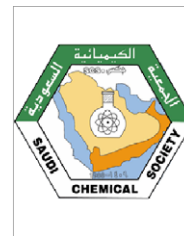King Saud University

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ORIGINAL ARTICLE

Solvent-free reactions using cetyltrimethylammonium permanganate and cetyltrimethylammonium dichromate-*cis*-1,2-dihydroxylation of alkenes, oxidation of alcohols and regeneration of aldehydes and ketones from oximes

B.C. Vimala *, Gepatur Nagendrappa

Department of Studies in Chemistry, Central College Campus, Bangalore University, Bangalore 560 001, India

Abstract Cetyltrimethylammonium permanganate (CTAP) and cetyltrimethylammonium dichromate (CTAD) have been known to be good oxidizing agents in organic solvent media. This homogeneous solution phase procedure itself is a useful advantage over oxidation reactions carried out employing inorganic manganese salts (e.g., $KMnO_4$) or chromium salts (e.g., $Kr_2Cr_2O_7$) performed under heterogeneous conditions. Now we have found that oxidation reactions using CTAP or CTAD do not require a solvent medium, and can be performed under completely solvent-free conditions. We have carried out 1,2-dihydroxylation of olefins with CTAP, oxidation of alcohols to aldehydes/ketones with CTAD, and regeneration of aldehydes and ketones from their oxime derivatives using either reagent, essentially under solid phase conditions. The results are excellent. As a dihydroxylating agent the CTAP is so good that it should be able to replace the highly toxic and expensive OsO_4 for this reaction.

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* Corresponding author.
E-mail address: bcvimala@yahoo.com (B.C. Vimala).

1. Introduction

Solvents in organic reactions are making a tremendous image changeover. Many of them are believed to be responsible, to a certain degree, for global warming and climate change that are causing great concern. Much emphasis is being laid on employing green solvents and reagents for organic synthesis. However, very few solvents are included in the category of those that are considered as desirable for use in reactions adopting

Green Chemistry practices (Alfonsi et al., 2008). The best practice that might have greater impact would, of course, be the one that avoids the use of any solvent in a reaction. Based on such considerations chemists are expending much effort in developing solvent-free synthetic procedures that yield good results (Loupy, 1999).

In this report, we describe the reactions of cetyltrimethylammonium permanganate (CTAP) and cetyltrimethylammonium dichromate (CTAD) that we have carried out under solvent-free condition and CTAP has been used earlier in solvent media for cis-hydroxylation of alkenes (Tanaka and Toda, 2000), oxidative cyclization to lactones (Nagendrappa, 2002), Nef reaction (Toda, 1999), and oxidation of alcohols (Eissen, 2001) and benzylamines (Nguyen and Weizmann, 2007). In the last two cases CTAP has been used only for kinetic studies (Eissen, 2001; Nguyen and Weizmann, 2007). We have used CTAP earlier in CH_2Cl_2 for the preparation of 1-trimethylsilylcycloalkan-1,2-diols from 1-trimethylsilylcycloalkenes and obtained them in high yields (Correa et al., 2003). Mendonca et al. have shown, quoting our work, that CTAP can bring about cis-dihydroxylation where Chas fails (Stoddard et al., 2007). Considering the high toxicity, excessive cost and other problems associated with OsO_4 (Villa et al., 2003), it is evident that CTAP is not only an environmentally desirable, inexpensive reagent, but also possibly superior one for cis-hydroxylation of alkenes. However, despite such merits, it has not earned the popularity and wider application in synthesis it so well deserves.

Besides its cis-dihydroxylating property, cetyltrimethylammonium permanganate has been found to be an effective reagent for the regeneration of ketones and aldehydes from their oxime derivatives (Shushan et al., 1984), like many other manganese compounds (Freeman and Kappos, 1989). Likewise, chromium compounds are also useful for deoximation reactions (Freeman and Kappos, 1989), and cetyltrimethylammonium dichromate has been shown to be one of the successful among them (Rathore et al., 1986; Vankar et al., 1987). Furthermore, CTAD is found to oxidize alcohols (Vankar et al., 1987; Sumichrast and Holba, 1992) and other functional groups (Holba and Sumichrast, 1995) quite efficiently. All the reactions of CTAP and CTAD cited above (Tanaka and Toda, 2000; Correa et al., 2003; Shushan et al., 1984; Rathore et al., 1986; Sumichrast and Holba, 1992) have been carried out in solution media using environmentally undesirable solvents (Alfonsi et al., 2008) such as chlorohydrocarbons, which need to be replaced by environmentally risk-free solvents or better still would be to perform reactions using these reagents under solvent-free conditions.

