

Electrochemical oxidation of primary alcohols – literature review



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Importance of alcohol oxidations in pharmaceutical synthesis.

The oxidation of alcohols to aldehydes, ketones and carboxylic acids is still a widely used chemical transformation in organic synthesis. Also, remains a dynamic field of research for the establishment of more effective and practical methods [1, 2-4]. The reason is the existence of a plenty of orthogonal protecting groups for alcohols, which make allowance for chemoselective deprotection to the desired alcohol before its oxidation to the required derivative [5].

Moreover, the choice of polyoxygenated synthetic targets usually demands an alteration of the oxidation state of an intermediate before further elaboration. Although the major part of oxidative methods are suitable for manufacturing at large scale, there is a notable exception of the Dess-Martin reagent [6], which has not been used at a large scale, mainly due to the safety issues in its preparation and its cost.

In the pharmaceutical industry, synthetic targets are often advantageous than natural products. These targets are appropriate to synthetic routes designed to carry an oxygenated functionality in the right oxidation state as a portion of the starting materials [7], achieving the avoidance of protecting groups and the reduction of the number of synthetic activities.

The catalytic oxidation of alcohol to aldehydes or ketones based on TEMPO, which is a versatile organocatalyst, was first synthesized by Lebedev and

Kazarnowskii in 1960 ^[8] as a highly selective metal-free route and is broadly employed by the fine chemicals and pharmaceutical industries ^[7] .

Initially, the technique that has been used by the industry was the one developed in 1990 by Anelli and Montanari, using aqueous NaOCl as primary oxidant kept under buffered alkaline conditions in contact with the alcohol solution in organic solvent at reaction temperature between 10 and 15 °C ^[9] .

Nowadays, pharmaceutical companies perform Anelli-Montanari reaction under flow, rising the yield from 75% to 90% ^[10] , or even eliminate the bleach by using air as the primary oxidant along with a catalytic amount of CuI, N-Methylimidazole (NMI) and less hindered ABNO (9-azabicyclo[3. 3. 1]nonane N-oxyl) at ambient temperature in high-flash-point N-Methylpyrrolidone solvent.

Another method that has been used massively in the pharmaceutical industry is the Swern oxidation ^[11] , where oxalyl chloride, dimethyl sulfoxide (DMSO) and an organic base are used. A major disadvantage of Swern oxidation on a large scale is the large amount of CO₂ and CO generated in the time of the reaction.

A more convenient route was revealed by Semmelhack et al. in 1983 ^[12] , and it was based on TEMPO-mediated electrochemical oxidation carried out in a simple electrochemical cell. The aldehyde and ketone reaction products thereby obtained are broadly used as valued drug precursors, fragrances and aromas ^[13] .

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Synthetic organic electrochemistry ^[14] in fine and medicinal chemistry continues to be applied to a number of industrial productions, mainly for pharmaceuticals, for instance cephalosporin antibiotic Ceftibuten ^[11] .

[1] Tilstam, U.; Weinmann, H. *Org. Process Res. DeV.* 2002, 6, 384.

[2] Kwon, M. S.; Kim, N.; Park, C. M.; Lee, J. S.; Kang, K. Y.; Park,

J. Org. Lett. 2005, 7, 1077.

[3] Matano, Y.; Hisanaga, T.; Yamada, H.; Kusakabe, S.; Nomura, H.;

Imahori, H. *J. Org. Chem.* 2004, 69, 8676.

[4] Mori, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am.*

Chem. Soc. 2004, 126, 10657.

[5] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic*

Synthesis; J. Wiley & Sons: New York, 1991

[6] Dess, D. B.; Martin, J. C. *J. Org. Chem.* 1983, 48, 4155.

[7] R. Ciriminna, M. Pagliaro, *Org. Process Res. Dev.* 2010, 14, 245– 251.

[8] O. L. Lebedev, S. N. Kazarnovskii, *Zhur. Obshch. Khim.* 1960, 30, 1631–
1635.

[9] P. L. Anelli, F. Montanari, S. Quici, *Org. Synth.* 1990, 69, 212.

[10] G. Samburski, Anelli's (TEMPO) Oxidation of alcohol by flow chemistry,
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industrial scale, 80th Annual Meeting of the Israel Chemical Society, Tel Aviv, 17–18 February 2015.

[11] Mancuso, A. J.; Huang, S.-L.; Swern, D. J. *Org. Chem.* 1978, 43, 2480

[12] M. F. Semmelhack, C. S. Chou, D. A. Cortes, *J. Am. Chem. Soc.* 1983, 105, 4492–4494.

[13] R. A. Sheldon, *Catal. Today* 2015, 247, 4–13.

[14] B. A. Frontana-Uribe, R. D. Little, J. G. Ibanez, A. Palma, R. Vasquez-Medrano, *Green Chem.* 2010, 12, 2099–2119.

