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Proceeding Paper

Comparative Study of Eco-Friendly Methoximation of Aldehydes and Ketones Using $MnCl_2.4H_2O$ and $CeCl_3.7H_2O$ as Catalysts [†]

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Abstract: Methoximes are a special group among oxime ethers; they are notoriously the most widely used oxime derivatives both, in chemical synthesis and in the pharmaceutical industry. For this reason, there is an interest in the synthesis of such compounds. More than 20 reactions were carried out with different aldehydes and ketones. Those under Mn(II) promotion proceeded generally in shorter reaction times and in some cases, even better yields were obtained when compared to the cerium-based catalysis. This is also advantageous, since manganese salts represent an even greener and inexpensive alternative, because manganese is of great abundance on Earth.

Keywords: methoximation; eco-friendly transformation; $MnCl_2$-promoted reaction

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1. Introduction

Oximation is a very efficient strategy for the derivatization of aldehydes and ketones. Theoretically and practically, the synthesis of methoximes is an important process in carbonyl chemistry [1]. Methoximation has been used for characterization and purification of carbonyl compounds, for the protection or activation of carbonyl groups in multistep synthesis, [2–5] as well as for C–H bond activation, Heck-type reactions, N–O bond cleavage/C–N bond formation, O–H bond cleavage and couplings [6].

Methoximes are also useful synthetic intermediates and many relevant compounds display this group as its characteristic motif. Many methoxime derivatives, such as **1** [7], the pesticide **2** [8] the fungicidal **3** [9], the antibacterial **4** [10], and the antiproliferative agent **5** [11] are found in patents. They have also been prepared as enzyme inhibitors (**6**, **7**) [12,13], antiparasitic agents (**8**) [14], prodrugs (**9**, anticonvulsant) [15], and receptor agonists (**10**) [16]. In addition, several methoxime derivatives are being currently marketed, such as moxidectin [17].

A variety of carbonyl substrates, including aliphatic, aromatic and heterocyclic have hitherto been subjected to methoximation. In view of this situation, developing a straightforward and practical catalytic system for the methoximation of aromatic aldehydes and ketones is desirable, especially in view that in a recent review it was pointed out that the metal-mediated oximation of carbonyl derivatives has been scarcely reported, being "still-uncommon" and that "the synthetic potential of many of these approaches is not high" [18].

We have recently shown that the methoximation of aldehydes and ketones can be accelerated by various Lewis acids, highlighting $CeCl_3.7H_2O$ as a suitable promoter, being efficient under mild conditions [19].

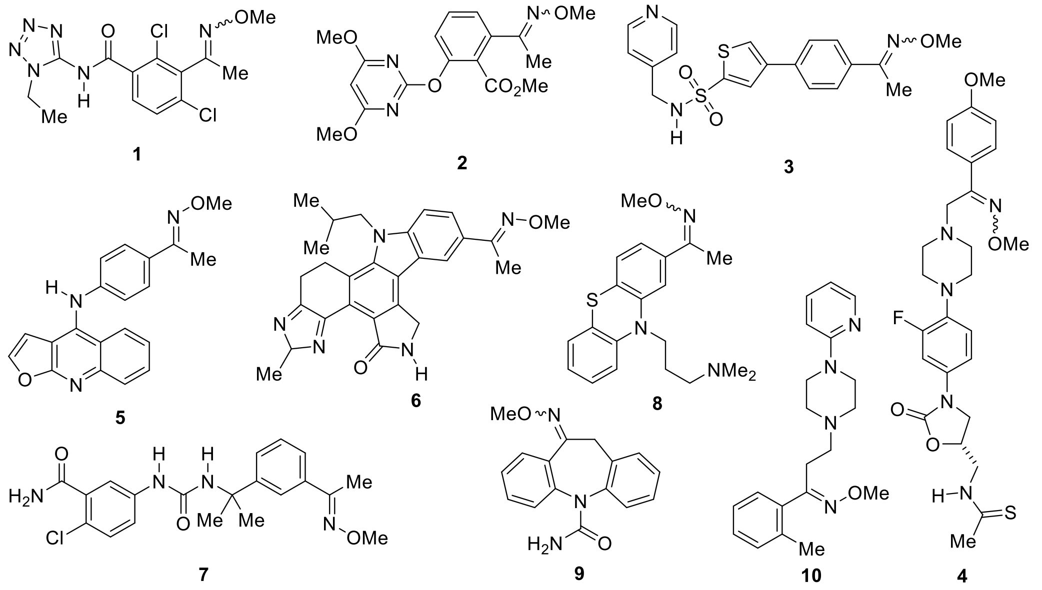


Figure 1. Selection of relevant bioactive methoxime derivatives.

