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Magtrieve™ (CrO_2) and MnO_2 mediated oxidation of aldoximes: studying the reaction course

Sandeep Bhosale, Santosh Kurhade, Samir Vyas, Venkata P. Palle, Debnath Bhuniya *

Drug Discovery Facility, Advinus Therapeutics, Quantum Towers, Plot-9, Rajiv Gandhi Infotech Park, Phase-I, Hinjewadi, Pune 411057, India

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DB dedicates this work to Dr. Santosh Maji on the occasion of his 60th birthday

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ABSTRACT

Magtrieve™ (CrO_2) and MnO_2 mediated oxidation of aldoximes to nitrile oxides were studied in details. In presence of external radical source, TEMPO, these reagents did not furnish nitrile oxides, instead favoured deoximation to aldehydes. A common trend of deoximation was established from electronically tuned aldoximes, which is: aliphatic>aromatic>aldoximes with strong electron-withdrawing group, though the extent of deoximation was less in case of CrO_2. Above effects were not observed with chloramine-T and diacetoxyiodobenzene, reagents known to produce nitrile oxides via hydroximoyl halide or equivalent ionic intermediates. A putative reaction mechanism is proposed for MO_2 (M=Cr, Mn) mediated oxidation of aldoximes through formation of a nitroso-oxime tautomeric pair. Formation of nitrile oxide is possibly occurred from the oxime tautomer via a σ-type iminoxy radical intermediate. The deoximation process, dominating in presence of external radical environment, is explained following decomposition of the nitroso tautomer.

1. Introduction

Nitrile oxides are versatile intermediates in organic synthesis. The most useful synthetic application of nitrile oxides is perhaps the synthesis of isoxazoline and isoxazole heterocycles, via 1,3-dipolar cycloaddition (1,3-DC) reactions.[1] Recently we have communicated[2a] an efficient methodology for direct oxidation of aldoximes to nitrile oxides using Magtrieve™ (CrO_2),[3] and subsequent 1,3-DC reactions with dipolarophiles to furnish the desired five-member heterocycles in one-step. Additionally for this type of synthesis, the use of CrO_2 has been shown to have specific advantages over some other previously known reagents,[2b] and particularly over direct oxidizing agents, such as MnO_2,[4] $Pb(OAc)_4$[5] and other transition metal complexes.[6]

While developing the CrO_2-methodology, two interesting observations motivated us to develop further understanding of these reactions. Firstly, a mixture of (*E*)- and (*Z*)-aldoximes **1** was also oxidized to nitrile oxides **2** in high yields upon treatment with CrO_2 (Scheme 1; Eq. 1). Such results hinted us that CrO_2 might follow a mechanism similar to MnO_2, which also has been reported[4a] to produce nitrile oxide with equivalent yield from both the stereoisomers of aldoximes (Scheme 1, Eq. 2). It is important to mention here that $Pb(OAc)_4$ has been known[5] to produce nitrile oxides only from (*E*)-aldoximes via a rigid six-member transition state **3** (Scheme 1, Eq. 3). Secondly, we noticed that CrO_2 led to significantly less deoximation compared to what was reported by Kiegiel et al.[4a] for MnO_2 especially in case of aromatic and aliphatic aldoximes. For MnO_2, involvement of iminoxy radical intermediates **4** has been invoked by the original investigators[4a] as common intermediates towards the formation of nitrile oxides **2** as well as the corresponding aldehydes **5** as deoximation product (Scheme 1, Eq. 2). However, no further mechanistic insights have been reported in the literature. Therefore, subsequent to our original communication, a series of experiments were designed and carried out in our laboratory to study the reaction course of Magtrieve™ and MnO_2 mediated oxidation of aldoximes. Herein, we report our observations, and at the end propose a putative reaction mechanism to account various facts.

2. Results and discussion

2.1. Reactions of CrO_2 with (*E*)- and (*Z*)-aldoximes

In our previous study with CrO_2, it was observed that 60:40 regioisomeric mixture of aliphatic aldoximes furnished 1,3-DC products in 63–75% isolated yields.[2a] Subsequently for the present investigation, pure (*E*)- and (*Z*)-benzaldoximes, (*E*)-**1a** and (*Z*)-**1a**

* Corresponding author. Tel.: +91 20 66539600; fax: +91 20 66539620; e-mail address: debnath.b@advinus.com (D. Bhuniya).

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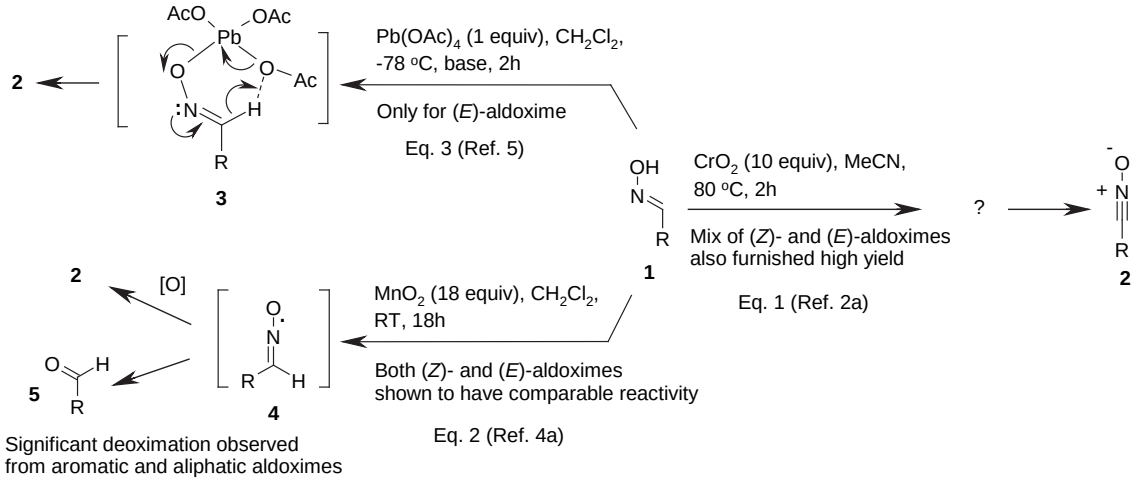
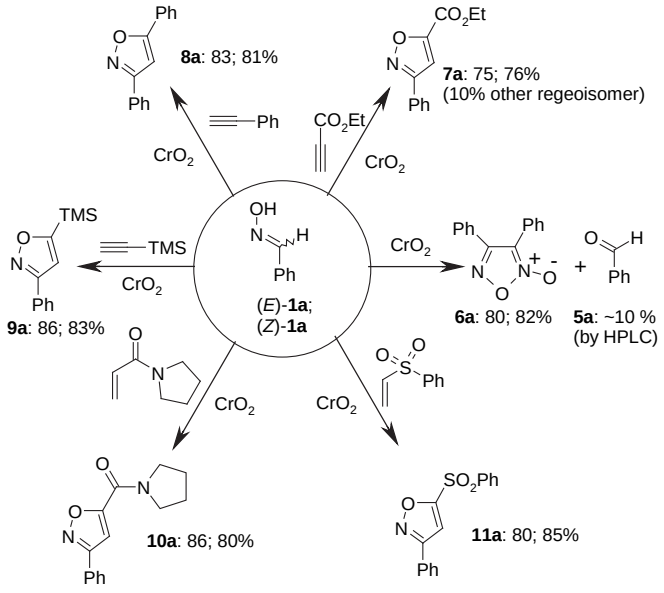