In addition to having excellent attributes as oxidizing reagents, both CTAP and CTAD possess a long hydrocarbon chain that can draw the substrate molecule close to MnO_4^- or $Cr_2O_7^{2-}$ ion in a micelle-like aggregation, thereby enabling the reactant molecule to efficiently interact with the oxidizing ion even if a homogenizing solvent is not present. Based on this assumption we have succeeded in achieving cis-hydroxylation of olefins with CTAP, oxidation of alcohols to aldehydes and ketones with CTAD, and deoximation of aldoximes and ketoximes using both the reagents under solvent-free condition. The results obtained are excellent. The benefits of employing these green reactions for synthesis are obvious, and we wish to report here the details of our study.

2. Experimental

Infrared spectra were obtained using KBr pellets for solids and thin film between NaCl plates for liquids. Gas chromatographic analyses were performed using a 15% FFAP on chromosorb W column (2 m × 2 mm i.d.). Column chromatography was carried out using silica gel (60–120 mesh) activated by heating to about 110 °C before use. The chemicals and solvents were purchased from reputed companies, and were purified wherever necessary following usual procedures.

The oximes were prepared by standard methods by treating aldehyde or ketone with hydroxylamine hydrochloride in presence of sodium acetate. Only general experimental methods are described for the dihydroxylation of alkenes by CTAP, oxidation of alcohols by CTAD, and the regeneration of aldehydes and ketones from their oxime derivatives using the two reagents.

2.1. Preparation of cetyltrimethylammonium permanganate

A solution of 4.25 g (27.0 mmol) of $KMnO_4$ in 25 ml of water placed in a 250 ml two-necked flask equipped with a mechanical stirrer and a dropping funnel was cooled in an ice–water bath to 8–10 °C. A solution of 9.10 g (25.0 mmol) of cetyltrimethylammonium bromide in 50 ml of dichloromethane was added in about 10 min. The mixture was stirred at 8–10 °C for 3–4 h when most of the permanganate had passed into the organic layer, which *was* separated and the solvent was recovered under reduced pressure. The purple coloured crystalline CTAP precipitated before the solvent was completely removed, which was collected by filtration, washed with water (50 ml) and ether (20 ml) and dried over P_2O_5 under vacuum in a desiccator; yield, 8.6 g (85%); decomposes above 115 °C.

2.2. Dihydroxylation of olefins using CTAP

To a ground paste of 2.10 g (5.2 mmol) of CTAP and 6–7 drops of water in a beaker cooled in an ice–salt mixture, was added 5.0 mmol of the olefin, drop wise slowly, because of the highly exothermic nature of the reaction, and mixing the contents with a flat-tipped glass rod. The addition was carried out over a period of 30–40 min. The mixture was stirred further occasionally for about 1 h and extracted with ether (3 × 50 ml). The ether extracts were combined, washed with water (2 × 50 ml), and saturated NaCl solution, and dried over Na_2SO_4. After removing ether on a rotary evaporator the slightly sticky residue was chromatographed on a column of silica gel. After eluting the non-polar impurities with petroleum ether (b.p., 60–80 °C), the diol was eluted with petroleum ether–diethyl ether mixture (2:3 v/v) and finally recrystallised from petroleum ether (b.p., 60–80 °C). The diols were identified by comparing their melting points and spectral data with that reported (Loupy, 1999) (Table 1).

2.3. Regeneration of aldehydes and ketones from oximes using CTAP

A mixture of 5.0 mmol of oxime, 5.2 mmol of CTAP and 5–6 drops of water was ground in an agate mortar and pestle for about 5–6 h intermittently. The reaction was followed by monitoring the disappearance of the oxime using TLC. At the end

Table 1 Solvent-free *cis*-dihydroxylation of olefin by CTAP.

Entry	Olefin	Diol	M.P. (°C)	Yield (%)
1	Cyclohexene	*cis*-1,2-Cyclohexanediol	97	78
2	Cycloheptene	*cis*-1,2-Cycloheptanediol	36	70
3	*cis*-Cyclooctene	*cis*-1,2-Cyclooctanediol	77	72
4	*cis*-Cyclododecene	*cis*-1,2-Cyclododecanediol	157	75
5	*cis*,*cis*-1,5-Cyclooctadiene	*cis*-1,2-Cyclooct-5-ene-*cis*-1,2-diol	105	58
6	Styrene	1-Phenyl-1,2-ethanediol	67	75

of the reaction the mixture was extracted with ether (3×30 ml), the combined ether extracts were washed with water (2×50 ml), saturated NaCl solution (50 ml) and dried over Na_2SO_4. After removing the solvent, the residue was chromatographed on a column of silica gel (60–120 mesh) using petroleum ether (b.p., 45–55 °C) as eluant to get the pure carbonyl compounds (Table 2).

