was purified by column chromatography using silica as stationary phase and ethyl acetate as eluent. Yield ~30%. HR-MS: *m/z* calculated for $C_{44}H_{80}N_8O_8S_2$ $M+2H^+$ 912.5535; found 912.5584.

TE-P radical was obtained dissolving 30 mg DAB-Am-4 dendrimer (polypropylenimine tetramine dendrimer, generation 1) with 1 g EEDQ and 750 mg of 3-carboxy-PROXYL free radical into a mixture formed by 80 mL DCM and 20 mL THF as solvent. After five days, 50 mL of DCM were added and the solution was extracted with 100 mL of sodium hydrogen carbonate (1 M); the organic layer was separated and dried over anhydrous magnesium sulfate, filtered off and the solvent removed under vacuum. Purification was performed by preparative TLC, using silica as stationary phase and a mixture of DCM and methanol 9/1 (v/v) as eluent. Yield ~20%. HR-MS: *m/z* calculated for $C_{52}H_{97}N_{10}O_8$ $M+H^+$ 989.7485; found 989.7488.

Reactions for oxidation of the alcohols were done in the following conditions: to 0.5 mmol of alcohol dissolved into 5 mL DCM were added 7 mg $NaNO_2$ (20% mol), 0.2 mL of acetic acid and 10% mol of free polyradical; the mixture was stirred for 24 hours and then the solution was filtered off and the solvent removed under vacuum. The residue was dissolved into 1 mL of deuterated chloroform and the yields of oxidation were measured by ^{1}H-NMR.

CONCLUSIONS

In conclusion, the polyradicals used can act as catalysts in selective oxidation processes of alcohols. Polyradicals containing TEMPO moieties gave better results than PROXYL ones. The yields depend on the reactivity of the alcohol and can be quantitative for benzyl alcohol and furfurol. The main drawback is the difficulty to recycle the catalyst.

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