Scheme 1. Comparative literature information of $Pb(OAc)_4$, MnO_2, and CrO_2 mediated oxidation of aldoximes.

were independently reacted with CrO_2 following the reported procedure[2a] in presence of various dipolarophiles. As anticipated, the corresponding 1,3-DC products **7a**–**11a** were obtained in 75–86% isolated yields irrespective of the geometry of starting aldoximes (Scheme 2). It was also noticed that, the furoxan **6a** was formed as dimerization product in absence of dipolarophile. These results confirm that both (*E*)- and (*Z*)-aldoximes were oxidized to nitrile oxide with equal ease, as was reported for MnO_2, and also suggest for involvement of a common reactive intermediate during the course of oxidation.



Scheme 2. CrO_2 mediated 1,3-DC reactions from (*E*) & (*Z*)-**1a**.

2.2. Effect of an external radical source

Based on literature knowledge[2,4] and the results described above, it was initially hypothesized that both CrO_2 and MnO_2 mediated oxidation of aldoximes might follow an identical mechanism, which would be completely different than the $Pb(OAc)_4$ mediated reactions.

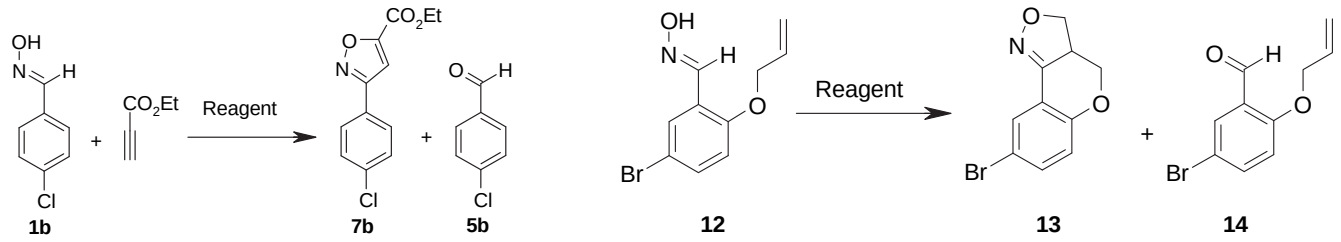
To confirm whether CrO_2 and MnO_2 mediated reactions proceed via a radical intermediate, as particularly was proposed by Kiegiel et al.[4a] for MnO_2, we decided to carry out control experiments where these reactions would be conducted in presence of stable external radical. Such experiments are well documented in the literature to prove the involvement of reactive or high energy radical intermediates either through scavenging the radial intermediates or by quenching excited state towards the formation of radical intermediates.[7] Two model reactions were considered: (i) intermolecular reaction using aldoxime (*E*)-**1b** and ethyl propiolate and (ii) intramolecular reaction from **12** (Table 1). Following the methodology as described in literature for CrO_2[2a] and MnO_2,[4a] reported yields were obtained for the 1,3-DC products **7b** and **13** starting from the respective aldoximes (*E*)-**1b** and **12** (Table 1: entries 1–3, 11–13). When the same set of reactions was carried out in presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or Galvinoxyl,[7] it was noticed that both the MnO_2 and CrO_2 mediated reactions were affected by these external radicals. Galvinoxyl led to rather untractable reaction mixture (multiple spots on TLC), hence could not be studied further. The TEMPO mediated reactions was found to be more composed, from which the corresponding aldehydes **5b** and **14** were isolated as major products instead of the cycloaddition products along with the recovery of TEMPO (Table 1: entries 6–8; 16–18). The effect of TEMPO was consistently observed even if the stoichiometry was varied from 0.2 to 2.0 mol equiv (Table 1, entries: 16, 18 *footnote* g). Formation of any stable TEMPO-adduct was not evident from HPLC-Mass analysis of a crude reaction mixture (see also Experimental section 4.2.2).

In another experiment, (*Z*)-**1b** also led to the formation of 4-Cl-benzaldehyde as major product when treated with MnO_2 or CrO_2 in the presence of TEMPO (results not shown here).

A careful monitoring of these reactions by TLC and HPLC further revealed that the CrO_2 mediated reactions in presence of TEMPO required 15 min for deoximation of aldoximes **1b** and **12** (Table 1, entries 6–7, 16–17). This is particularly interesting as it usually require 2 h for nitrile oxide formation.