2.4. Preparation of cetyltrimethylammonium dichromate

To a mechanically stirred solution of 7.72 g (26.0 mmol) of $K_2Cr_2O_7$ in 25 ml of water taken in a 250 ml two-necked flask and cooled to about 10 °C was added a solution of 9.10 g (25.0 mmol) of cetyltrimethylammonium bromide in 50 ml of dichloromethane over a period of 10 min. The stirring was continued for nearly 4 h when most of the dichromate had migrated to the organic phase, which was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The precipitated orange CTAD crystals were filtered off washed with water (100 ml) and ether (20 ml), and dried over P_2O_5, in a vacuum desiccator; yield, 16.1 g (82.5%). It decomposes when heated above 125 °C.

2.5. Oxidation of alcohols by CTAD

A mixture of 10 mmol of alcohol, 10.5 mmol of CTAD, and 2 ml of glacial acetic acid in a 25 ml flask fitted with a condenser and a calcium chloride guard tube was heated to about 110 °C, with slow stirring, for 4 h, the progress of the reaction being monitored by TLC or GC. Then it was cooled, 10 ml of water was added, and the product (ketone or aldehyde) was extracted into ether (2×40 ml). The ether was removed on a rotary evaporator and the crude product was purified by passing through silica gel column using petroleum ether as eluant. The products were identified by comparing their IR spectra, and the melting points of their 2,4-dinitrophenyl-hydrazone or semicarbazone derivatives with those of the authentic samples of ketones or aldehydes (Table 4).

2.6. Regeneration of aldehydes and ketones from (mimes by CTAD)

A mixture of 10 mmol of oxime, 10.5 mmol of CTAD and 1–2 ml of glacial acetic acid taken in a 25 ml flask fitted with a condenser and a $CaCl_2$ guard tube was heated with slow stirring to 60–80 °C for 3–4 h, when the oxime had reacted completely as indicated by TLC analysis. It was then cooled, 10 ml of water was added, and further worked up as described for oxidation of alcohols. The products were identified by their

IR spectra superimposable on those of the original aldehydes and ketones (Table 3).

3. Results and discussion

3.1. Solvent-free *cis*-1,2-dihydroxylation by CTAP

Since CTAP is proven to be a good oxidizing agent in solvent media, to test its efficacy in solvent-free conditions it was just enough to exclude the solvent in the reaction and find the suitable condition to achieve the desired results, which turned out to be an extremely simple experimental procedure, and is as follows. The required quantity of CTAP taken in a flask or a beaker is mixed with a few drops of water to form, and cooled in an ice–salt bath to about -10 °C, followed by adding the required quantity of olefin cautiously, as the reaction is exothermic, with gentle mixing using a glass rod or a magnetic stirrer. The reaction is run for an hour, and the product diol is isolated by usual work-up procedure.

Six olefins were used for the reaction. All of them produced the corresponding diols in good yield, except *cis*,*cis*-1,5-cyclooctadiene, which gave a moderate yield of *cis*-1,2-cyclooct-5-ene-*cis*-1,2-diol. The idols were identified by comparing their melting points and spectra with those of the authentic compounds. The results are given in Table 1.