Use of TEMPO (and derivatives) for aerobic oxidation of primary alcohols

- The catalytic oxidation of alcohols is important for the preparation of many synthetic intermediates in organic chemistry ^[1].
- Typical methods of oxidations normally use stoichiometric quantities of inorganic oxidants. However, the need for effective catalytic systems that utilize clean and unexpensive oxidants like oxygen and therefore the existence of more “green” methods, has as a consequence the requirement for developed aerobic oxidation methods.
- Despite the development of many catalytic oxidation methods, there is still an extensive interest in methods that have the potential to use O₂

as an oxidant. Nevertheless, methods of aerobic oxidation, usually, do not correspond to the synthetic scope and usefulness of typical alcohol oxidations, thus they are unfrequently used in laboratory.

- Frequently, in aerobic alcohol oxidations, the use of a Group VIII metal complexes as catalysts, is involved. [2] More specific, ruthenium compounds are broadly used as catalysts in organic synthesis.
- However, the metal systems require large amounts of catalyst and the utilize of a cocatalyst and a drying agent to attain their action.
- In expansion to metal systems, stable nitroxyl radicals, like TEMPO(2, 2', 6, 6'-tetramethylpiperidine *N*-oxyl), can be used as a catalyst for the conversion of alcohols to aldehydes, ketones and carboxylic acids. [3]
- Cu/TEMPO and Cu/nitroxyl catalyst are considered as some of the most efficient catalysts for aerobic alcohol oxidation.
- These catalysts are able to use ambient air as oxidant in many cases and also they are compatible with both activated and unactivated alcohols. Moreover, another advantage over typical alcohol oxidation methods, is their chemoselectivity and functional group compatibility.
- An example of oxidative process based on TEMPO, used in industry, is the Novartis aerobic oxidation with Cu^+ / O_2 developed by Semmerick for the synthesis of retinal from retinol.

[1] R. A Sheldon and J. K. Kochi, "Metal Catalysed Oxidations of Organic Compounds", Academic Press, New York, 1981

[2] R. A. Sheldon, I. W. C. E. Arends and A. Dijkstra, *Catalysis Today*, 2000, 57, 157

[3] A. E. J. de Nooy, A. C. Besemer and H. van Bekkum, *Synthesis*, 1999, 1153

Use of TEMPO (and derivatives) for electrochemical oxidation of primary alcohols

- *N*-Oxyl compounds constitute a versatile group of organic radical reagents with special properties and reactivity that can be used as catalysts both in chemical and electrochemical oxidation reactions. [1]
The two most broadly used members of this group are TEMPO (2, 2', 6, 6'-tetramethylpiperidine *N*-oxyl) and PINO (phthalimide *N*-oxyl). TEMPO is stable under ambient conditions, while PINO is produced via oxidation of NHPI (*N*-hydroxyphthalimide). Another stable aminoxyl radical is ABNO (9-azabicyclo[3. 3. 1]nonane *N*-oxyl), and due to its stability, has been intensively investigated.
- In 1973, Tamura and co-workers, were the first to study the electrochemical properties of TEMPO by cyclic voltammetry. [2]
- In TEMPO-mediated oxidations, the oxidant species, which in this case is the oxoammonium ion, is produced in situ electrochemically by the application of a small electric potential to a solution of nitroxyl radicals. [3]

The oxoammonium ion oxidizes the alcohol function and then is regenerated electrochemically from the hydroxylamine or in solution by a reaction of latter species with unreacted TEMPO. [4]

- There are many advantages in the electrochemically oxidation of primary alcohols mediated by TEMPO-like nitroxyl radicals. First of all, the reaction can be run at relatively low cost and can provide pure oxidized reaction products with minimum or no waste. Moreover, the hazards that are associated with working in systems that contain oxygen in aerobic alcohol oxidation, can be avoided. [5]

[1] Bobbitt, J. M.; Brückner, C.; Merbouh, N. Oxoammonium- and Nitroxide-Catalyzed Oxidations of Alcohols. In *Organic Reactions*, Wiley: Hoboken, NJ, 2009, pp 103–424.

[2] Tsunaga, M.; Iwakura, C.; Tamura, H. Electrode Reactions of Nitroxide Radicals at Platinum in Acetonitrile. *Electrochim. Acta* 1973, 18, 241–245.

[3] M. F. Semmelhack, C. S. Chou, D. A. Cortes, *J. Am. Chem. Soc.* 1983, 105, 4492–4494.

[4] A. E. J. de Nooy, A. C. Besemer, H. van Bekkum, *Synthesis* 1996, 1153–1176.

[5] E. J. Horn, B. R. Rosen, P. S. Baran, *ACS Cent. Sci.* 2016, 2, 302–308.

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