Oxidation of Primary Alcohols to Aldehydes with *N*-Halamine-Containing Polymers

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This work is dedicated to Professor S. D. Worley of Auburn University.

Abstract: Polymeric *N*-halamines have been previously employed for organic reactions such as sulfide oxidation. In the present study, we employed polymeric *N*-halamines to oxidize primary alcohols selectively to the corresponding aldehydes in excellent yields. After reaction, the polymers can be recycled and then reused for the next reaction process.

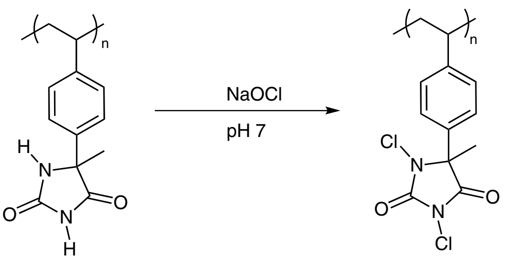
Key words: alcohols, aldehydes, oxidation, solid-phase synthesis, halogens, green chemistry

Oxidation of alcohols to the corresponding carbonyl compounds is one of the key functional group transformations in synthetic organic chemistry.[1] There is a continuing search for new methods and reagents tolerating a wide variety of conditions for this transformation,[2] particularly with the aim to develop sustainable and green methodology.[3] When a primary alcohol is oxidized to the corresponding aldehyde, the aldehyde is sometimes further oxidized to a carboxylic acid depending upon the oxidant.[4] In many situations, the aldehydes are synthetically more valuable than the carboxylic acids; therefore, terminating oxidation at the aldehyde stage can be crucial.

2,2,6,6-Tetramethylpiperidine *N*-oxide (TEMPO), a versatile organic oxidant, has frequently been used in the oxidation of alcohols.[5] TEMPO requires a secondary oxidant to activate it for the oxidation and to refurbish it after each completed oxidation and many different co-oxidants have been used.[6] Even though such systems have found utility, lengthy purification from unwanted products may limit the use of these oxidants despite the mildness of TEMPO oxidation conditions. TEMPO has been incorporated into polymers, and these polymers have also been employed in the oxidation reactions of primary and secondary alcohols using the co-oxidants mentioned above.[7]

N-Halamine-containing polymers (containing N–X, where X is either Cl or Br) were developed and used for their biocidal properties,[8] although the N–X (X = Cl, Br) bond can be used as a co-oxidant in TEMPO-mediated oxidations, in the same way as the related *N*-chlorosuccinimide (NCS) and trichloroisocyanuric acid (TCA).[9] Moreover, polymeric *N*-halamines offer an advantage over NCS and TCA because they can be easily separated from the reaction medium and regenerated to be reused in further oxidations. These materials have been mainly synthesized for sanitization purposes[10] and one of these polymers (Scheme 1) was developed by Worley et al. and commercialized by HaloSource, Inc., for disinfection of water.[11] These polymers have also been employed in disulfide formation, detoxification of mustard gas, and oxidation of secondary alcohols.[12] However, there have been no reports in which they have been employed to oxidize primary alcohols to aldehydes.

Akin Akdag received his BS and MS at the Middle East Technical University, Ankara, Turkey. He then moved to Auburn University and received his Ph.D. under the supervision of Professor S. W. Schneller in 2005. He stayed at the Auburn University for a postdoc with Professor S. D. Worley and then moved to the University of Colorado at Boulder, where he worked with Professor Josef Michl. He is currently an Assistant Professor in the Department of Chemistry at the Middle East Technical University. His current research interests are green chemistry, molecular recognition, solar energy, polymers, chiral sulfoxides, and reactive intermediates.