3.2. Deoximation using CTAP

Our successful application of CTAP for *cis*-dihydroxylation of olefins under solvent-free conditions encouraged us to explore the possibility of extending its use to other reactions under similar conditions. We considered the regeneration of ketones and aldehydes from their oxime derivatives which is an important functional group transformation reported to be accomplished in solvent medium (Shushan et al., 1984). The CTAP reagent proved to be highly effective also in the absence of organic solvent for the conversion of oximes to the corresponding carbonyl compounds. However, the presence of a small quantity of water is necessary for the reaction to occur. The experimental procedure in this case also is very simple, which consists of occasional grinding at room temperature a paste of the oxime (usually 10 mmol), about 1.05 molar equivalent of CTAP and a few drops of water in an agate mortar till the oxime has completely reacted (checked by TLC), finally isolating the product by ether extraction. The regenerated ketones and aldehydes were identified by their spectra superimposable on those of the original carbonyl compounds. The results are presented in Table 2. In all, 18 oximes were used in this study. Some of them contained other functional groups
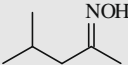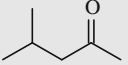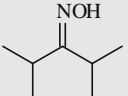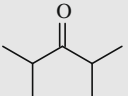
Table 2 Deoximation with CTAP by solvent-free method.
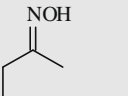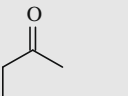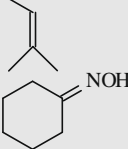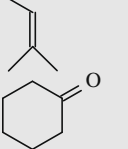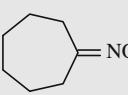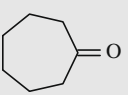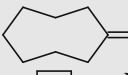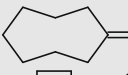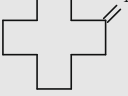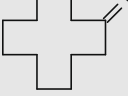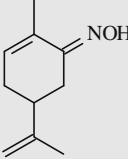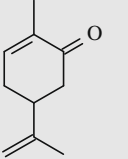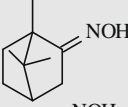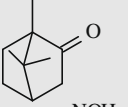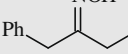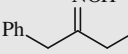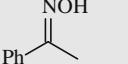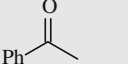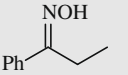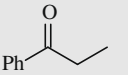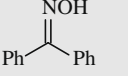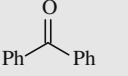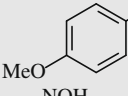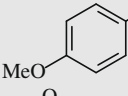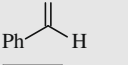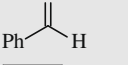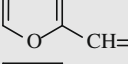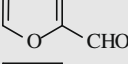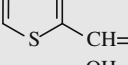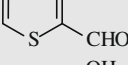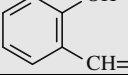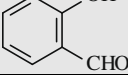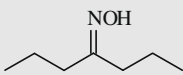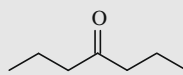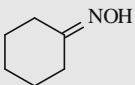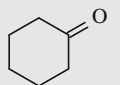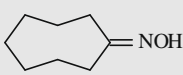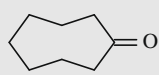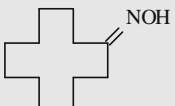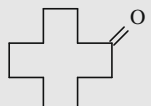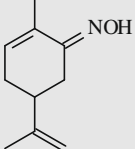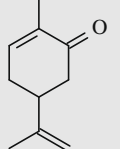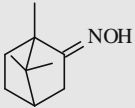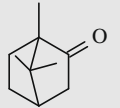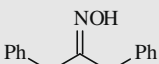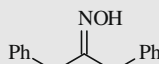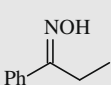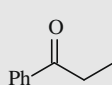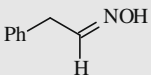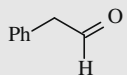
Entry	Oxime	Product	Reaction time (h)	Yield (%)
1			5	80
2			8	75
3			8	85
4			6	85
5			6	90
6			5	85
7			8	80
8			8	80
9			5	75
10			8	85
11			5	90
12			6	85
13			8	85
14			6	85
15			6	95
16			8	75
17			8	80
18			9	80

Table 3 Deoximation using CTAD in the absence of solvent.

Entry	Oxime	Product	Reaction time (h)	Yield (%)
1	(heptan-4-one oxime, =NOH)	(heptan-4-one, =O)	3	85
2	(cyclohexanone oxime, =NOH)	(cyclohexanone, =O)	4	88
3	(cyclooctanone oxime, =NOH)	(cyclooctanone, =O)	4	88
4	(cyclooctanone-type oxime, =NOH)	(ketone, =O)	4	85
5	(carvone oxime, =NOH)	(carvone, =O)	4	85
6	(bicyclic oxime, =NOH)	(bicyclic ketone, =O)	5	82
7	Ph⌣⌣Ph (NOH)	Ph⌣⌣Ph (NOH)	4	90
8	Ph⌣ (NOH)	Ph⌣ (O)	3	95
9	Ph⌣ (NOH)	Ph⌣ (O)	3	92
10	Ph⌣Ph (NOH)	Ph⌣Ph (O)	4	88
11	Ph⌣H (NOH)	Ph⌣H (O)	3	92
12	Ph⌣ (NOH, H)	Ph⌣ (O, H)	4	85

also (entries 8, 16, 17 and 18) which remained unaffected under these conditions.