During this study, we also observed that manganese salts [$Mn(OAc)_3{\cdot}2H_2O$, $MnSO_4{\cdot}4H_2O$, $MnCl_2{\cdot}4H_2O$] were able to accelerate the methoximation of a model ketone, with the chloride salt exhibiting the best performance [19]. Since manganese is the third most abundant transition metal in the Earth's crust, and it is environmentally benign, its derivatives are particularly attractive, because of their low cost and low toxicity, compared to other transition metals [20,21].

Taking into account our interest in the development of simple, efficient and eco-conscious transformations and synthetic procedures [22–24], we decided to make a comparison between the performances of the methoximation reaction under $MnCl_2.4H_2O$ [25] and $CeCl_3.7H_2O$ [19] catalysis.

2. Results and Discussion

At the outset of the investigation, initial conditions for the transformation were defined based on our experience. The suitability of the different alternatives were confirmed, monitoring by TLC (run every 10 min) the time required for complete consumption of the starting material.

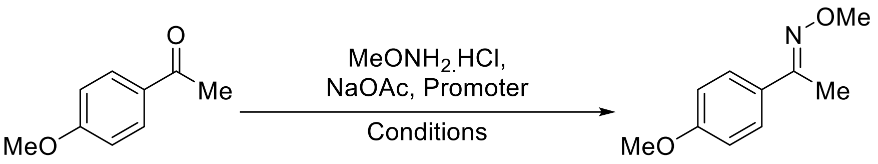
The reaction temperature was set at 50 °C, as it is a suitable reaction condition, still mild compared to methods that require solvent reflux. NaOAc was employed as base to remove HCl and set free the methoxylamine. The anhydrous form of the salt was used for the experiments. NaOAc is a GRAS (Generally Regarded as Safe) substance, which helps to fulfil our aim of process eco-friendliness [26,27]. We also observed that the presence of small amounts of H_2O did not hinder the transformation under $CeCl_3$ catalysis (entry 13 and 14), but it seemed to slightly lower the reaction rate. Therefore, the hydrated salts were used in both cases.

As shown in Table 1, when the reactions were performed in absolute EtOH, it was observed that in the absence of promoter, the starting ketone was not fully consumed even after 120 min (entry 1). Considering that the catalytic ability of simple manganous salts also depends on the counterion [28,29], the effect of 5 mol% of different manganous salts such as the sulfate (entry 2), acetate (entry 3), perchlorate (entry 4) and $MnCl_2.4H_2O$ (entry 5), was examined. Even though it may be argued that addition of NaOAc to the reaction may afford $Mn(OAc)_2$, it was found that the transformation was most efficient in the presence of $MnCl_2.4H_2O$, resulting in complete consumption of the starting ketone in only 30 min (entry 5 vs. entry 3). Therefore, the latter was employed for further studies. $MnCl_2.4H_2O$ is also a GRAS substance [26]. The salt is a mild and moisture compatible

Lewis acid, suitable for use in protic solvents, that has been rather scarcely used in organic chemistry.

Considering that the transformation proceeds optimally in alcoholic media, the performances of MeOH (Entry 6 and 7), and 2-PrOH (Entry 8 and 9) were compared against the use of EtOH (Entry 5 and 12). It was verified that in the latter case the reaction was completed in 30 min, whereas the transformation was slower in the other media, not reaching completeness even after 75 min. This observation enabled to conclude that EtOH should be the solvent of choice.

Table 1. Optimization of the reaction conditions.



