

PS-TEMPO, a Mild, Rapid, Self-Indicating Bound Reagent for Oxidation

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Introduction

An oxidation method using a novel solid phase oxidant, based on a covalently polystyrene bound, sulfonic ester linked 2,2,6,6-tetramethylpiperidine-1-oxyl species is presented, **PS-TEMPO** (Fig. 1a&1b).^{1,2} The reagent showed fast room temperature kinetics compared to similar known systems³ when used to oxidize primary and secondary alcohols to aldehydes and ketones, respectively (Table 1). The products were in general of high purity and the isolated yields were good to excellent. The colour change observed as the oxidation state of the reagent changed, gave an indication of the extent to which the reagent had been used.

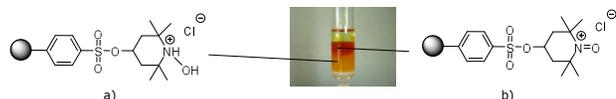


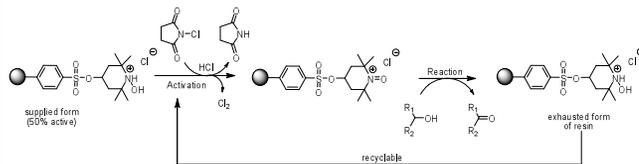
Figure 1a: PS-TEMPO unactivated (yellow).

Figure 1b: PS-TEMPO activated (red)

Results and discussion

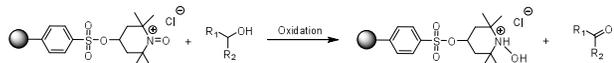
Activation and Recycling (Scheme 1)

Activation of the PS-TEMPO was performed by treating the material with chlorine which was produced by adding a solution of HCl in dioxane to *N*-chlorosuccinimide. The yellow coloured inactive resin turned a deep red at activation.



Scheme 1: Activation, oxidation and recycling of the supported PS-TEMPO reagent.

Oxidation (Scheme 2)



Scheme 2: Oxidation of a Range of Alcohols using PS-TEMPO resin

The alcohol, dissolved in an appropriate solvent, was added to an excess of the activated PS-TEMPO reagent, typically 2.5 equivalents, and the mixture was gently swirled at room temperature. Samples were taken from the mixture and analyzed by LC-MS. When the reaction was completed the resin, now yellow coloured, was filtered off, washed and the solvents were removed *in vacuo*. The residue was weighed and analyzed.

Table 1 shows that in the case of deactivated or unactivated primary benzyl alcohols (entries 1-7), the conversions are almost quantitative within an hour. Activated primary benzyl alcohols on the other hand (entries 8-9) showed a somewhat lower conversion.

| Entry | R1 | R2 | Product | Time, hr | Conversion % LC-MS | Yield % | Purity % ¹ H NMR |
|-------|-----------------------|-------|---------|----------|--------------------|---------|-----------------------------|
| 1 | 4-NO ₂ -Ph | H | | 1 | >99 | >99 | >97 |
| 2 | 2-NO ₂ -Ph | H | | 1 | 98 | >99 | >97 |
| 3 | 3-NO ₂ -Ph | H | | 1 | 98 | >99 | >97 |
| 4 | 4-Br-Ph | H | | 1 | >99 | >99 | >97 |
| 5 | 4-F-Ph | H | | 0.5 | >99 | 80 | >97 |
| 6 | 4-Biphenyl | H | | 1 | 98 | >99 | >97 |
| 7 | 4-Me-Ph | H | | 0.5 | 99 | 99 | >97 |
| 8 | 4-MeO-Ph | H | | 2 | 92 | >99 | 89 |
| 9 | 4-BzIO-Ph | H | | 1 | 88 | 89 | 88 |
| 10 | 2-Furanyl | H | | 0.5 | >99 | >99 | >97 |
| 11 | 2-Thienyl | H | | 0.5 | >99 | >99 | >97 |
| 12 | Ph | Me | | 0.5 | >99 | >99 | >97 |
| 13 | 4-F-Ph | Me | | 0.5 | >99 | 82 | >96 |
| 14 | 1-Naphthyl | Me | | 1.5 | 95 | 86 | >95 |
| 15 | 4-MeO-Ph | Me | | 2 | 35 | 88 | 32 ^a |
| 16 | Ph | Et | | 1 | 99 | 78 | >97 |
| 17 | Ph | Ph | | 2 | 95 | >99 | >94 |
| 18 | o-OH-Benzyl | Ph | | 25 | 74* 22** | >99 | 93 |
| 19 | 1-Tetralinyl | (=R1) | | 1 | 71 | 65 | 60 |
| 20 | 9-Fluorenyl | (=R1) | | 1 | >99 | 89 | >98 |
| 21 | Ph ₂ CH | H | | 2 | 59 | >99 | 57 |
| 22 | 1-Styryl | H | | 0.5 | >99 | 91 | >97 |
| 23 | 2-Adamantanyl | (=R1) | | 2 | 96 | 90 | >98 |
| 24 | (-)-Bornyl | (=R1) | | 2 | 98 | 87 | >98 |