To rule out any possibility of TEMPO interfering with either formation of nitrile oxide intermediate or with the cycloaddition reaction, aldoximes (*E*)-**1b** and **12** were independently treated with two different reagents from the literature known for oxidation of aldoximes to nitrile oxides: (i) chloramine-T[8]—known to produce hydroximoyl chloride, and (ii) diacetoxyiodobenzene (DIB)[9]—a hypervalent reagent possibly work via an ionic intermediate[9b] but not have been investigated in past for the possibility of involvement of radical intermediate. From the results shown in Table 1 (compare entry 4 vs 9; and entry 14 vs 19; also see experimental section 4.2.4. *Method A* and *B*), it is evident that TEMPO neither reacted with

Table 1
Effect of TEMPO in CrO_2 and MnO_2 mediated oxidation of aldoximes[a]



Reagent	Condition	Entry No.	Starting aldoxime	Major product (% isolated yield)	Entry No.	Starting aldoxime	Major product (% isolated yield)
CrO_2	MeCN, 80 °C, 2 h	1[b]	**1b**	**7b** (83)	11[b]	**12**	**13** (85)
CrO_2	Toluene, 80 °C, 2 h	2[b]	**1b**	**7b** (83)	12[b]	**12**	**13** (85)
MnO_2	CH_2Cl_2, rt, 18 h	3[c]	**1b**	**7b** (40); **5b** (45)	13[c]	**12**	**13** (46); **14** (36)
Chloramine-T	MeOH/CH_2Cl_2, rt, 2 h	4[d]	**1b**	**7b** (75)	14[d]	**12**	**13** (80)
DIB	CH_2Cl_2, rt, 2 h	5[e]	**1b**	**7b** (83)	15[e]	**12**	**13** (85)
CrO_2+TEMPO	MeCN, 80 °C, 15 min	6[f]	**1b**	**5b** (90)	16[f]	**12**	**13** (12); **14** (70)[g]
CrO_2+TEMPO	Toluene, 80 °C, 15 min	7[f]	**1b**	**5b** (92)	17[f]	**12**	**13** (15); **14** (75)
MnO_2+TEMPO	CH_2Cl_2, rt, 18 h	8[f]	**1b**	**5b** (88)	18[f]	**12**	**13** (20); **14** (60)[g]
Chloramine-T+TEMPO	MeOH/DCM, rt, 2 h	9[f]	**1b**	**7b** (70)	19[f]	**12**	**13** (80)
DIB+TEMPO	CH_2Cl_2, rt, 2 h	10[f]	**1b**	**7b** (80)	20[f]	**12**	**13** (82)

[a] Formation of nitrile oxides was correlated to isolated yields of corresponding 1,3-DC products **7b** and **13**.
[b] Followed Ref 2a.
[c] Followed Ref 4a.
[d] Followed Ref 8b.
[e] Followed Ref 9b.
[f] See Experimental section for typical experiments.
[g] Similar result obtained even if when different stoichiometries of TEMPO, such as 0.2, 1.0 and 2.0 mol equiv were used.

nitrile oxides nor interfered with the conversion of hydroximoyl chlorides to nitrile oxides and subsequent cycloaddition reactions using chloramine-T. Use of DIB provided us similar result like of chloramine-T (Table 1; compare entry 5 vs 10; and entry 15 vs 20) which is in line with the originally proposed mechanism of DIB mediated oxidation of aldoximes.[9b,c]

Possibility of deactivation or poisoning of CrO_2 or MnO_2 in presence of TEMPO was also ruled out as both the oxidizing agents indeed oxidized benzyl alcohol to benzaldehyde, as known in the literature,[3b,c] even when the reactions were carried out in presence of the radical source (results not shown here).

2.3. Probable reaction mechanism

The above results (Table 1) strongly suggest that both CrO_2 and MnO_2 mediated oxidation of aldoximes to nitrile oxides involve a radical pathway[7b,h] and might have originated from the common intermediate conceptualized in previous Section 2.1. In presence of an external radical environment, such a high energy radical pathway could be interfered and hence did not yield nitrile oxide. That raises a question of how to explain the formation of aldehyde as deoximation product when the radical path is blocked? None the less, a simplistic diagram is initially put forward in Fig. 1 to integrate the observed experimental results. Upon treatment with MO_2 (M=Mn or Cr), both (*E*)- and (*Z*)-aldoximes form a common non-radical intermediate. Such early intermediate has two paths to progress: a radical pathway for nitrile oxide formation and a non-radical path towards deoximation.

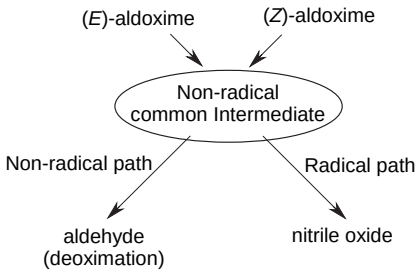
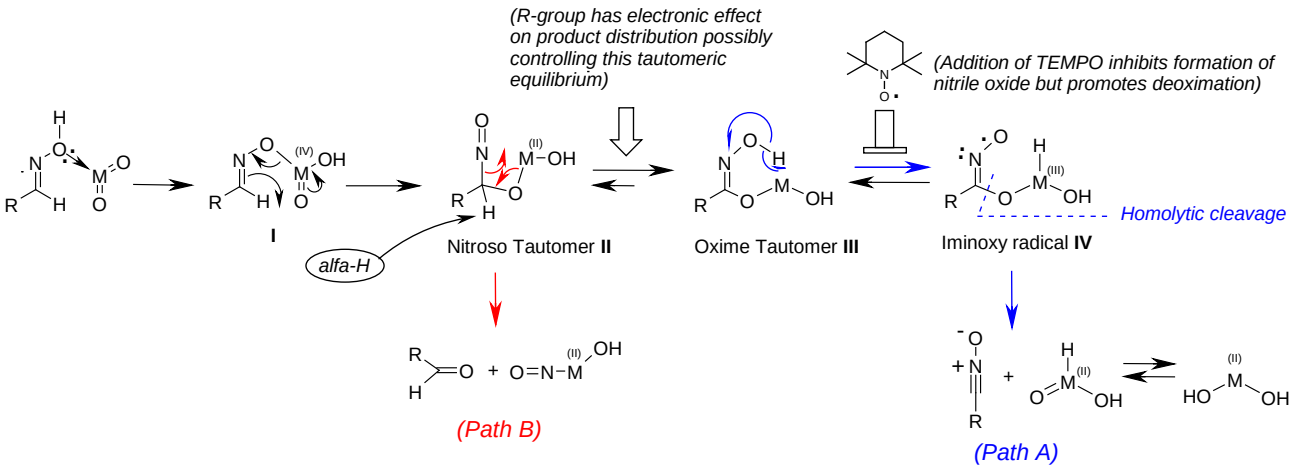


Fig. 1. Diagram to fit facts with MO_2 (M=Mn, Cr).