Scheme 1 Polystyrene hydantoin and its chlorination with hypochlorous acid

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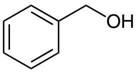
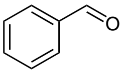
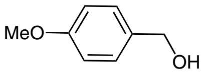
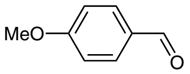
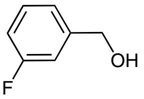
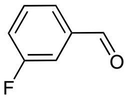
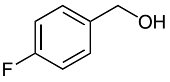
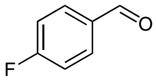
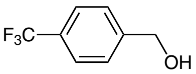
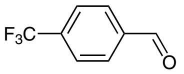
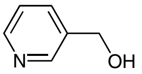
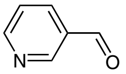
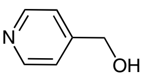
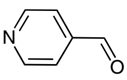
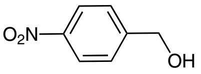
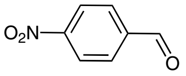
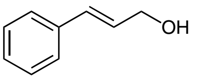
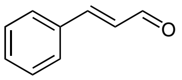
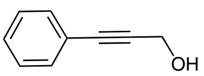
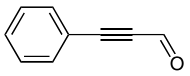
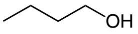
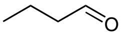
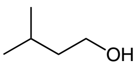
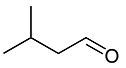
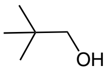
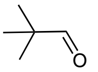
In this communication we report the use of chlorinated polystyrene hydantoin beads as the co-oxidant for TEMPO-mediated oxidation reactions of primary alcohols. The polymer was chlorinated on the imide and amide nitrogens by treating it with household bleach (NaOCl) at around pH 7. Then, these polymeric beads were used as the co-oxidant for oxidation of primary alcohols in a water/dichloromethane mixture in the presence of TEMPO. After the reaction was completed (TLC), a simple filtration separated the partially chlorinated polymer from the filtrate containing the aldehyde. The polymers could be reused after they were regenerated with bleach. All of the experiments reported in this study were performed with 10 grams of polymer repeated at least three times wherein we observed no material loss, activity change, or deformation of the polymer.

We initiated our studies with benzyl alcohol, and water and dichloromethane mixture (1:1) as the solvent system. When the reaction was carried out without TEMPO (simply in the presence of chlorinated polymer); no formation of the aldehyde was observed after 12 hours. The reaction was repeated with the addition of TEMPO to the medium, when we observed only small amounts (<2%) of the oxidized products after 12 hours. Next, $NaHCO_3$ was added to the reaction medium and complete conversion to the benzaldehyde was observed within 2 hours. Encouraged by the results, we repeated the reaction on a range of alcohols, most of which were completely oxidized to the corresponding aldehydes within 3 hours.[13] In fact, the reactions were usually complete in less than two hours; the extra hour was spent in order to ascertain whether the reaction produced any overoxidation product. Gratifyingly, we did not observe any carboxylic acids during the course of these reactions (Table 1) as monitored by ^{1}H NMR and TLC. Substituted benzyl alcohols were oxidized with relative ease. However, when an electron-withdrawing group was present at the *para* position of the benzyl alcohol, additional time was required for complete conversion to the aldehyde; 4-(trifluoromethyl)benzyl alcohol, 4-fluorobenzyl alcohol, and 4-nitrobenzyl alcohol required more than 3 hours to be completely oxidized. Meanwhile, the reactions involving benzyl alcohols bearing electron-donating groups proceeded smoothly to completion within 3 hours. These results are in keeping with accumulation of positive charge at the benzylic carbon in the transition state.

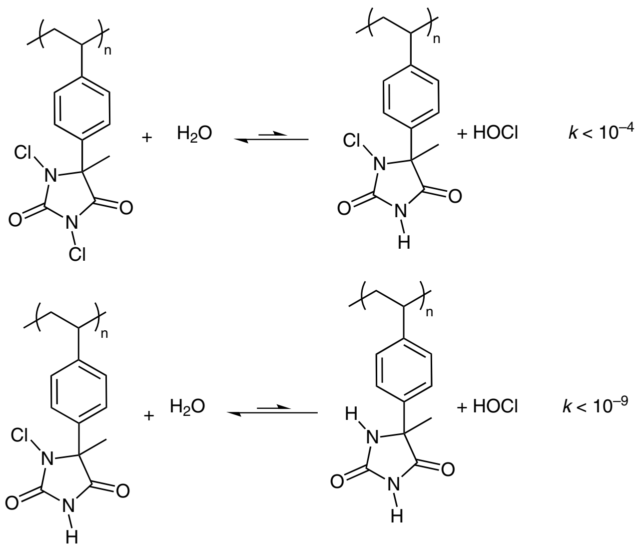
Table 1 The Alcohols, Oxidation Products, and the Reaction Duration[a]

