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Efficient oxidation of arylmethylene compounds using nano-MnO_2

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ABSTRACT

Nano-MnO_2 has been developed as an efficient and mild reagent for the high-yield oxidation of arylmethylene compounds to the corresponding aldehydes and ketones as well as benzylic ethers to esters. The reagent is conveniently prepared and shows reactivity superior to synthetic (Attenburrow) MnO_2 and commercial MnO_2 under both microwave and conventional conditions. Typical reactions are performed using 25 wt % of nano-MnO_2 relative to the substrate, and the reagent can be recycled up to six times without significant loss of activity. The observed conversions correlate well with surface-water content in the different MnO_2 samples, as determined by thermogravimetric analysis.

Oxidation of arylmethylene compounds is an important transformation for the synthesis of numerous chemical targets.[1] Although several oxidants are available, most benzylic oxidations to date have employed chromium-based reagents.[2] While effective, these reagents are messy, require (at least) stoichiometric amounts of oxidant, and produce environmentally hazardous chromium residues that demand extensive remediation.[3] Though literature is available on the use of MnO_2 for this transformation, the method suffers drawbacks due to the large quantity of reagent needed (400–4000 wt % or 4- to 40-fold excess by weight). This requirement results in impaired stirring, which leads to low conversion, less convenient product isolation, and significant waste.[4] Since the synthesis of several important natural products including vitamins A (retinol), E (tocopherol), and B_6 (pyridoxal) still rely on MnO_2 for mild oxidation,[5] the development of more efficient, catalytic alternatives is desirable and significant.

In our continuing search for more efficient and mild reagents, we report herein the use of nano-MnO_2, which gives remarkably high performance using catalytic oxidant and allows reusability for up to six cycles. Our preferred synthetic protocol employs nano-MnO_2 in conjunction with microwave heating under solvent-free conditions. The solvent-free option, coupled with the recyclability of the reagent, makes this an attractive alternative from an environmental perspective. Additionally, heterogeneous nano-MnO_2 can also be employed in various solvents with conventional heating. In the current study, various arylmethylene oxidations were accomplished in high yields using 25 wt % of nano-MnO_2 relative to the substrate. The oxidant not only permits conversion of benzylic carbons into aldehydes or ketones, but also offers a direct route from benzylic ethers to esters. [*Note*: Although 25 wt % of the oxidant was used, as little as 10 wt % was effective in many cases.]

The current study reports a comparative study of nano-MnO_2,[6] Attenburrow MnO_2,[7] and commercial MnO_2 for arylmethylene oxidations. Preparation of Attenburrow MnO_2, the most commonly used MnO_2 oxidant, involves reaction of $KMnO_4$ with $MnCl_2{\cdot}2H_2O$ in the presence of 40% NaOH and requires a tedious filtration and washing sequence to remove excess base and permanganate.[7] Nano-MnO_2, on the other hand, is prepared under neutral sonication conditions from $KMnO_4$ and D-glucose in water containing a small amount of PEG-600.[6] Though filtration is also necessary for the isolation of nano-MnO_2, this process is far easier than that required for Attenburrow MnO_2 and eliminates the potential for residual base and permanganate in the final reagent. Scanning electron microscopy confirmed the previously reported nanoparticulate morphology of this MnO_2.[6]

The reactions were performed using microwave heating without solvent and conventional heating with solvent. In the microwave procedure, the reactants were mixed thoroughly with 25 wt % of MnO_2 and heated at 105 °C[8] for 150–240 s to give high yields of the desired products. The same microwave procedure using Attenburrow or commercial MnO_2 (25 wt %) generally gave significantly lower conversions. To optimize the conventional conditions with nano-MnO_2, toluene (**1a**) was oxidized to benzaldehyde (**2a**) in anhydrous EtOH, CH_2Cl_2, $CHCl_3$, THF, CH_3CN, C_6H_6, and DMF using 25 wt % of the oxidant. Maximum conversions (78–84%) were achieved using THF at 67 °C or DMF at 80 °C for 6–24 h. Both methods afforded clean products that were conveniently isolated. Microwave reactions required cooling, addition

