Tetra-*n*-propyl Ammonium Perruthenate (TPAP) – An Efficient and Selective Reagent for Oxidation Reactions in Solution and on the Solid Phase

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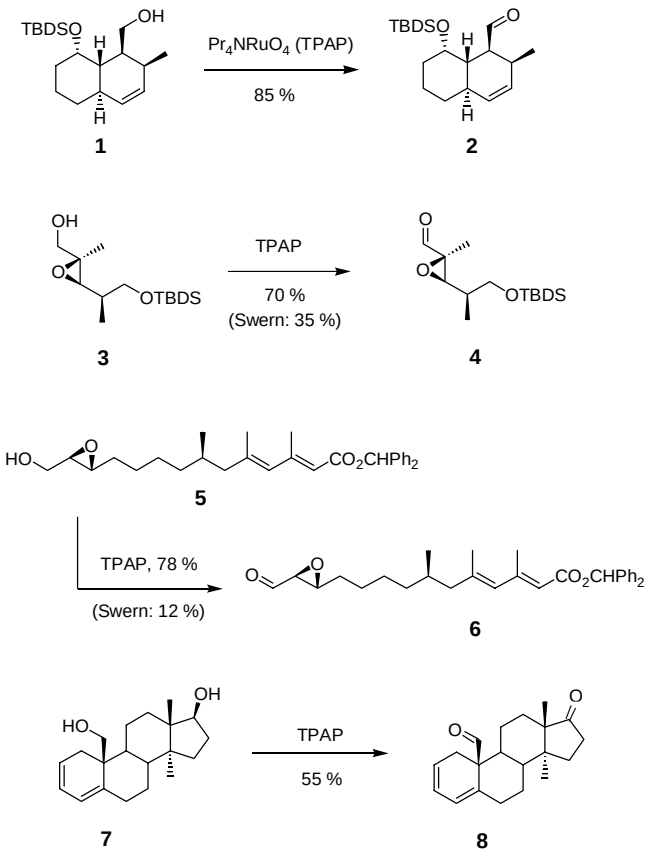
Oxidising reagents are an essential part of modern organic chemistry. Over the years reagents have been developed to show higher selectivity and functional group tolerance, thus permitting the preparation of target molecules with ever increasing levels of structural complexity. Therefore, we have seen reagents for the oxidation of alcohols to carbonyl compounds change from the more aggressive strongly acidic or basic chromium systems of the past [1] to milder and more selective procedures using activated dimethyl sulfoxide reagents [2], enzymes [3], catalytic oxidants [4] and the increasingly popular hypervalent iodine compounds, of which the stoichiometric Dess-Martin periodinane reagent is outstanding [5].

1. Practical Aspects

In 1987 the use of tetrapropylammonium perruthenate, TPAP, as a readily soluble, nonvolatile, air stable oxidant for alcohols was introduced by S. V. Ley and coworkers [6, 7]. The reagent operates at room temperature and is devoid of obnoxious or explosive side products. Although this reagent is commercially available, it can be readily prepared in a one-pot synthesis in which $RuCl_3 \times nH_2O$ is oxidized with excess sodium bromate ($NaBrO_3$) in molar aqueous carbonate to $[RuO_4]^-$. Subsequent addition of $(Pr_4N)OH$ gives TPAP as dark green crystals [8]. It is stable at room temperature and may be stored for long periods of time, especially if kept refrigerated. The TPAP reagent can be rendered catalytic if suitable co-oxidants are added, of which *N*-methylmorpholine-*N*-oxide (NMO) is most effective. The turnovers are typically around 250 and 5 mol-% of the catalyst is typically used. Very recently, the efficient aerobic oxidation of primary and secondary alcohols using catalytic amounts of TPAP was reported [9]. In general, the use of the finely ground version of molecular sieves (4 Å) greatly improves the rate and the efficiency of the oxidation reactions. Dichoromethane is mostly used as the solvent. However, in some cases better catalytic turnovers are observed when acetonitrile or acetonitrile/dichloromethane mixtures are used. Very often, there is no need for elaborate or hydrolytic workups.

2. Chemoselectivity and Functional Group Compatibility

One of the key factors in the development of new chemical oxidants is consideration of their selectivity in reactions and their functional group compatibility. Primary alcohols are more readily oxidized by TPAP than secondary alcohols, al-



Scheme 1 Chemoselectivity and functional group tolerance of TPAP

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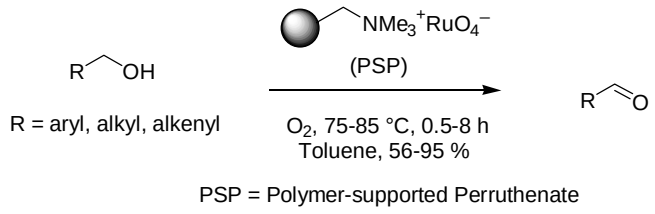
though the latter can be selectively oxidized in the presence of other functionalities [7]. One of the key features of the TPAP oxidant is its ability to tolerate other potentially reactive groups. For example, double bonds, polyenes, enones, halides, cyclopropanes, epoxides and acetals all remain intact during TPAP oxidation. Other groups such as esters, amides, lactones, amines, peroxides and catechols similarly do not react. Equally important for organic synthesis is that protecting groups such as SEM, MOM, BOM, MEM, DBS, TEOC, trityl, silyl, benzyl, PMB, THP, acetate and benzoate are stable to the reaction conditions. Even piperidines, pyrroles, indoles, furans, thiophenes and pyridines are unreactive. Clean oxidation of alcohols occurs in examples where competitive β-elimination can be a problem with other oxidants. Also, oxidation can be achieved without racemization of adjacent stereogenic α-centres or double-bond migration.