In absence of direct evidence of TEMPO-adduct of any radical intermediate, precise mechanism of these reactions and structure of the radical intermediate remains unclear. While further mechanistic investigation is beyond our scope, we propose here a putative mechanism for these reactions as depicted in Scheme 3. Interaction of aldoxime on MO_2 surface (heterogeneous!) may lead to formation of a complex structure **I**, which in turn can rearrange to structure **II** as suggested in the literature[10a] for MnO_2 mediated deoximation of oximes into carbonyl compounds. The structure **II**, which is predicted here to be the non-radical common intermediate, as described in Fig. 1, can lead to either deoximation or formation of nitrile oxide. The nitroso intermediate **II** can stay in equilibrium with its oxime tautomeric structure **III**. A hydrogen radical capture from oxime-OH by M(II) in an intramolecular fashion[11] may lead to formation of a high energy radical intermediate **IV**. Such radical intermediate **IV** is a kind of σ-type iminoxy radical, well documented in the literature.[12] The intermediate **IV** would subsequently undergo homolytic cleavage to furnish nitrile oxide and $M(OH)_2$ (Scheme 3, *path A*). In presence of TEMPO, it is possible that an exited-state structure, towards formation of the high energy iminoxy radical **IV** from the oxime tautomeric structure **III**, is quenched. There are literature reports suggesting such a role of TEMPO.[7i–k] Under such condition, the radical generation is slowed down. Therefore, decomposition of the nitroso intermediate **II** becomes a major process resulting into aldehyde as deoximation product (Scheme 3, *path B*).

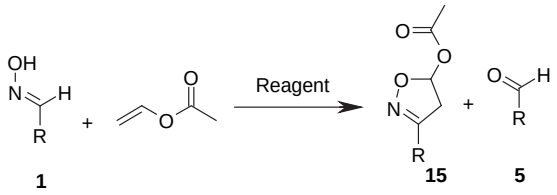
It is fundamental to conceive that an electron-withdrawing group −R attached to α-C of structure **II** could certainly make the α-C−H more labile and therefore shift the equilibrium towards the right (in favour of oxime structure **III**). Thus the present mechanism can also explain why MnO_2 led to exclusive formation of 1,3-DC product from electron deficient aldoxime (e.g., R=−CO_2Me) whereas, aldehydes were the sole products from aliphatic aldoximes (e.g., R=−$C_{11}H_{23}$), as reported by Kiegiel et al.[4a]



Scheme 3. A putative reaction mechanism for MO_2 (M=Cr, Mn) mediated oxidation versus deoximation of aldoximes.

Further support to the proposed mechanism was obtained from a comparative reaction profile between CrO_2 and MnO_2 towards 1,3-DC reaction versus deoximation of electronically tuned aldoximes (results in Table 2). The observed trend of deoximation of aldoximes having various 'R-group' are: aliphatic (Ph–$(CH_2)_2$–; **1d**)>aromatic (Ph–; **1a**)>strong EWG (–CO_2Et; **1c**) for both the CrO_2 and MnO_2 mediated reactions (Table 2, entries 1–6) with the difference that CrO_2 led to significantly lesser deoximation compared to MnO_2. In a controlled study, such differential effect of the 'R-group' was not observed from chloramin-T mediated reactions (Table 2, entries 7–9).

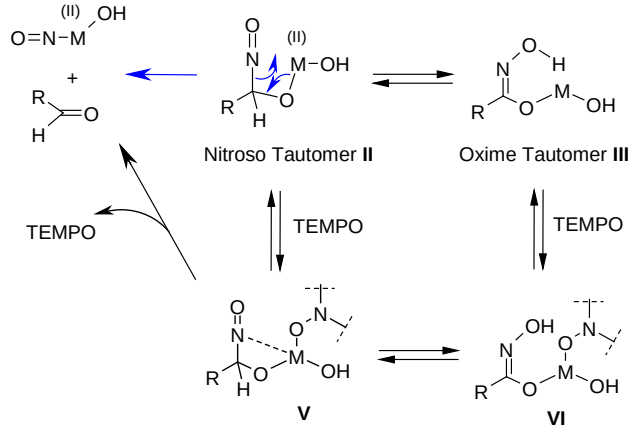
Table 2
Electronic effect on deoximation versus nitrile oxide formation[a]



Entry No.	1	R–	Reagent	Product (% isolated yield)
1	**1a**	Ph–	CrO_2[b]	**15a** (84); **5a** (10)
2	**1c**	–CO_2Et		**15c** (95); —[c]
3	**1d**	–$(CH_2)_2$–Ph		**15d** (75); **5d** (20)
4	**1a**	Ph–	MnO_2[d]	**15a** (42); **5a** (40)
5	**1c**	–CO_2Et		**15c** (84); —[c]
6	**1d**	–$(CH_2)_2$–Ph		**15d** (18); **5d** (80)
7	**1a**	Ph–	Chloramin-T[e]	**15a** (85); —[c]
8	**1c**	–CO_2Et		**15c** (95); —[c]
9	**1d**	–$(CH_2)_2$–Ph		**15d** (75); —[c]

[a] Formation of nitrile oxides was correlated to isolated yields of corresponding 1,3-DC products **15**.
[b] Procedure from Ref. 2a.
[c] No aldehyde observed in TLC and HPLC-MS analysis of the crude reaction mixture.
[d] Procedure from Ref. 4a.
[e] Procedure from Ref. 8b.