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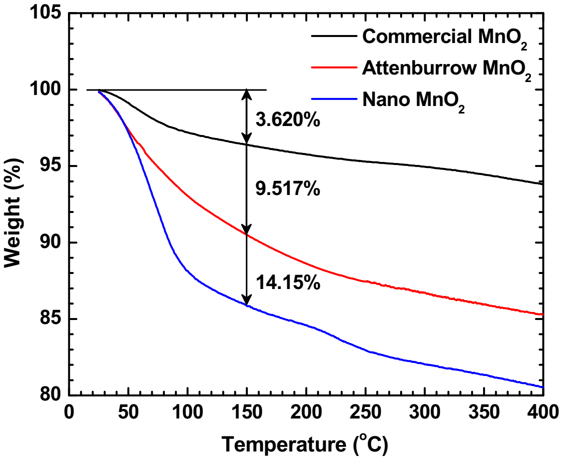


Figure 1. TGA results for MnO_2 samples.

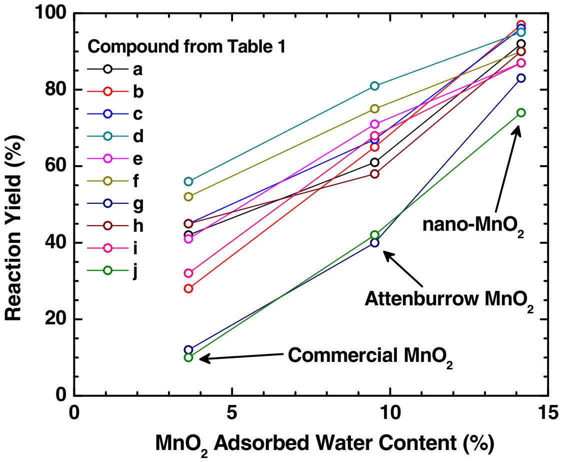


Figure 2. Correlation of MnO_2 surface-bound water with reactivity.

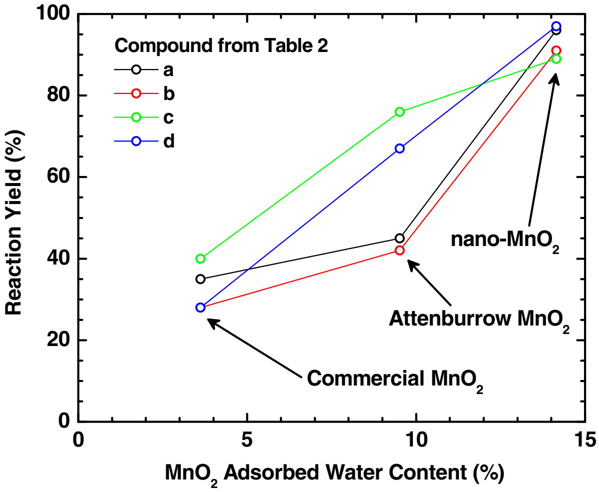


Figure 3. Correlation of MnO_2 surface-bound water with reactivity.

of ether or ethyl acetate, filtration to remove the MnO_2, and concentration. Conventional reactions in THF followed essentially the same product isolation sequence, while reactions in DMF required an extractive work-up. Following filtration, the MnO_2 was easily regenerated and reused (see below).