Entry N°	Solvent	Promoter (5 mol%)	Temperature (°C)	Time (min) [a]
1	EtOH	-	50	>120
2	EtOH	$MnSO_4.H_2O$	50	45
3	EtOH	$Mn(OAc)_2.4H_2O$	50	60
4	EtOH	$Mn(ClO_4)_2.6H_2O$	50	60
5	EtOH	$MnCl_2.4H_2O$	50	30
6	MeOH	$CeCl_3.7H_2O$	50	>50
7	MeOH	$MnCl_2.4H_2O$	50	>75
8	2-PrOH	$MnCl_2.4H_2O$	50	>75
9	2-PrOH	$CeCl_3.7H_2O$	50	>50
10	EtOH	$MnCl_2.4H_2O$	27	>60
11	EtOH	$MnCl_2.4H_2O$	40	50
12	EtOH	$CeCl_3.7H_2O$	50	30
13	EtOH 96%	$CeCl_3.7H_2O$	50	30
14	EtOH 80%	$CeCl_3.7H_2O$	50	40

[a] Time to achieve complete consumption of the starting material, according to the TLC.

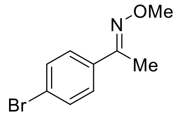
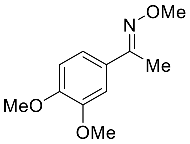
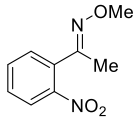
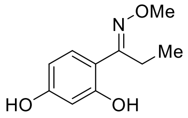
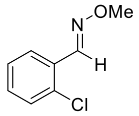
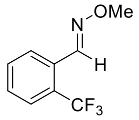
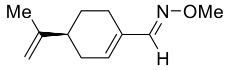
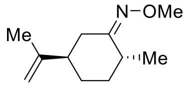
Once the optimal reaction conditions were established, the scope of the method was examined, by subjecting to methoximation various aldehydes and ketones, with different steric and electronic characteristics.

In general, it was observed that the transformation was efficient with aldehydes and ketones, generally proceeding with a yield greater than 75%. Aldehydes were more reactive than ketones, and reactions were generally completed in less than 5 min. Besides, the process showed to be insensitive to steric effects, since the yields of the methoximes of *ortho*-substituted aldehydes or those carrying additional functionalities in other positions were similar enough to the derivatives of aldehydes lacking *ortho* substituents. On the other hand, the results appeared to show that ketones lacking an *ortho* substituent gave the corresponding products in about 15-30 min, while some of their congeners that had an *ortho*-carbonyl functionalization reacted at a rate that depended on the nature of the substituent.

Curiously, in most cases, the signals of *E*/*Z* (*anti*/*syn*) mixtures of methoximes (with one of them clearly predominant) were easily visible in the NMR spectra of the compounds. Nevertheless, unfortunately, these mixtures could not be separated by column chromatography.

With all the acquired data, a comparison was made between the performances obtained with $CeCl_3.7H_2O$ and $MnCl_2.4H_2O$ as catalysts (Table 2). It was carried out on a set of eight compounds, including aromatic aldehydes and ketones, as well as a pair of alicyclic derivatives.

Table 2. Comparative performance of $CeCl_3.7H_2O$ and $MnCl_2.4H_2O$ as catalysts for the methoximation of aldehydes and ketones.

Entry N°	**Compound**	**$CeCl_3.7H_2O$**		**$MnCl_2.4H_2O$**	
		Time (min)	**Yield (%)**	**Time (min)**	**Yield (%)**
1		40	80	20	93
2		60	84	18	96
3		1080	98	360	89
4		1080[a]	89	2100	86
5		40	92	5	97
6		24	88	5	68
7		36	79	15	80
8		24	96	35	81

[a] The reaction was incomplete at the time.

The analysis revealed that $MnCl_2.4H_2O$ showed a performance at least similar and often even superior to that of the cerium (III) salt, and that it can conveniently act as its alternative or substitute of the latter under analogous reaction conditions. Furthermore, it is highly advantageous that the manganese (II) salt is easily available and less expensive than $CeCl_3$. $7H_2O$.

3. Experimental Section

3.1. General Experimental Details

The reactions were executed with oven-dried glassware and freshly distilled anhydrous solvents. The reactions were monitored by TLC, where the spots were detected by exposure to 254 nm UV light, and by spraying with ethanolic *p*-anisaldehyde/H_2SO_4. All new compounds gave single spots on TLC plates run in different solvent systems. The flash column chromatographies were run with silica gel 60 H (particle size 63–200 μm), eluting under positive pressure with hexane-EtOAc mixtures, and employing gradient of solvent polarity techniques.