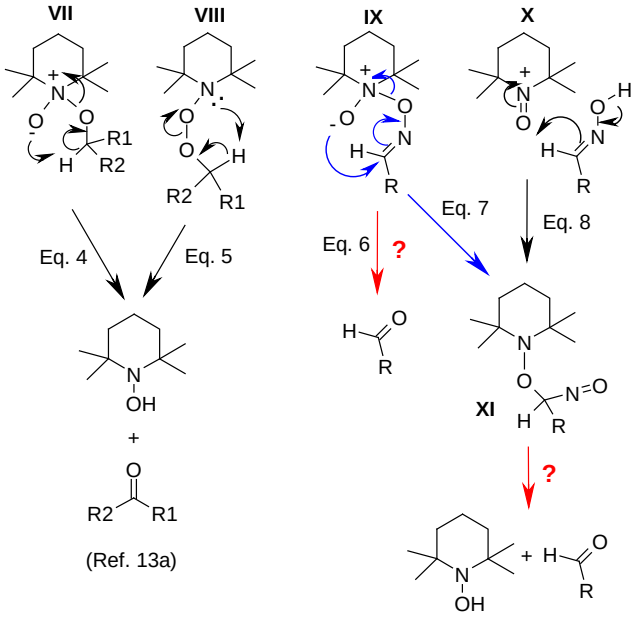
We would also like to put forward the alternative mechanistic possibilities in addition to what has been hypothesized in Scheme 3. In literature, deoximation of oximes to carbonyl compounds have also been reported to proceed via iminoxy radical, however, under photosensitized electron-transfer reaction conditions.[10b] On the contrary, MnO_2 mediated deoximation has been proposed to proceed via non-radical pathway.[10a] Together with the literature reports and our experimental results with TEMPO, we believe that both the MnO_2 and CrO_2 mediated deoximation processes do not involve radical intermediate. However, in presence of TEMPO, deoximation via the proposed nitroso tautomer **II** may not be an exclusive path. As shown in Scheme 4, TEMPO could form adduct through metal centre of both the tautomeric forms **II** and **III** and might facilitate the deoximation process via intermediates like **V** and **VI** in a competitive manner against formation of the iminoxy radical intermediate **IV**. Such a mechanism also accounts why TEMPO mediate deoximation is a faster process (requiring 15 min compared to 2 h for nitrile oxide formation; see Table 1) as well as, why less than 1 equiv of TEMPO was equally effective to promote deoximation.



Scheme 4. TEMPO mediated deoximation, another possibility.

In another consideration, CrO_2 or MnO_2 could also oxidize TEMPO, at least in catalytic quantity, to the corresponding oxoammonium species (T^+), a species known in the literature.[13] As shown in Eq. 4 and 5, in Scheme 5, adducts like **VII** and **VIII** have been proposed in the literature to explain T^+ mediated oxidation of alcohols to carbonyl compounds. However, in light of what is recorded in the literature, a hypothetical oxidative deoximation reaction (Eq. 6) is unlikely from an equivalent adduct structure **IX** derived from aldoxime and T^+. A nitroso intermediate **XI** may be conceived either from **IX** or from an assembly **X** following Eq. 7 and 8 respectively.

Again the structure **XI** is very unlikely to produce aldehyde and regenerate the reduced product of oxoammonium species.



Scheme 5. Feasibility of TEMPO-derived oxoammonium species to promote deoximation.

2.4. Fate of CrO_2, reactivation and recycling

CrO_2 has several unique advantages over many other reagents towards industrial or large scale use. For the reactions discussed in this work, simple decantation of solvent or magnetic retrieval of CrO_2 allowed us complete recovery of the reagent. It has been known in the literature that upon oxidation of substrates, the surface of CrO_2 gets reduced, which can be reactivated by heating in air.[3b] To demonstrate potential for the present CrO_2 methodology towards industrial application, synthesis of **7b**, **8a** and **13** were chosen as examples. Following a typical experimental procedure given for **8a**, we were able to carry out three consecutive reactions upon a recovery, followed by reactivation using simple laboratory condition, and recycling of CrO_2 for each of these examples without losing any significant yield thereof. It was also observed that without the reactivation of CrO_2 the next recycled reaction did not progress, which suggests that the reagent was reduced while aldoximes were oxidized to nitrile oxides.

3. Conclusions

Based on several experimental results (Scheme 2; Table 1, 2) a putative mechanism is derived for CrO_2 and MnO_2 mediated direct oxidation of aldoximes to nitrile oxides. To illustrate the mechanism, initial interaction of either (*E*)- or (*Z*)-aldoximes with MO_2 (M=Cr, Mn) lead to formation of a nitroso-oxime tautomeric pair **II** and **III** as non-radical common intermediates (Scheme 3). The formation of nitrile oxide is proposed to occur from the oxime tautomer **III** via a σ-type iminoxy radical intermediate **IV** (*path A*). The involvement of radical intermediate is evident only for the nitrile oxide formation and not for deoximation process based on the experimental results with TEMPO. The observed deoximation (minor for CrO_2 and occasionally major for MnO_2) is explained through decomposition of nitroso tautomer **II** as previously described by Yoshihara (*path B*). Electronics of the 'R-group' in aldoximes is shown to play a key role in dictating product distribution between nitrile oxide versus aldehyde arguably by influencing on p*K*a of α-C–H in structure **II**. Thus the aldoximes bearing electron-withdrawing groups preferentially yield nitrile oxide. A shift in product formation (from nitrile oxide to aldehyde) in presence of TEMPO is probably due to excited-state quenching phenomena towards generation of the radical intermediate **IV** in presence of the external radical environment. Another possible mechanism of TEMPO mediated deoximation has also been proposed in Scheme 4, which accounts the fact that TEMPO was equally effective when used in less than 1 equiv. Further support to the proposed mechanism was gathered from the facts that neither TEMPO nor the 'R-group' of aldoximes affects the product distribution in chloramine-T mediated reactions (Tables 1 and 2), which are known to proceed via hydroximoyl chloride intermediate and not via direct oxidation of aldoximes. We hope that all these new informations will further drive for a more precise mechanistic study, which is beyond our scope of investigation.