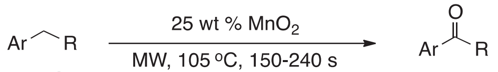
The observation that this reaction requires as little as 10 wt % of nano-MnO_2 in anhydrous solvent under inert atmosphere is interesting, since Attenburrow and commercial MnO_2 generally require 1000 wt % (10-fold excess by weight) of reagent for similar oxidations.[4] There is not sufficient oxygen in this quantity of MnO_2 to effect the oxidation, and thus, other oxygen sources may be important. Since the reactions are performed under argon or nitrogen, atmospheric oxygen does not play a role. However, another possible source of oxygen may be water associated with the oxidant. Indeed, surface-bound water content, measured by thermogravimetric analysis (TGA),[9] was found to closely correlate with the activity of the reagent. The nano-MnO_2 showed a mass loss of 14.2% over a temperature range of 100–150 °C, while the Attenburrow and commercial MnO_2 samples registered mass losses of 9.5%[10] and 3.6%, respectively (see Fig. 1). These results proved highly reproducible, even with different batches of the prepared (nano and Attenburrow) reagents. Thus, due to its greater porosity and surface area, nano-MnO_2 retains more adsorbed water and exhibits greater reactivity than the Attenburrow and commercial MnO_2 (see Figs. 2 and 3). This surface water, while relatively easily lost at 100–150 °C, is only slowly desorbed upon storage at 90 °C as the prepared reagent retains its potency even after 4–6 months at this temperature. Only after 8–10 months at this temperature is a gradual decrease in reactivity observed. The TGA experiments also showed a further decrease in mass upon heating from 150 to 400 °C. This reduction in mass occurs more slowly and corresponds to the loss of structural water from the MnO_2, as has been previously reported.[11] Finally, regeneration of the nano-MnO_2 involves washing with 1 M HCl, 1 M NaOH, and water to remove residual organic material followed by drying at 90 °C for 12 h. Assuming minimal degradation of the nano-MnO_2 structure during reaction, this treatment would replace much of the water adsorbed on the reagent.[12] A more extensive study of the properties and the morphological changes that occur upon repeated use of nano-MnO_2 is currently underway and will be reported in due course.

The results of our optimized MnO_2 oxidations on a series of arylmethylene substrates under both microwave and conventional conditions are summarized in Table 1. All oxidations proceeded in excellent yields[13–15] except for the reaction to form **2c**, where (*E*/*Z*)-1-phenyl-1-propene failed to react. In this case, cinnamyl alcohol (**1c**) was employed as the substrate, which further established the potential utility and efficiency of nano-MnO_2 as a mild oxidant for benzylic and allylic alcohols. For reactions involving volatile substrates (bp <200 °C, e.g., **1a**, **1b**, **1e**, and **3a**, **3b**), the oxidation was facilitated by pre-adsorption of the substrate onto neutral alumina. Additionally, reactants having two benzylic sites (e.g., **1e**, **1f**, and **1h**) were observed to give only a single oxidation as has been previously observed with chromium-based reagents.[16] Presumably, the presence of electron-withdrawing groups on the aromatic ring deactivates other benzylic positions toward oxidation, even when not in conjugation with the electron-withdrawing group. This was confirmed by attempted oxidation of 2-nitrotoluene as well as 2-, 3-, and 4-methylacetophenone, all of which were unreactive toward nano-MnO_2.

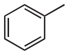
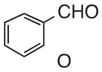
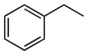
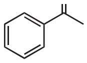
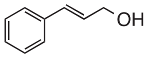
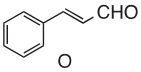
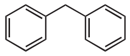
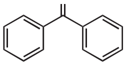
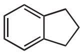
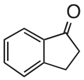
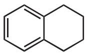
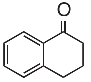
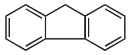
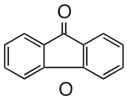
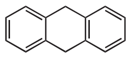
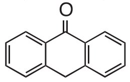
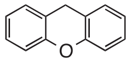
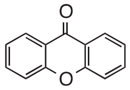
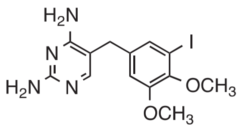
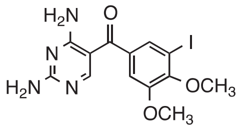
Finally, the reaction of **1j** highlights the mild conditions of the current process. This reaction proceeded smoothly to give the oxidized product in 74% yield with no degradation of the 2,4-diaminopyrimidine or the dimethoxy-substituted aromatic ring. Compound **1j** is a key intermediate in the synthesis of drug candidates currently being investigated for activity against *Bacillus anthracis*[17] and multi-resistant *Staphylococcus aureus*.[18] A similar transformation has been previously reported on a related derivative using MnO_2 (source not reported) in yields of 56% and 65%.[19]

