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Tetrahedron Letters 45 (2004) 6381–6383

Tetrahedron
Letters

Oxidation of tartronic acid and dihydroxyacetone to sodium mesoxalate mediated by TEMPO

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Accepted 6 July 2004

Abstract—Using catalytic TEMPO with bleach as regenerating oxidant in water tartronic acid (TA) and dihydroxyacetone (DHA) are converted to mesoxalic (ketomalonic) acid. The DHA oxidation results in partial degradation of the reaction product, while conversion of tartronic acid is complete providing another viable chemical route to a potent hypoglycemic agent starting from relevant commercial products.

The selective oxidation of renewable products is an ongoing relevant objective of academic and industrial efforts devoted in the last decade to the search of suitable conversions, which might yield a number of useful substances from abundant and cheap feedstocks of agricultural origin.[1] In this context we recently reported a one-pot oxidative route[2] to ketomalonic (or mesoxalic) acid based on the oxidation of glycerol (1,2,3-propanetriol) yielding a highly functionalized molecule with potential applications as organic synthon, whose calcium salt is a potent commercial hypoglycemic agent (Mesoxan^{TM})[3a] and the chlorophenylhydrazone is an active anti HIV species.[3b]

Other oxygenate glycerine derivatives such as tartronic acid (obtained by malonic acid oxidation with HNO_3)[4a] and dihydroxyacetone (via an enzymatic process)[4b] are important commercial fine chemicals; and we now report that the stable organic nitroxyl radical TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) with aqueous NaOCl as regenerating oxidant affords ketomalonic acid also in the oxidation of these commercial products offering a viable route alternative to the elegant aerobic processes over supported Pt/Bi catalysts.[5]

The homogeneous oxidation of tartronic acid smoothly proceeds at 0 °C upon addition of TEMPO to a solution of substrate kept at pH 10 in the presence of a 20% molar excess of NaOCl and catalytic bromide (Scheme 1):

$$Na_2(OOC)_2\text{-}CHOH + OCl^- \xrightarrow[\text{pH 10, 0° C}]{\text{TEMPO, Br}^-} Na_2(COO)_2C(OH)_2 + Cl^-$$

Scheme 1.

Like in the oxidation of glycerol,[2] no induction time typical of TEMPO-mediated sugar oxidations[6] is observed (Fig. 1), and the consumption of 1.5 mmol of hydroxyls per millimole of substrate, due to the consumption of hypochlorite in equilibrium with HOCl (Scheme 2), indicates complete oxidation of the secondary hydroxyl tartronic acid.

Compared to the glycerol conversion, however, the kinetics is different with a faster, almost linear reaction stage up to consumption of 1 equiv of hydroxyls, followed by a slower stage probably involving the acid–base equilibrium of the *gem*-diol thereby formed. The product is stable and readily soluble in water but rapid decarboxylation occurs at pH values below 3. Interestingly, no polymerization of ketomalonate is observed, as a minimum 10% concentration of monomer is required for the condensation to proceed.[7]

The nitrosonium ion TEMPO$^+$ is the actual oxidant since when no TEMPO is added to the substrate solution, the oxidation does *not* proceed, while upon addition of 6.5 mol% TEMPO all (98%) the added

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Keywords: DHA; Tartronic acid; Mesoxalic; TEMPO; Oxidation.

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doi:10.1016/j.tetlet.2004.07.021