4. Experimental section

4.1. Synthesis of 6a, 7a, 8a, 9a, 10a, 11a

Following the procedure described in our previous communication, the above compounds were synthesized.[2a] Both (*E*) and (*Z*)-benzaldoximes provided us identical results. Analytical data of **6a**,[14] **7a**,[15] **8a**,[16] **9a**[17] and **11a**[8b] were matched with the literature values.

*4.1.1. 3,4-Diphenylfuroxan (**6a**).* R_f value: 0.8 (10% ethyl acetate in hexanes). Mp: 115–117 °C (observed), 114–115 °C (lit.[14b]). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.52–7.63 (aromatics, 6H); 8.17–8.25 (aromatics, 4H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 124.58, 127.25, 127.83 (2C), 128.47(2C), 129.18(2C), 129.42(2C), 131.51, 133.06, 169.26, 176.01. HPLC-MS (*m*/*z*): 239.1 [M+1], 222.9 [(M−16)+1] base peak. HPLC purity: 98%; t_R: 15.21 min.

*4.1.2. 3-Phenylisoxazole-5-carboxylic acid, ethyl ester (**7a**).* R_f value: 0.8 (20% ethyl acetate in hexanes). Mp: 45–46 °C (observed), 47 °C (lit.[15b]). ^{1}H NMR (400 MHz; CD_3OD): δ 1.42 (t, *J*=7.1 Hz, 3H); 4.44 (q, *J*=7.1 Hz, 2H); 7.48–7.51 (aromatics, 3H), 7.54 (s, 1H), 7.88–7.91 (aromatics, 2H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 14.48, 62.63, 107.65, 127.19 (2C), 128.37, 129.41 (2C), 130.86, 157.13, 161.30, 163.28. HPLC-MS (*m*/*z*): 218.0 [M+1]. HPLC purity: 99.1%; t_R: 26.69 min.

*4.1.3. 3,5-Diphenylisoxazole (**8a**).* R_f value: 0.8 (20% ethyl acetate in hexanes). Mp: 141–143 °C (observed), 140–142 °C (lit.[16d]). ^{1}H NMR (400 MHz; $CDCl_3$): δ 6.84 (s, 1H); 7.44–7.52 (aromatics, 6H); 7.84–7.89 (aromatics, 4H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 97.79, 126.14 (2C), 127.12 (2C), 127.78, 129.22 (2C), 129.30 (2C), 129.46, 130.30, 130.51, 163.28, 170.72. HPLC-MS (*m*/*z*): 221.9 [M+1]. HPLC purity: 98.6%; t_R: 30.24 min.

*4.1.4. 3-Phenyl-5-trimethylsilanylisoxazole (**9a**).* R_f value: 0.5 (20% ethyl acetate in hexanes). ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.39 (s, 9H); 6.74 (s, 1H); 7.41–7.48 (aromatics, 3H); 7.82 (dd, *J*=7.8 Hz, 1.9 Hz, 2H). ^{13}C NMR (100 MHz; $CDCl_3$): δ −1.60 (3C), 110.99, 127.33 (2C), 129.15 (2C), 129.55, 129.96, 161.08, 179.08. HPLC-MS (*m*/*z*): 218.3 [M+1]. HPLC purity: 98.3%; t_R: 29.44 min.

*4.1.5. 5-Benzenesulfonyl-3-phenyl-4,5-dihydroisoxazole (**11a**).* R_f value: 0.3 (20% ethyl acetate in hexanes). MP: 135–137 °C (observed), 137–138 °C (lit.[8b]). ^{1}H NMR (400 MHz; DMSO-d_6): δ 3.95 (dd, *J*=18.8 Hz, 4.6 Hz, 1H); 4.03 (dd, *J*=18.8, 10.3 Hz, 1H); 6.13 (dd, *J*=10.3, 4.6 Hz, 1H); 7.41–7.51 (aromatics, 3H), 7.62–7.67 (aromatics, 4H), 7.76 (dt, *J*=7.5 Hz, 1.4 Hz, 1H), 7.93 (dd, *J*=7.2 Hz, 1.5 Hz, 2H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 36.59, 92.87, 127.04 (2C), 127.17, 128.83 (2C),

129.28 (2C), 129.40 (2C), 130.95, 134.62, 135.18, 157.24. HPLC-MS (*m*/*z*): 288.2 [M+1] base peak, 305.2 [M+18]. HPLC purity: 98.2%; t_R: 21.99 min.

*4.1.6. (3-Phenyl-4,5-dihydroisoxazol-5-yl)pyrrolidin-1-yl-methanone (**10a**).* Analytical data were in agreement with its 4-Cl analogue reported[2a] previously. R_f value: 0.5 (40% acetone in hexanes). MP: 115–116 °C (observed). IR (neat): 1649 (amide) cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6): δ 1.77–1.82 (m, 2H); 1.86–1.96 (m, 2H); 3.30–3.34 (m, 2H); 3.51–3.62 (m, 3H); 3.74 (dd, *J*=17.1, 7.3 Hz, 1H); 5.40 (dd, *J*=11.3 Hz, 7.3 Hz, 1H); 7.43–7.47 (aromatics, 3H); 7.69 (dd, *J*=7.6 Hz, 2.2 Hz 2H). ^{13}C NMR (100 MHz; CD_3OD): δ 24.96, 26.98, 38.35, 47.53, 47.77, 79.73, 127.93 (2C), 129.87 (2C), 130.25, 131.48, 158.29, 169.05. HPLC-MS: *m*/*z* 245.3 [M+1] base peak, 489.4 [M_2+1]; purity: 99.8%; t_R: 17.48 min.