The NMR spectra were recorded on a Bruker Avance 300 spectrometer (300.13 MHz for ^1H and 75.48 MHz for ^{13}C). The melting points (uncorrected) were measured on an

Ernst Leitz Wetzlar model 350 hot-stage microscope. The FT-IR spectra were acquired with a Shimadzu Prestige 21 spectrophotometer, with the samples as solid dispersions in KBr disks or as thin films held between NaCl. High-resolution mass spectra were obtained from UMYMFOR (Buenos Aires, Argentina) with a Bruker MicroTOF-Q II instrument. Detection of the ions was performed in ESI+ mode.

3.2. Compound Characterization

3.2.1. (E)-2-Bromo-5-methoxybenzaldehyde O-Methyloxime

Yellow oil; yield: 87%. IR (film, υ̃): 3003, 2963, 2936, 2899, 2833, 2818, 1591, 1564, 1464, 1418, 1404, 1348, 1292, 1273, 1233, 1171, 1061, 1047, 1016 and 910 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.41 (1H, s, H-1), 7.42 (1H, d, *J* = 8.9, H-6′), 7.39 (1H, d, *J* = 3.1, H-3′), 6.81 (1H, dd, *J* = 3.1 and 8.8, H-4′), 4.00 (3H, s, N-OMe) and 3.83 (3H, s, OMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9 (C-5′), 148.0 (C-1), 133.7 (C-3′), 132.1 (C-1′), 118.5 (C-4′), 114.6 (C-2′), 111.2 (C-6′), 62.3 (N-OMe) and 55.6 (OMe). HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd. for $C_9H_{11}BrNO_2$: 243.9968; found: 243.9970.

3.2.2. (E)-1-(3,4-Dimethoxyphenyl)ethan-1-one O-Methyloxime

White solid; yield: 96%; mp 58–59 °C. IR (KBr, υ̃): 2961, 1576, 1516, 1464, 1416, 1339, 1277, 1252, 1231, 1175, 1150, 1045, 1020, 918, 866 and 812 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (1H, d, *J* = 2.0, H-2′), 7.14 (1H, dd, *J* = 2.1 and 8.4, H-6′), 6.85 (1H, d, *J* = 8.5, H-5′), 3.99 (3H, s, N-OMe), 3.93 (3H, s, 4′-OMe*), 3.90 (3H, s, 3′-OMe*) and 2.21 (3H, s, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.2 (N-OMe), 150.0 (C-4′), 148.9 (C-3′), 129.4 (C-1′), 119.1 (C-6′), 110.6 (C-5′), 108.6 (C-2′), 61.8 (N-OMe), 55.9 (3′-OMe and 4′-OMe) and 12.5 (C-2).

4. Conclusions

We carried out a comparative study between $MnCl_2.4H_2O$ and $CeCl_3.7H_2O$ as promoters of the methoximation of aromatic aldehydes and ketones, which revealed that using $MnCl_2.4H_2O$ results in equal or better yields and shorter reaction times compared to $CeCl_3.7H_2O$. The transformation, which is of considerable substrate scope, features low catalyst loading, proceeds without the use of an external ligand and illustrates a unique catalytic use, recently reported by us [25], of manganese salts for derivatization of carbonyl compounds under mild conditions, when so far this transformation has been carried out under generally harsher conditions.

Although catalysis with $MnCl_2.4H_2O$ has been shown to be barely outperformed in some cases, both approaches are promising and complementary, as the use of excess reagents or more expensive or even toxic additives is avoided.