3.3. Deoximation using CTAD
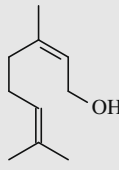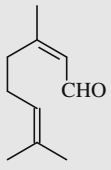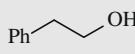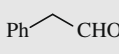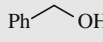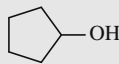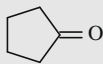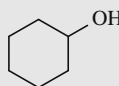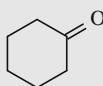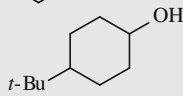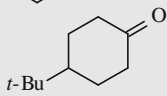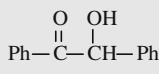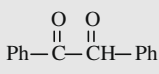
The observation that CTAP is able to regenerate the ketones and aldehydes from their oximes in high yield in the absence of organic solvent suggested the possibility of similar behavior of cetyltrimethy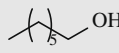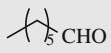lammonium dichromate in respect of deoximation of aldoximes and ketoximes. With this presumption we treated the oximes with CTAD in the absence of an organic solvent. We noted that the reaction proceeds smoothly, but a small quantity of acetic acid is to be present and the reaction mixture warmed to 60–70 °C, though no solvent was needed. The duration of the CTAD reaction as compared to that using CTAP is just about half. The results are presented in Table 3.

3.4. Oxidation of alcohols with CTAD in solvent-free condition

When we discovered that CTAD functions as an efficient deoximating oxidant in the absence of organic solvent, we considered its application to the oxidation of primary and secondary alcohols to aldehydes and ketones, respectively, which is one of the most important functional group transformations and would be the best test for appreciating the effectiveness of CTAD as an oxidizing agent under solvent-free

Table 4 Solvent-free oxidation of alcohols by CTAD.

Entry	Oxime	Product	Reaction time (h)	Yield (%)
1	(CH₃)₂CH–CH₂OH	(CH₃)₂CH–CHO	3	90
2	branched chain (subscript 5) ...OH	branched chain (subscript 5) ...CHO	4	85
3	unsaturated terpenoid ...OH	unsaturated terpenoid ...CHO	3	88
4	Ph–CH₂CH₂–OH	Ph–CH₂–CHO	4	90
5	Ph–CH₂–OH	Ph–CHO	3	95
6	(CH₃)₂CH–OH	(CH₃)₂C=O	3	85
7	cyclopentyl–OH	cyclopentanone (=O)	3	85
8	cyclohexyl–OH	cyclohexanone (=O)	3	90
9	t-Bu-cyclohexyl–OH	t-Bu-cyclohexanone (=O)	3	88
10	Ph—C(=O)—CH(OH)—Ph	Ph—C(=O)—C(=O)—Ph	3	85

conditions. We found to our delight that the reagent indeed performs this task excellently. We oxidized five primary alcohols and five secondary alcohols, all of which underwent oxidation to the respective aldehyde or ketone in high yield. The experimental procedure in this case too is very simple, and consists of gently heating equimolar quantities of alcohol and CTAD to about 100–110 °C. Here also the presence of a small amount of acetic is essential to bring about the reaction. The procedural details are provided in the experimental section, and the results are presented in Table 4.

The results show that both CTAP and CTAD are efficient oxidizing agents in solvent-free processes and do not need any eco-risky organic solvents to make them work. An important observation that is worth noting is that the success of the CTAP reaction depends on the presence of a little water which seems to be required for the hydrolysis of the intermediate olefin–MnO₄ adduct (Scheme 1).
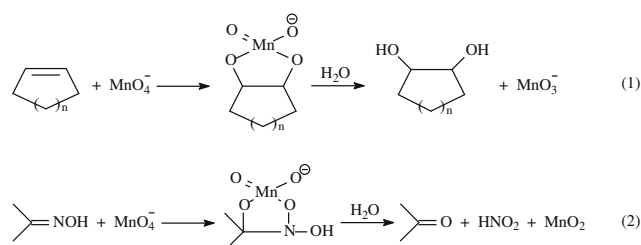
In the case of CTAD the presence of acetic acid is necessary for the reaction to take place. Though we have not investigated the role of acetic acid, however, it is well known that dichromate and acetic acid form mixed anhydride as intermediate (Scheme 2) (Shukla et al., 2003). The results of CTAD oxidation clearly indicate that it is a very effective reagent for deoximation as well as for oxidation of alcohols to aldehydes and ketones in the absence of an organic solvent.