Table 1

Arylmethylene oxidations using nano-, Attenburrow and commercial MnO_2



1a-j 2a-j

	Substrate **1**	Product **2**	Yield (%)[a,b]		
			A[c]	B[c]	C[c]
a			92 (95)	61	42
b			97[d] (94)	65[d]	28[d]
c			96[e] (88)	67	45
d			95 (91)	81	56
e			87 (88)	71	41
f			90 (87)	75	52
g			83 (88)	40	12
h			90 (87)	58	45
i			87 (84)	68	32
j			74 (70)	42	10

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[a] The product spectra matched those in Ref. 14.

[b] A: nano-MnO_2; B: Attenburrow MnO_2; C: commercial MnO_2.

[c] Yields refer to reactions without solvent at 105 °C for 150–240 s. Yields in parenthesis refer to reactions performed under conventional conditions in dry DMF at 80 °C for 6–24 h.

[d] The reactant was adsorbed onto neutral alumina prior to MW reactions.

[e] Attempts to directly oxidize (*E*,*Z*)-1-phenyl-1-propene gave no reaction.

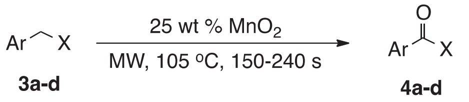
Table 2 shows the oxidation results for several benzylic ethers and amines. Ethers **3a**–**3c** were successfully oxidized to the corresponding esters, revealing a potentially useful ether to ester conversion. Furthermore, for the unsymmetrical substrate **3c**, selectivity was observed for oxidation to the conjugated ester rather than the ketone. We also attempted the oxidation of tetrahydroisoquinoline (**3d**) using nano-MnO_2. Interestingly, when exposed to nano-MnO_2, this substrate underwent aromatization to afford isoquinoline as the only product in nearly quantitative yield;[20] none of the expected lactam was produced. Thus, for oxygen, which is normally divalent, oxidation occurs at the adjacent benzylic position to give the ester, while nitrogen can accommodate the additional bond required for aromatization.

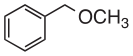
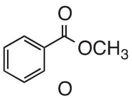
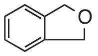
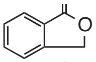
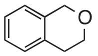
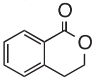
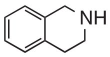
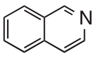
In summary, we have developed an efficient protocol for the conversion of arylmethylene compounds into aryl ketones and aldehydes as well as benzylic ethers to esters using nano-MnO_2. The process is highly efficient compared to earlier methods and requires only catalytic quantities (generally 25 wt %) under microwave or conventional heating conditions. The reactive nature of the oxidant coupled with a solvent-free procedure and its recyclability allows arylmethylene oxidation reactions to proceed in higher yields with simple work-up and less waste.

Acknowledgments

C.F. wishes to thank the Oklahoma State University for support in the form of a Niblack Scholarship. Funding for the 300 MHz NMR spectrometer of the Oklahoma Statewide Shared NMR facility was provided by NSF (BIR-9512269), the Oklahoma State Regents for Higher Education, the W. M. Keck Foundation, and Conco, Inc. The authors are also indebted to Professor Frank Blum for allowing them to use his TGA instrument. Finally, the authors wish to express their appreciation to the OSU College of Arts and Sciences for funds to upgrade our departmental FT-IR instruments.

Table 2
Oxidation of benzylic ethers and amines using nano-, Attenburrow, and commercial MnO_2



	Substrate **3**	Product **4**	Yield (%)[a,b]		
			A[c]	B[c]	C[c]
a			96[d] (92)	45[d]	35[d]
b			91 (90)	42	28
c			89 (92)	76	40
d			97 (92)	67	28

[a] The product spectra matched those in Ref. 14.