4.2. Typical procedure for conducting experiments in presence of TEMPO

4.2.1. For CrO_2 (Table 1, entry 6). Reaction was done following the CrO_2-methodology as described in our previous communication[2a] however in presence of TEMPO. Magtrieve™ (Aldrich cat. No. 480037; CAS no. 12018-01-8; 538 mg, 6.45 mmol, 10 equiv) was added in one portion to a solution of 4-chlorobenzaldoxime **1b** (100 mg, 0.64 mmol, 1.0 equiv), ethyl propiolate (190 mg, 1.93 mmol, 3.0 equiv) and TEMPO (100 mg, 0.64 mmol, 1.0 equiv) in acetonitrile (3.2 mL), and the reaction mixture was stirred under heating at 80 °C. Progress of the reaction was monitored by TLC. In contrast to the previous occasion,[2a] the starting aldoxime **1b** was fully consumed in 15 min of heating in presence of TEMPO. The reaction mixture was filtered through Celite bed. Magtreive™ was washed with ethyl acetate (20 mL×2). The combined filtrate was condensed to obtain the crude. 4-Chlorobenzaldehyde **5b** (81.4 mg, 90%) was isolated as major product after column chromatography (silica gel; ethyl acetate/hexanes) along with essential recovery of TEMPO. Only trace amount of cyloaddition product **7b** could be seen on TLC, which was found to be less than 5 mg after isolation.

4.2.2. For CrO_2 (Table 1, entry 16). To a solution of 2-Allyloxy-5-bromo-benzaldehyde oxime **12** (300 mg, 1.17 mmol, 1.0 equiv) and TEMPO (182.8 mg, 1.17 mmol, 1.0 equiv), in 6.0 mL acetonitrile, Magtrieve™ (984.4 mg, 11.72 mmol, 10 equiv) was added in one portion, and the reaction mixture was stirred under heating at 80 °C. Progress of reaction was monitored by TLC, which indicated consumption of the starting material after 15 min. An aliquot was analyzed by HPLC, which revealed a product distribution of the corresponding aldehyde **14** and TEMPO as major components (75 and 100%, respectively) along with a minor amount of the cycloaddition product **13** (16%), and trace amounts of starting aldoxime **12** (3%) and the corresponding nitrile oxide (6%) in the reaction mixture. There was no other HPLC signal noticed, which could provide an indication of possible TEMPO-adduct. The reaction mixture was filtered through Celite bed and Magtreive™ was washed with ethyl acetate (20 mL×2). The combined filtrate was condensed to get the crude product, which was then purified by silica gel column chromatography (ethyl acetate/hexanes) to isolate pure **14** (198.1 mg, 70%), **13** (36.2 mg, 12%), the corresponding nitrile oxide (8 mg, 3%; characteristic signals IR: 2230 cm^{-1}. ^{13}C NMR: δ 104.4 ppm, mass: *m*/*z* 255.1 (^{79}Br) and 256.9 (^{81}Br) as [M+1]) along with recovery of TEMPO (150 mg, 82%).

4.2.3. For MnO_2 (Table 1, entry 8). Reaction was done following MnO_2-methodology as described in the literature[4a] however in presence of TEMPO. To a solution of 4-chlorobenzaldoxime (100 mg, 0.64 mmol, 1.0 equiv), ethyl propiolate (190 mg, 1.93 mmol, 3.0 equiv) and TEMPO (100 mg, 0.64 mmol, 1.0 equiv) in dichloromethane (5.0 mL), was added MnO_2 (168 mg, 1.93 mmol, 3 equiv) and the reaction mixture was stirred at rt. After every 3 h, additional 3 equiv of MnO_2 was added and the reaction was monitored by checking TLC till 18 equiv of MnO_2 was used up in a total 18 h, when the starting material was fully consumed. The reaction mixture was filtered through Celite bed. MnO_2 was washed with dichloromethane (20 mL×2). The combined filtrate was condensed to obtain the crude product. 4-Chlorobenzaldehyde **5b** (79.4 mg, 88%) was isolated as major product after column chromatography (silica gel; ethyl acetate/hexanes). A trace amount of the cycloaddition product **7b** was observed in TLC, which was found to be less than 5 mg after isolation.

4.2.4. For chloramine-T (Table 1, entry 9). Reaction was done following two different methods as described in the literature.[8] TEMPO was added at different stages of the reaction.

Method A:[8b] chloramine-T trihydrate (99.7 mg, 0.35 mmol, 1.1 equiv) was added to a solution of 4-chlorobenzaldoxime (50 mg, 0.32 mmol, 1.0 equiv) in MeOH (1.5 mL) and was allowed to stir at rt for 10 min. The reaction mixture was concentrated (rotavapor, operated at rt) to remove MeOH, dissolved in diethylether (10 mL), and was washed with 1(N) aq NaOH (10 mL). The organic layer was concentrated (rotavapor, operated at rt) to get 4-chlorobenzonitrile-*N*-oxide (confirmed by the appearance of strong signal at δ 100.93 ppm in ^{13}C NMR), which was then dissolved in dichloromethane (1.5 mL). To this, TEMPO (50.3 mg, 0.32 mmol, 1.0 equiv) and ethyl propiolate (98.4 mg, 0.96 mmol, 3.0 equiv) were added and the reaction mixture was stirred at rt for 2 h (guided by TLC). After a column chromatography (silica gel; ethyl acetate/hexanes) of the crude reaction mixture, the cycloaddition product **7b** was isolated as major product (56.6 mg, 70%) with no indication for the formation of aldehyde **5b** (by TLC and HPLC of the reaction mixture). This experiment ruled out two possible scenario: (i) possibility of TEMPO interfering with the 1,3-DC reaction, (ii) possibility of TEMPO reacting with nitrile oxide.

