Sodium Chlorite-Hydrogen Peroxide – A Mild and Selective Reagent for the Oxidation of Aldehydes to Carboxylic Acids

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The oxidation of aldehydes to carboxylic acids is in principle easy to achieve. A number of reagents are known for this transformation [1], nevertheless, only few selective methods that reliably work with all types of aldehydes and also tolerate a broad range of other functional groups are available. Sodium chlorite had been discovered [2] to be effective for the conversion of aldehydes to carboxylic acids under mild conditions (equation 1), but side reactions could not always be avoided.

$$RCHO + HClO_2 \rightarrow RCOOH + HOCl \quad (1)$$

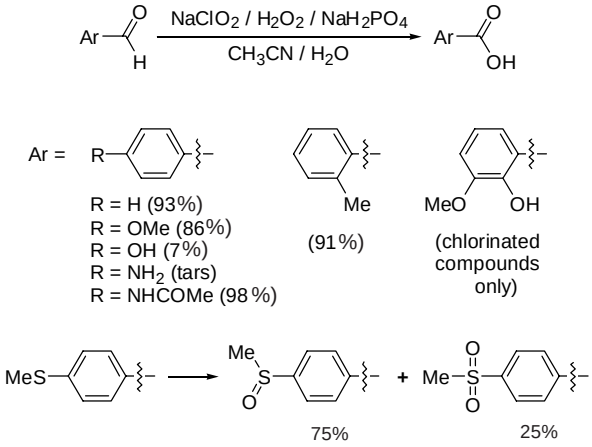
Problems arise due to the formation of hypochlorite, which is a more powerful oxidation reagent than chlorite and moreover, is able to oxidize the latter to chlorine dioxide. Consequently, to circumvent the complications described scavengers for hypochlorite were tested such as 2-methyl-2-butene [3], resorcinol [4] or sulfamic acids [5]. All these additives, although effective, display certain disadvantages. Eventually, hydrogen peroxide was introduced as trapping reagent by Dalcanale and Montanari [6], which subsequently had been adopted for many oxidations of aldehydes with sodium chlorite.

$$HOCl + H_2O_2 \rightarrow HCl + O_2 + H_2O \quad (2)$$

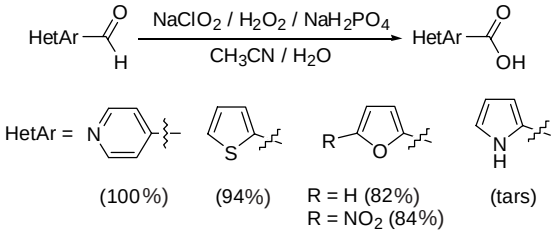
A distinct advantage of the combination of hydrogen peroxide-sodium chlorite is the exclusive formation of inorganic by-products in the course of the oxidation. From an operational point of view the formation of oxygen, as depicted in equation 2, is a good indication for the progress of the reaction. Best reaction conditions have been achieved in aqueous acetonitrile buffered with NaH_2PO_4 at pH 4.3, while with very sensitive substrates up to 5 equivalents of hydrogen peroxide at pH 2 are employed in order to accelerate the reduction of HOCl. Reactions are carried out at room temp. or even at 0 °C.

Following these procedures, aliphatic, α,β-unsaturated and aromatic aldehydes can be converted to carboxylic acids with very few limitations. Moreover, this protocol has been proved so versatile that it had become also the method of choice as the final transformation for the two step conversion of alcohols to carboxylic acids which is initiated by the selective formation of aldehydes by periodinane [7], MnO_2 [8] or Swern-oxidation [9].

Carboxylic acids are readily obtained from the corresponding aromatic and hetero aromatic aldehydes (Scheme 1 and 2). Electron rich substrates can be troublesome, giving rise to side products formed by chlorination or oxidation of the aromatic ring. The substitution of H_2O_2 by DMSO as trapping reagent has been demonstrated to be a viable alternative to circumvent such problems. Oxidation of an electron donor has also to be considered as a possible obstacle. Unprotected aromatic amines and pyrrols are not tolerated as substrates resulting in no defined products, while thioethers are oxidized to sulfoxides and sulfones [6].



Scheme1 Oxidation of aromatic aldehydes



Scheme 2 Oxidation of hetero aromatic aldehydes

α,β-Unsaturated aldehydes can also be employed, as long as the double bond is not substituted with additional strong electron donating groups. Even triple bonds can be present in direct proximity of the aldehyde group [6] or in conjugation with other double bonds [10] (Scheme 3).