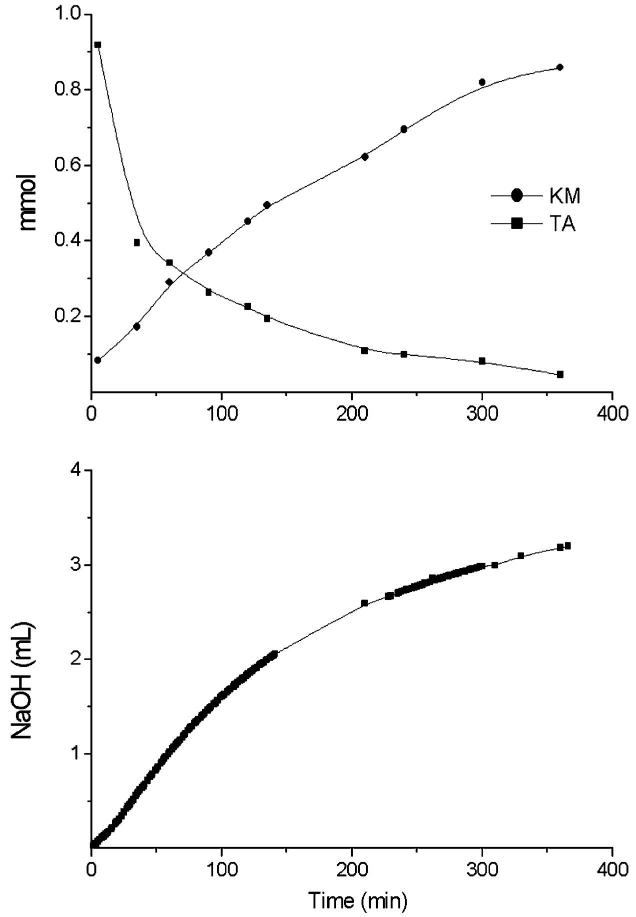

Figure 1. Kinetics of the NaOBr tartronic acid oxidation mediated by TEMPO at pH 10.

$$OCl^- + H_2O \rightleftharpoons HOCl + OH^-$$

Scheme 2.

substrate is directly converted to sodium ketomalonate (in hydrate form).[8]

The low (for a TEMPO mediated oxidation) reaction rate (average TOF ~ 3 h^{-1}) is due to the known chemoselectivity of the oxoammonium ion $TEMPO^+$ for the oxidation of primary versus secondary alcohols in an alkaline environment.[6] Such faster reactivity is indeed confirmed in the oxidation of commercial DHA (a dimer). In this case, the reaction proceeds much more rapidly and a molar excess of 4.5 mmol OH^- per mole of substrate are eventually consumed in the process (Scheme 3).

The reaction kinetics in this case (Fig. 2) is similar to that observed in the oxidation of glycerol,[2] with an extremely fast reaction stage up to consumption of 4 mmol of OH^- (8 mL in Fig. 2), corresponding to the complete oxidation of both the DHA –CH_2OH groups into carboxylates. Interestingly, however, *intermolecular* degradation of the mesoxalate appears to be promoted by DHA, or by other intermediate oxygenates; and the concentration of mesoxalate formed in solution declines rapidly after reaching a 70% maximum yield corresponding to the initial trait of the slow course of the reaction (Fig. 2). Eventually, a 45% yield of mesoxalate at 95% DHA conversion (Fig. 2, top) is obtained.

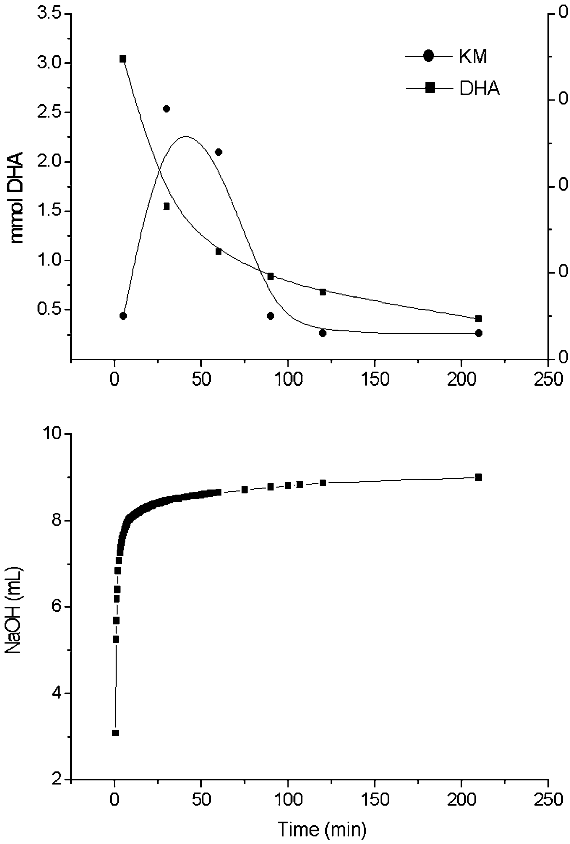

Figure 2. Kinetics of the NaOBr dihydroxyacetone oxidation mediated by TEMPO at pH 10.