Method B:[8a] the above reaction was also carried out having added TEMPO from the beginning. Thus, to a solution of 4-chlorobenzaldoxime **1b** (50 mg, 0.32 mmol, 1.0 equiv), ethyl propiolate (98.4 mg, 0.96 mmol, 3.0 equiv) and TEMPO (50.3 mg, 0.32 mmol, 1.0 equiv) in MeOH (1.5 mL), was added chloramine-T trihydrate (99.7 mg, 0.35 mmol, 1.1 equiv) at rt. This reaction mixture was stirred at rt for 10 min (to allow formation of the nitrile oxide), and then diluted with dichloromethane (1.5 mL) before the stirring was continued for 2 h (needed for cycloaddition reaction). Outcome was essentially the same as observed in *Method A*. This result further ruled out the possibility of TEMPO interfering with the formation nitrile oxide in a reaction, that is, known to proceed without involving radical intermediate.

4.2.5. For DIB (Table 1, entry 20). To a solution of 2-Allyloxy-5-bromo-benzaldehyde oxime **12** (100 mg, 0.39 mmol, 1.0 equiv) and TEMPO (60.9 mg, 0.39 mmol, 1.0 equiv), in 8.0 mL CH_2Cl_2, was added DIB (138.4 mg, 0.43 mmol, 1.1 equiv) at 0 °C in one portion. The reaction mixture was stirred at rt for 2 h at which point TLC indicated consumption of the starting material. The reaction mixture was diluted with 20 mL CH_2Cl_2 and then washed with water (20 mL), dried over anhydrous sodium sulfate, and concentrated to obtain the crude product, which was then purified by silica gel column chromatography (ethyl acetate/hexanes) to isolate pure **13** (82.0 mg, 82%). This result further suggests that TEMPO has no effect on DIB mediated oxidation of aldoximes to nitrile oxides. Therefore it is inferred here that the DIB mediated reactions work solely via ionic intermediates as was suggested by Das et al.[9b]

Analytical data of **7b**, **13** and **14** were matched with our previously reported values from authentic samples.[2a]

4.3. Synthesis of 15a, 15c and 15d (Table 2)

As described in Table 2, reported procedures were followed for the respective methodologies using CrO_2, MnO_2 and chloramine-T. Analytical data of **15a**[18] and **15c**[19] were matched with the literature values.

*4.3.1. 3-Phenyl-5-acetoxy-4,5-dihydroisoxazole (**15a**).* R_f value: 0.5 (30% ethyl acetate in hexanes). Mp: 99–100 °C (observed), 98–100 °C (lit.[18a]). IR (neat): 1755 (ester) cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$): δ 2.08 (s, 3H); 3.37 (dd, J=17.9 Hz, 1.2 Hz, 1H); 3.62 (dd, J=17.9 Hz, 6.8 Hz, 1H); 6.84 (dd, J=6.9 Hz, 1.2 Hz, 1H); 7.42–7.48 (aromatics, 3H); 7.70–7.73 (aromatics, 2H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 21.24, 41.61, 96.19, 127.31 (2C), 128.57, 129.13 (2C), 131.07, 157.28, 169.93. HPLC-MS (m/z): 206.1 [M+1], 223.1 [M+18], 228.2 [M+23], 433.1 [M_2+23]. HPLC purity: 99.79%, t_R: 19.22 min.

*4.3.2. 5-Acetoxy-4,5-dihydroisoxazole-3-carboxylic acid, ethyl ester (**15c**).* R_f value: 0.5 (30% ethyl acetate in hexanes). ^1H NMR (400 MHz; $CDCl_3$): δ 1.39 (t, J=7.1 Hz, 3H); 2.09 (s, 3H); 3.24 (dd, J=18.8 Hz, 1.7 Hz, 1H); 3.45 (dd, J=19.1 Hz, 7.3 Hz, 1H); 4.39 (q, J=7.1 Hz, 2H); 6.83 (dd, J=7.3 Hz, 1.7 Hz, 1H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 14.29, 21.03, 40.13, 62.74, 96.77, 152.224, 159.95, 169.38. HPLC-MS (m/z): 202.2 [M+1], 425.1 [M_2+23]. HPLC purity: 97.2%; t_R: 7.62 min.

*4.3.3. 3-(2-Phenylethyl)-5-acetoxy-4,5-dihydroisoxazole (**15d**).* R_f value: 0.6 (20% ethyl acetate in hexanes). IR (neat): 1755 (ester) cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$): δ 2.06 (s, 3H); 2.76 (t, J=8.3 Hz, 2H), 2.81 (d, J=18.0 Hz, 1H); 2.96 (t, J=8.1 Hz, 2H), 3.15 (dd, J=18.0 Hz, 6.8 Hz, 1H); 6.63 (d, J=6.6 Hz, 1H); 7.20–7.26 (aromatics, 3H); 7.28–7.34 (aromatics, 2H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 21.23, 29.19, 32.78, 43.85, 95.57, 126.71, 128.50 (2C), 128.83 (2C), 140.33, 159.10, 169.92. HPLC-MS: m/z 234.2 [M+1], 256.1 [M+23]; purity: 98.5%; t_R: 10.73 min.

4.4. Recycling Magtrieve™ (CrO_2) in synthesis of 8a

To a solution of benzaldoxime (1.0 g, 8.26 mmol, 1.0 equiv) and phenyl acetylene (2.71 mL, 24.79 mmol, 3.0 equiv) in 41 mL acetonitrile, taken in a single neck round bottom flask, was added Magtrieve™ (6.93 g, 82.6 mmol, 10 equiv) and the reaction mixture was heated at 80 °C for 2 h while stirring. The solvent was decanted and Magtreive™ was washed with acetonitrile (50 mL×2). The combined acetonitrile pool was condensed to get a crude product. Whereas, the recovered Magtrieve™ (6.90 g) was sequentially treated with acetonitrile (50 mL) and distilled water (20 mL×2) each at 60 °C for 0.5 h to remove traces of organic materials. Finally the flask containing Magtrieve™ was heated on a sand bath at 320–340 °C for 4 h (air exposed).[3b] Reactivated Magtrieve™, thus obtained, was reused for the synthesis of another crop of **8a**.

The whole process was repeated two more times to get three crops of crude compounds, which were then combined and purified by silica gel column chromatography (EtOAc/hexane) to obtain **8a** in pure form (4.16 g, combined yield 76%).

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