For example, the alcohol function of decaline **1** was chemoselectively oxidized in the presence of a double bond and of a silyl protecting group (Scheme 1) [10]. The open-chain alcohol **3** was chemoselectively oxidized in the presence of an epoxide [11]. Alcohol **5** was oxidized in good yield in the presence of a highly unsaturated ester and an epoxide function [11]. Both the primary and the secondary alcohol groups of steroid **7** were oxidized by TPAP [12]. The examples illustrate the applicability of TPAP in modern organic synthesis of complex molecules.

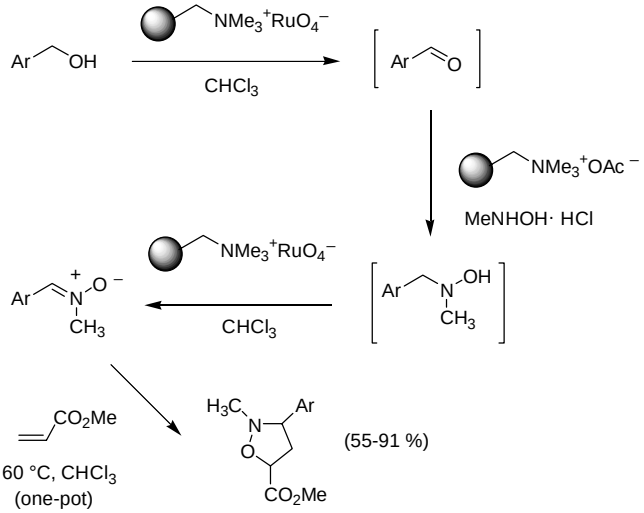
3. Polymer-supported Perruthenate (PSP)

The growing importance of combinatorial chemistry has led to an increasing demand in clean technology processes, i.e. reactions that use environmentally friendly reagents and avoid the need for time-consuming purification steps. Very recently, a polymer bound version of TPAP was developed by Ley *et al*.: The polymer supported perruthenate (PSP) reagent was obtained by adding Amberlyst anion exchange resin (IR 27) containing quaternary ammonium groups, to an aqueous solution of powdered potassium perruthenate and exposing the mixture to ultrasound for 5 min [13]. The reagent thus obtained was used in sub-stoichiometric amounts (20 mol-%) for the oxidation of primary and secondary alcohols using NMO or trimethylamine *N*-oxide (TMAO) as the co-oxidant. The amines produced during the reaction are volatile and can be removed *in vacuo*. It is noteworthy, that stoichiometric amounts of PSP can be used. In this case, no cooxidant is required for the reaction. The filtered spent polymer reagent can be reused in combination with a cooxidant or by external treatment with NMO. The state of the art represents the clean oxidation of primary alcohols using catalytic amounts of PSP and oxygen as cooxidant (Scheme 2) [14].

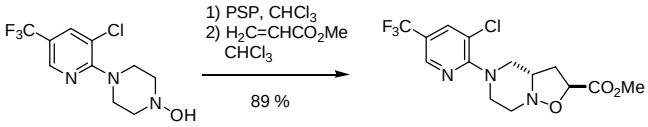


Scheme 2 Aerobic oxidations of alcohols using polymer-supported perruthenate (PSP)

Based on the use of PSP and other polymer-supported reagents an automated synthesis of biologically relevant sulfonamides was developed [15]. In addition, a clean three step process for the synthesis of 1,2-aminoalcohols [16] and multi-step syntheses of isoxazoles, 4,5-dihydro-1*H*-pyrazoles and 1*H*-pyrazoles [17] was reported. The products were obtained in good overall yield and high purities without any chromatographic purification. Isoxazolidines [18] and trisubstituted pyrroles (from isocyanides) [17] were prepared using polymer-supported reagents including PSP.



Scheme 3 Synthesis of isoxazolines using PSP



Scheme 4 Chemoselectivity of PSP

The isoxazolines were prepared by PSP oxidation of alcohols to the corresponding aldehydes which were transformed into hydroxylamines using hydroxymethylamine hydrochloride and polymer-supported acetate as a buffer (Scheme 3). The hydroxylamine was oxidized by PSP into the nitrone which could be used crude in the subsequent [3+2] cycloaddition reaction with electron poor dienophiles. In all steps using polymer-supported reagents no purifications were required. Owing to the high chemoselectivity of the perruthenate oxidant the transformations are possible in the presence of other functional groups. For example, the tertiary amine

functionality and the pyridine moilty in a piperazine derivative were inert under the reaction conditions (Scheme 4).

All reaction sequences mentioned in this paragraph allow the efficient synthesis of libraries of pharmacologically relevant heterocycles [19].

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