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References

1. Mirjafary, Z.; Abdoli, M.; Saeidian, H.; Boroon, S.; Kakanejadifard, A. Oxime ethers as versatile precursors in organic synthesis: A review. *RSC Adv.* **2015**, *5*, 79361–79384, doi:10.1039/c5ra15299b.
2. Vargas, D.F.; Larghi, E.L.; Kaufman, T.S. The 6π-azaelectrocyclization of azatrienes. Synthetic applications in natural products, bioactive heterocycles, and related fields. *Nat. Prod. Rep.* **2019**, *36*, 354–401, doi:10.1039/c8np00014j.
3. Kaufman, T.S.; Bracca, A.B.J.; Cortés, I.; Etichetti, C.M.B.; Girardini, J.E. Total Synthesis and Cytotoxic Activity of 6,8-Dimethoxy-1,3-dimethylisoquinoline Isolated from Ancistrocladus tectorius: A 6π-Azaelectrocyclization Approach. *Synthesis* **2018**, *51*, 433–440, doi:10.1055/s-0037-1610276.
4. Fonzo, S.; Vargas, D.F.; Kaufman, T.S. A Ruthenium-Catalyzed C–H Activation Strategy as an Efficient Shortcut in the Total Synthesis of 6,8-Dimethoxy-1,3-dimethylisoquinoline. *Synthesis* **2019**, *51*, 3908–3914, doi:10.1055/s-0037-1610720.
5. Vargas, D.F.; Larghi, E.L.; Kaufman, T.S. First total synthesis of ampullosine, a unique isoquinoline alkaloid isolated from Sepedonium ampullosporum, and of the related permethylampullosine. *RSC Adv.* **2019**, *9*, 33096–33106, doi:10.1039/c9ra06839b.
6. Li, J.; Hu, Y.; Zhang, D.; Liu, Q.; Dong, Y.; Liu, H. Transition Metal-Catalyzed Reactions Involving Oximes. *Adv. Synth. Catal.* **2017**, *359*, 710–771, doi:10.1002/adsc.201600807.
7. Waldraff, C.; Braun, R.; Dietrich, H.; Gatzweiler, E.; Rosinger, C. Substituted Ketoxime Benzoylamides. US20180235224A1, 2018.
8. Ikeuchi, T.; Ohkawa, T.; Ohno, S.; Kawasaki, H.; Hanai, R.; Ogawa, Y.; Fujinami, M. Agricultural Chemical Composition. EP1776863A4, 2007.
9. Lohmann, J.K.; Grammenos, W.; Puhl, M.; Dietz, J.; Mueller, B.; Rheinheimer, J.; Renner, J. Thiophene-Sulfonic Acid Picolyl Amides. WO2008022937A1, 2008.
10. Ramachandran, U.; Guha, M.; Tadiparthi, R.; Prabhu, G.; Vadarevu, V.; Pushpan, S.; Anantharaman, V.; Subramanian, S.; Solanki, S.; Samuel, M.; et al. Novel Oxazolidinone Derivatives. WO2008010070A2, 2008.
11. Tzeng, C.C.; Chen, Y.L.; Chen, Y.W.; Lu, P.J. 4-Anilinofuro [2,3-b]Quinoline Derivatives, Their Preparation Processes, and Pharmaceutical Compositions Comprising the Same. WO2012102965A1, 2012.
12. Gorla, S.K.; Kavitha, M.; Zhang, M.; Liu, X.; Sharling, L.; Gollapalli, D.R.; Striepen, B.; Hedstrom, L.; Cuny, G.D. Selective and Potent Urea Inhibitors of Cryptosporidium parvum Inosine 5′-Monophosphate Dehydrogenase. *J. Med. Chem.* **2012**, *55*, 7759–7771, doi:10.1021/jm3007917.
13. Bhardwaj, Y.R.; Pareek, A.; Jain, V.; Kishore, D. Chemical delivery systems and soft drugs: Retrometabolic approaches of drug design. *Saudi Pharm. J.* **2014**, *22*, 290–302, doi:10.1016/j.jsps.2013.04.004.
14. Chan, C.; Yin, H.; Garforth, J.; McKie, J.H.; Jaouhari, R.; Speers, P.; Douglas, K.T.; Rock, P.J.; Yardley, V.; Croft, S.L.; et al. Phenothiazine Inhibitors of Trypanothione Reductase as Potential Antitrypanosomal and Antileishmanial Drugs. *J. Med. Chem.* **1998**, *41*, 148–156, doi:10.1021/jm960814j.
15. Learmonth, D.A.; Benes, J.; Parada, A.; Hainzl, D.; Beliaev, A.; Bonifácio, M.J.; Matias, P.M.; Carrondo, M.A.; Garrett, J.; Soares-Da-Silva, P. Synthesis, anticonvulsant properties and pharmacokinetic profile of novel 10,11-dihydro-10-oxo-5H-dibenz/b,f/azepine-5-carboxamide derivatives. *Eur. J. Med. Chem.* **2001**, *36*, 227–236, doi:10.1016/s0223-5234(01)01220-x.
16. Kolasa, T.; Matulenko, M.A.; Hakeem, A.A.; Patel, M.V.; Mortell, K.; Bhatia, P.; Henry, R.; Nakane, M.; Hsieh, G.C.; Terranova, M.A.; et al. 1-Aryl-3-(4-pyridine-2-ylpiperazin-1-yl)propan-1-one Oximes as Potent Dopamine D4Receptor Agonists for the Treatment of Erectile Dysfunction. *J. Med. Chem.* **2006**, *49*, 5093–5109, doi:10.1021/jm060279f.
17. Awasthi, A.; Razzak, M.; Al-Kassas, R.; Harvey, J.; Garg, S. Analytical Profile of Moxidectin. In *Profiles of Drug Substances, Excipients, and Related Methodology*; Elsevier: Amsterdam, The Netherlands, 2013; Volume 38, pp. 315–366.
18. Bolotin, D.S.; Bokach, N.A.; Demakova, M.Y.; Kukushkin, V.Y. Metal-Involving Synthesis and Reactions of Oximes. *Chem. Rev.* **2017**, *117*, 13039–13122, doi:10.1021/acs.chemrev.7b00264.
19. Cortés, I.; Kaufman, T.S.; Bracca, A.B.J. A convenient and eco-friendly cerium(III) chloride-catalysed synthesis of methoxime derivatives of aromatic aldehydes and ketones. *R. Soc. Open Sci.* **2018**, *5*, 180279, doi:10.1098/rsos.180279.
20. Metal Ions in Life Sciences. In *Interrelations between Essential Metal Ions and Human Diseases*; Avila, D., Puntel, R., Aschner, M., Eds.; Springer Netherlands: Dordrecht, Netherlands, 2013; pp 199–227.
21. Goldhaber, S.B. Trace element risk assessment: Essentiality vs. toxicity. *Regul. Toxicol. Pharmacol.* **2003**, *38*, 232–242, doi:10.1016/s0273-2300(02)00020-x.
22. Silveira, C.C.; Mendes, S.R.; Villetti, M.A.; Back, D.F.; Kaufman, T.S. CeIII-promoted oxidation. Efficient aerobic one-pot eco-friendly synthesis of oxidized bis(indol-3-yl)methanes and cyclic tetra(indolyl)dimethanes. *Green Chem.* **2012**, *14*, 2912–2921, doi:10.1039/c2gc36131k.
23. Amongero, M.; Kaufman, T.S. Synthesis of optically active 1,2,3-trisubstituted azetidines employing an organocatalytic approach with l-proline. *Tetrahedron Lett.* **2013**, *54*, 1924–1927, doi:10.1016/j.tetlet.2013.01.090.
24. Silveira, C.C.; Mendes, S.R.; Martins, G.A.M.; Schlösser, S.C.; Kaufman, T.S. Modular CeCl3·7H2O-catalyzed multi-component synthesis of 1,2,3,4-tetrasubstituted pyrroles under microwave irradiation and their further trichloroisocyanuric acid-mediated conversion into 5-sulfenylpyrrole derivatives. *Tetrahedron* **2013**, *69*, 9076–9085, doi:10.1016/j.tet.2013.08.035.