The mechanism of oxidation of alcohols (Shukla et al., 2003) by $Cr_2O_7^{2-}$ and the mechanism of dihydroxylation of olefins by MnO_4^- are thoroughly investigated. Based on the available literature accounts, we have presumed that similar mechanistic routes are possibly involved in the deoximation processes as well, as shown in Scheme 1, Eq. (2) and Scheme 2, Eqs. (5) and (6).

It should be noted that a wide variety of aldoximes and ketoximes are smoothly converted into aldehydes and ketones. The double bonds present in some of the oximes are not affected further by either CTAP (Table 2, entries 3 and 8) or CTAD (Table 3, entry 5). It is also noteworthy that the free

$$\text{(cyclic alkene)} + MnO_4^- \longrightarrow \text{(Mn–diolate adduct)} \xrightarrow{H_2O} \text{(cis-diol)} + MnO_3^- \quad (1)$$

$$\text{>C=NOH} + MnO_4^- \longrightarrow \text{(Mn–N–OH adduct)} \xrightarrow{H_2O} \text{>C=O} + HNO_2 + MnO_2 \quad (2)$$

Scheme 1

$$2\ AcOH\ +\ Cr_2O_7^{2-} \rightleftharpoons 2\ AcOCrO_3^- + H_2O \qquad (3)$$

$$(4)$$

$$(5)$$

$$(6)$$
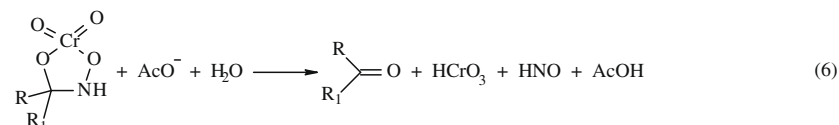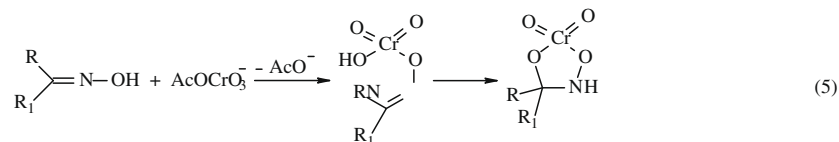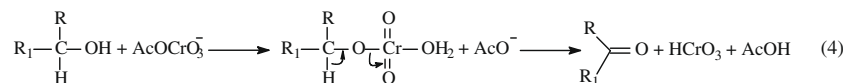
Scheme 2

aldehydic function released after deoximation from aldoximes does not undergo further oxidation to carboxylic acid. Similarly, phenolic and heteroaromatic groups are unaffected. Between CTAD and CTAP, the latter should be the preferred reagent for deoximation, although it is slower reacting, as it works efficiently under much milder conditions, requires only a little water for reaction, and is far less toxic than chromium compounds.

4. Conclusion

In the context of the present study, we would like to draw the attention of synthetic chemists to the valuable and useful properties of CTAP, which seem to have not been recognized to the extent it deserves. Some of them are mentioned here. CTAP, unlike many other quaternary ammonium permanganates, is quite stable. We have used samples stored for many months in refrigerator at 5 °C without any noticeable loss of reactivity. We have not experienced cracking or exploding at any stage of handling it, such as during its preparation (15–20 g), weighing, transfer or during reaction in solvent medium or without solvent (usually carried out at 0 °C or below), or during work-up procedure.

Furthermore, it is easy to prepare. As a dihydroxylating agent it gives excellent yields of 1,2-diols, which are as good as those obtained from osmium tetroxide reaction and it has been shown that it can work where OsO_4 fails (Stoddard et al., 2007). Considering the high cost and severe toxicity of OsO_4, CTAP should be the reagent of choice, even if OsO_4 is used only in catalytic quantities where it needs co-oxidants. Another advantage of MnO_4 over OsO_4 is that while the latter, being an electrophilic reagent, is reactive towards olefins with electron donating substituents, the permanganate being ambiphilic reacts with olefins with wider range of substituents. CTAP is definitely a "greener" reagent and we fervently recommend its use in place of OsO_4 wherever possible, particularly in laboratory scale preparations. This investigation shows that CTAD is a good and efficient oxidant in solvent-less reactions; however,

one should exercise restrain in its use, because chromium is a relatively toxic substance.

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