There is a delicate balance of success and failure for the oxidation of aldehydes containing C–C-double bonds as il-

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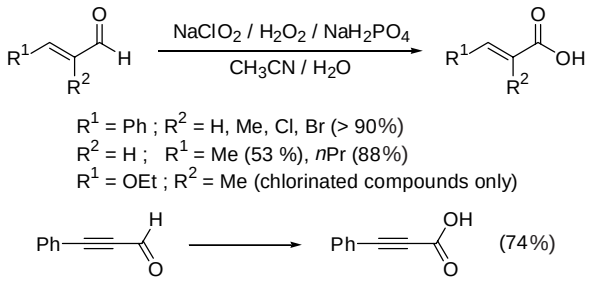
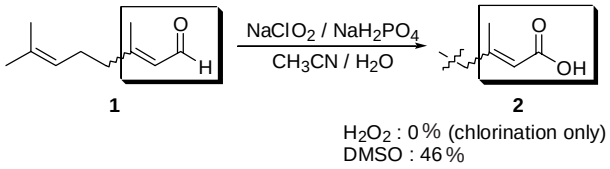


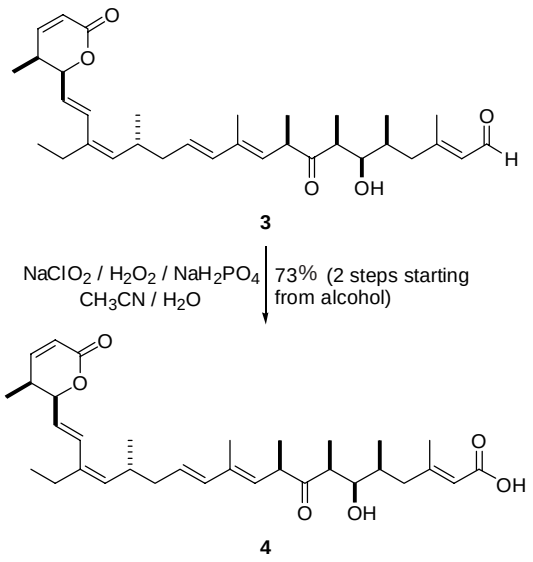
Scheme 3 Oxidation of α,β-unsaturated aldehydes

lustrated in the next two examples. If isolated double bonds are present in a substrate, *e.g.* in **1**, chlorination of the double bond cannot be prevented with the reagent combination $NaClO_2$–H_2O_2 (Scheme 4). This side reaction might be circumvented if DMSO is used as a scavenger instead, however, oxidations still occur only in moderate yields [6].



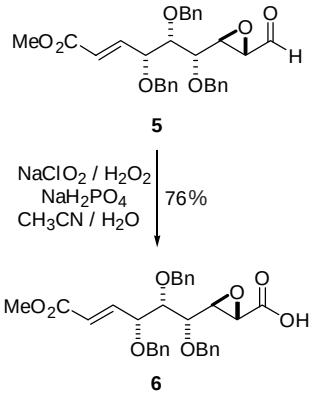
Scheme 4 Oxidation of substrates containing isolated double bonds

In contrast, double bonds being in conjugation with electron demanding substituents or another double bond seem to be oxidized well with $NaClO_2$–H_2O_2, as demonstrated impressively by the conversion of the highly unsaturated aldehyde **3** to the carboxylic acid **4** (Scheme 5) [11].



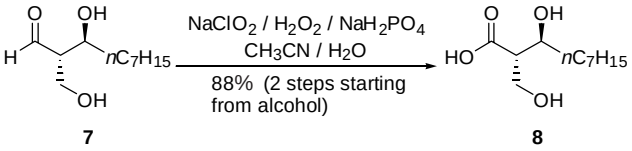
Scheme 5 Oxidation of substrates containing conjugated double bonds

The strength of the oxidation method presented here becomes further apparent when highly functionalized substrates are employed. In a total synthesis of (+)–cyclophellitol the intermediate **5** could be cleanly converted to the acid **6** (Scheme 6) [12]. Especially noteworthy in this transformation are the stability of the epoxide towards ring opening and the tolerance of benzyl ethers. Since the double bond in **5** is substituted by electron withdrawing groups, there is no danger of its chlorination as pointed out before.



Scheme 6 Oxidation step in the total synthesis of (+)-Cyclophellitol

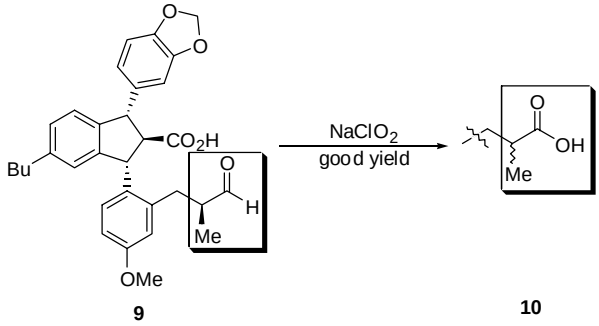
Protection of hydroxyl groups has proved to be not necessary as demonstrated in the oxidation of hydroxyaldehyde **7** [13] (Scheme 7, *cf.* also Scheme 5). As can be seen from this and other examples [14], there seems to be in general no erosion of stereocenters in substrates.