Alcohol	Product	Isolated yield (reaction time)
		96% (3 h)
		90% (3 h)
		85% (3 h)
		85% (6 h)
		90% (8 h)
		85% (6 h)
		85% (6 h)
		90% (8 h)
		90% (3 h)
		85% (3 h)
		75% (3 h)
		70% (3 h)
		75% (3 h)

[a] A general procedure is given13 and except for the reaction time, all conditions were identical.

Aliphatic alcohols were also subjected to the oxidation reactions under identical conditions. Although complete conversion of the alcohol to the corresponding aldehyde was observed within 3 hours, the isolated yields were not as high as those of aromatic aldehydes; possibly due to the low boiling point of these aldehydes. Allylic alcohols and propargylic alcohols were oxidized efficiently. 3-Pyridinemethanol and 4-pyridinemethanol were also subjected to oxidation to observe the effect of a heteroatom on these oxidations. Except for a slower conversion than that for the benzylic alcohols, we did not observe any other effect of the heteroatom on these oxidations. The slow kinetics are most probably again due to the oxidation involving positive charge accumulation on the benzylic carbon.

After reaction was complete, the mixture was filtered to remove the solid. This was washed with water and diethyl ether and the residual polymer was tested for remaining chlorine by iodometric titration. Since we systematically used excess of the active polymer, there was always some chlorine left on the polymer but this did not result in overoxidation; whereas overoxidation was noted when hypochlorous acid was used in previous studies.[4] In the present work hypochlorous acid is present only in minute amounts due to the very low hydrolysis equilibrium constants (Scheme 2).[14] Subsequently, we rechlorinated the polymer [NaOCl solution (HOCl) at pH ca. 7] for reuse. The polymers were recycled for at least ten reactions and could still be reused after this. Acetonitrile was also examined as a substitute for dichloromethane. However, even though complete oxidation was observed (TLC and GC–MS), the isolated yields were less than 20%. This observation is still under investigation.



Scheme 2 Dissociation constants for the chlorinated polymer

In conclusion, we have utilized a polymeric *N*-halamine as co-oxidant for TEMPO oxidation of a wide variety of primary alcohols chemoselectively to aldehydes and it has been shown that the reaction conditions are tolerant of different functional groups. The ease of performing the reaction and workup provides the synthetic community with an efficient method for chemoselective oxidation of primary alcohols to aldehydes.

Acknowledgment

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(13) The procedure for the oxidation of benzyl alcohol is as follows: A mixture of H_2O (5 mL) and CH_2Cl_2 (5 mL) was added to the chlorinated polymeric beads (2 g). (The unchlorinated beads were obtained from HaloSource, Inc. The unchlorinated beads were chlorinated by soaking the beads in bleach solution, with pH adjusted to 7 by addition of AcOH, for an hour. Then, the chlorinated beads were filtered and dried in air.) After addition of TEMPO (10 mg, 0.064 mmol) and benzyl alcohol (0.2 g, 1.8 mmol), $NaHCO_3$ (0.5 g) was added to the mixture. The mixture was stirred at r.t. for 3 h and filtered. The residue on the filter paper was washed with H_2O (20 mL) and CH_2Cl_2 (10 mL), and the organic phase of the filtrate was separated, dried over $MgSO_4$, and filtered. The solvent was removed under vacuum to obtain benzaldehyde.
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