25. Ontivero, M.C.; Kaufman, T.S.; Cortés, I.; Bracca, A.B.J. Eco-friendly methoximation of aromatic aldehydes and ketones using MnCl 2 .4H 2 O as an easily accessible and efficient catalyst. *R. Soc. Open Sci.* **2021**, *8*, 210142, doi:10.1098/rsos.210142.
26. Select Committee on GRAS Substances (SCOGS) Opinion: Manganous Salts. SCOGS Report No 67-Manganous Chloride, Manganous Citrate, Manganous Gluconate, Manganous Oxide, Manganous Sulfate. 1979 NTIS Accession Number PB301404.
27. Food and Drug Administration. 2000 CFR Title 21, Volume 3, Sect, 184-1721, Sodium Acetate.
28. Krishnaiah, G.; Sandeep, B.; Kondhare, D.; Rajanna, K.; Reddy, J.N.; Rao, Y.R.; Zhubaidha, P. Manganese(II) salts as efficient catalysts for chemo selective transesterification of β-keto esters under non-conventional conditions. *Tetrahedron Lett.* **2013**, *54*, 703–706, doi:10.1016/j.tetlet.2012.12.030.
29. Hu, A.-J.; Lü, C.-X.; Wang, H.-Y.; Li, B.-D. Selective oxidation of p-chlorotoluene with $Co(OAc)_2/MnSO_4/KBr$ in acetic acid–water medium. *Catal. Commun.* **2007**, *8*, 1279–1283, doi:10.1016/j.catcom.2006.11.023.