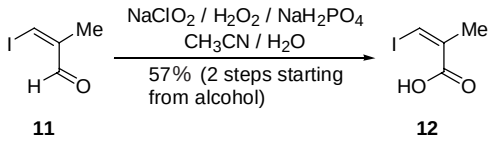
Scheme 7 Oxidation step in the total synthesis of the Hypocholesterolemic Agent 1233A

However, there are also a few cases reported in which difficulties to maintain the stereochemical integrity were encountered: the oxidation of aldehyde **9** was affected with sodium chlorite in good yield, but epimerization of the neighboring center to the acid had surprisingly occurred (Scheme 8) [15]. For this particular substrate, stoichiometric amounts of $NaClO_2$ combined with catalytic amounts of TEMPO and bleach were found to suppress the loss of stereochemical information.

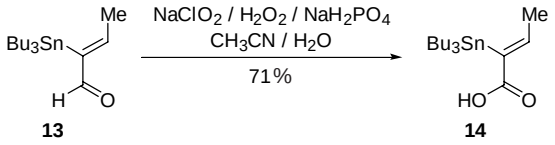
Halides, most notably iodides such as **11** [16] (Scheme 9), and stannanes such as **13** [17] (Scheme 10) are tolerated well. These examples also illustrate that double bonds, in particular trisubstituted double bonds, do not undergo *E/Z*-isomerization in the course of the reaction.



Scheme 8 Oxidation step in the total synthesis of an Endothelin Receptor Antagonist

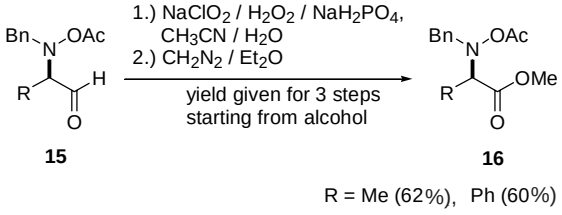


Scheme 9 Iodides in the oxidation with $NaClO_2$–H_2O_2



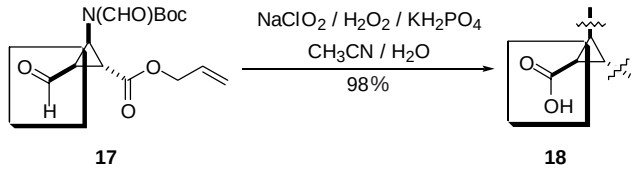
Scheme 10 Stannanes in the oxidation with $NaClO_2$–H_2O_2

α-Aminoaldehydes are known to be particularly labile substrates, both, toward condensation reactions as well as toward epimerization. Their oxidation is further complicated by the general ease with which an amino group is transformed to its corresponding *N*-oxide. Attachment of standard carbamate protecting groups [18] to the amino group or even twofold protection as exemplified with the oxidation of **15** [19] seems therefore to be a prerequisite, after which oxidation to amino acids becomes possible (Scheme 11).



Scheme 11 Oxidation of α-aminoaldehydes

β-Aminocyclopropanecarboxylic acids are also accessible *via* oxidation with sodium chlorite of the corresponding aldehydes [20], while various standard reagents [1] completely failed in this transformation. *E.g.*, **17** [21] could be converted in almost quantitative yield to the amino acid **18** without affecting the hydrolytically labile and potentially oxidizable *N*-formyl group, the acid sensitive *N*-Boc group, or the allyl ester functionality. Moreover, no ring opening of the vicinal donor-acceptor substituted cyclopropane moiety and no epimerization of the especially sensitive stereocenter bearing the amino group had occurred (Scheme 12).



Scheme 12 Oxidation of β-aminocyclopropanecarbaldehydes

In conclusion, oxidation of aldehydes with $NaClO_2$–H_2O_2 is a reliable and high yielding method for the synthesis of carboxylic acids. As side products, only water and NaCl are formed, which makes this procedure also from an environmental point acceptable. Clearly, direct oxidation of aldehydes by H_2O_2 would be an even more desirable process, and indeed recent results [22] demonstrate that this transformation is possible. Nevertheless, the reaction temperatures required (90 °C) for the latter process cannot compare with the mild conditions (0 °C to room temp.) used in the sodium chlorite procedure.

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