[b] A: nano-MnO_2; B: Attenburrow MnO_2; C: commercial MnO_2.

[c] Yields refer to reactions performed under MW conditions without solvent at 105 °C for 150–240 s. Yields in parenthesis refer to reactions performed under conventional conditions in DMF at 80 °C for 6–24 h.

[d] The reactant was adsorbed onto neutral alumina prior to MW reaction.

Supplementary data

Supplementary data (general experimental details, procedures for the preparation and regeneration of nano-MnO_2, a deactivation profile for recycled nano-MnO_2 and ^1H and ^{13}C NMR spectral data for **2j**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.009.

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8. The temperature on the microwave oven was set at 105 °C, but due to the small quantities used and the design of the temperature probe holder assembly, the sensor did not actually contact the reactants. The temperature measured just above the reaction mixture, however, never exceeded 90 °C.
9. The TGA experiments were performed on synthetic MnO_2 samples prepared according to the literature procedures followed by drying at 90 °C and 1 atm for 1 week. Commercial MnO_2 was also dried at 90 °C and 1 atm for 1 week.
10. This reagent has been previously reported to contain 3–4% of firmly bound water, see Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons: New York, 1967.
11. Khan, Y.; Durrani, S. K.; Mehmood, M.; Khan, M. R. *J. Mater. Res.* **2011**, *26*, 2268–2275.
12. For optimum activity, the water must be adsorbed to the oxidant prior to the reaction. Control experiments revealed that addition of small quantities of water to reactions using Attenburrow and commercial MnO_2 did not improve the reaction yields.
13. *Oxidations under microwave conditions*: To a Greenchem Plus glass microwave reactor tube were added the arylmethylene substrate (**1** or **3**) and 25 wt % of nano-MnO_2. The tube was flushed with argon and sealed using a Teflon cap. The sample was placed inside a CEM (Mars Model 230/60) microwave unit and irradiated at 400 W and 105 °C for 150–240 s.[8] The resulting mixture was cooled, diluted with 30 mL of ether (ethyl acetate for **2j**), filtered, and concentrated. The crude product was purified on a silica gel column eluted with increasing concentrations of ethyl acetate in hexanes to give the pure carbonyl compound. *Note*: In the oxidations of **1a**, **1b**, **1e** and **3a**, **3b**, the compounds were pre-adsorbed onto neutral alumina prior to microwave heating due to the volatility of the substrates.
    Oxidations under conventional conditions: To a stirred solution of the arylmethylene substrate (**1** or **3**) in THF, 25 wt % of MnO_2 was added and the reaction mixture was heated under reflux for 6–24 h until TLC indicated complete consumption of the starting material. The crude reaction mixture was filtered and washed with ethyl acetate, then dried with $MgSO_4$, filtered, and concentrated under vacuum. Purification by column chromatography afforded analytical samples of the aldehyde or ketone products. The products were identified by comparison with known spectra.[14] *Note*: The same reactions were performed in DMF at 80 °C for 6–24 h. For these reactions, the MnO_2 was removed by filtration and the filtrate was added to ice-cold water. The resulting aqueous mixture was extracted with ethyl acetate (3×10 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under vacuum to give the desired product.
14. Compounds were characterized by comparison with known spectra, see Pouchert, C. J.; Behnke, J. *The Aldrich Library of ^{13}C and ^1H FT NMR Spectra*, 1st ed.; Aldrich Chemical Co., 1993. Compound, Volume, Spectra Number: **2a**, 2, 932B; **2b**, 2, 802A; **2c**, 2, 926C; **2d**, 2, 884C; **2e**, 808C; **2f**, 810C; **2g**, 2, 903B; **2h**, 2, 903C; **2i**, 2, 921A **2j**, see Supplementary data; **3a**, 2, 1240A; **3b**, 2, 1306C; **3c**, see Ref. 15; **3d**, 3,456B.
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