Table 1: Oxidation of a variety of alcohols.

*Benzil **Benzoin

This tendency was even more evident in the case of the secondary benzylic alcohols: the deactivated or unactivated alcohols (entries 12-14 & 16-17) showed a conversion almost as fast and complete as the primary benzylic alcohols while the activated (entries 15 & 19) exhibited considerably lower conversion and also gave substantial amounts of by-products. In entry 15, one of the major by-products appeared to be a dimeric ether which indicates an intermediate formation of the benzylic carbocation.

The benzylic di-alcohol hydrobenzoin (entry 18) proved to be very sluggish: after a reaction time of 25 hours, only 74 % complete conversion to benzil was established while 22 % still consisted of the half-oxidized intermediate benzoin.

Oxidation of non-benzylic secondary alcohols such as 2-adamantanol and borneol (entries 23 & 24) resulted in almost complete conversion within 2 hours and products of high purity and high yields. High purity and high yield, after a rapid reaction, was also obtained with the allylic cinnamyl alcohol (entry 22).

General experimental procedure

Activation

3.0 ml (3 equiv.) of a 1.07 M filtered solution of *N*-chloro-succinimide in DCM:MeCN (1:1) and 0.8 ml (3 equiv.) 4 M HCl in dioxane was added to 0.5 g PS-TEMPO (2.11 mmol/g). The mixture was swirled gently at room temperature for 10 min. The resin was filtered off, washed 5 times with 4 ml DCM:MeCN (1:1) and then directly used in the oxidation step.

Oxidation

0.5 g activated PS-TEMPO (1.06 mmol, 2.5 equiv.) was added to 0.422 mmol alcohol dissolved in 2.5 ml DCM:MeCN (1:1). The mixture was swirled gently at room temperature and samples were taken from the mixture for LC-MS analysis every 30 min. When the oxidation had ceased, see the times stated in Table 1, the resin was filtered off and washed 5 times with 2.5 ml DCM:MeCN (1:1). The solvent were removed *in vacuo* from the combined filtrate and washings. The residue was weighed and analyzed by LC-MS at an appropriate wavelength and ¹H NMR.

Conclusion

A novel oxidizing resin based on a sulfonic ester linkage to the TEMPO reagent is presented. The resin showed promise in a variety of oxidation reactions, and the visually self-indicating nature of its oxidation states provided a qualitative guide to the extent of the oxidation reaction.

References & notes:

- 1 Lebelev, O. L. and Kazarnovskii, S. N. *Zhur. Obshch. Kim.* 30, **1960**, 1631
- 3 Booth, R. J. and Hodge, J. C. J. *Am. Chem. Soc.* 119, **1997**, 4882
- 5 a. MP-TsO-TEMPO, Synthesis and Purification Catalog, 2007, Biotage, pages 108-113
b. TEMPO polystyrene, The Polymer Supported Reagent Handbook, Novabiochem
- 4 After 16 h reaction at RT, Biotage's ionic bound MP-TsO-TEMPO gave a product of 77 % purity.

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<http://www.biotage.com>