Clearly, several intermediate by-products are likely to form in the reaction mixture,[9] such as hydroxypyruvic acid; however, no degradation of the three carbon atoms skeleton of all these compounds (glycerol, DHA and tartronic acid) takes place in their mild TEMPO-mediated oxidation at 0 °C since, for instance, no oxalic acid is observed at the HPLC during reaction.

In conclusion, the general scope of the TEMPO/NaOCl oxidation protocol[10] applied to the conversion of glycerol

$$CH_2OH\text{-}(CO)\text{-}CH_2OH + 4NaOCl \xrightarrow[\text{pH 10, 0° C}]{\text{TEMPO, Br}^-} (COONa)_2C(OH)_2 + 2HCl + 2NaCl + H_2O$$

Scheme 3.

oxygenate derivatives has been shown. Tartronic acid affords high yields of ketomalonate, whereas DHA gives place to partial degradation of the mesoxalate reaction product.

Acknowledgements

Thanks to Dr. Paul McMorn (Department of Chemistry, University of Cardiff) and to Dr. Hiroshi Kimura (Kao Corporation, Japan) for the valuable correspondence.

References and notes

1. To find practical applications and replace current commercial conversions, however, such processes will need to be economic (low capital investment) or afford high value-added products. For a recent account on recent important advancements in the field, see: Bragd, P. L.; van Bekkum, H.; Besemer, A. C. *Top. Catal.* **2004**, *27*, 49–66.
2. Ciriminna, R.; Pagliaro, M. *Adv. Synth. Catal.* **2003**, *345*, 383–388. A vast 10% w/w surplus of glycerine is obtained in biodiesel production and with a UE directive requiring 5.75% of the entire fuel consumption coming from biodiesel by 2005, 400,000 t of glycerine are expected to reach the market: a 7-fold increase from the 60,000 t produced in 2001.
3. (a) Trademark of ICN Pharmaceuticals (now Valeant); (b) Davis, W. R.; Tomsho, J.; Nikam, S.; Cook, E. M.; Somand, D.; Peliska, J. A. *Biochemistry* **2000**, *39*, 14279–14291.
4. (a) The starting material of tartronic acid is malonic acid and the price of TA is currently 30 times higher that that of ketomalonic acid monohydrate; (b) Currently the bioprocess affords a yearly worldwide production of 2000 t of DHA mainly for use in cosmetics due to the skin-binding properties of the molecule.
5. Despite notable recent improvements such as the syntheses of mesoxalic acid from tartronic reported in Kimura, H. Japanese Patent Laid Open 1,51,346, 1996 and Fordham, P.; Besson, M.; Gallezot, P. *Catal. Lett.* **1997**, *46*, 195–199, heterogeneous aerobic catalytic processes have not yet found commercial applications mainly due to the low stability of supported metals in the oxidative environment, which requires high metal/substrate ratios and a thorough control of the reaction conditions to minimize the formation of undesired byproducts, which, nonetheless, are always present in the reaction mixture and high selectivities becoming more difficult as the compounds become more oxidized.
6. de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153–1174.
7. Oxidation of a 10% TA solution over a single multifunctional supported BiPtPd/CeO_2 catalyst affords high molecular weight poly(ketomalonate): (a) Kimura, H. *Polym. Adv. Technol.* **2001**, *12*, 697–710.
8. ^{13}C NMR shows that the reaction product is sodium mesoxalate (hydrate) with the NMR signal of the carboxyls and the *gem*-diol carbons resonating at 175 and at 165 ppm.
9. Carrettin, S.; McMorn, P.; Johnston, P.; Griffin, K.; Kiely, C. J.; Attard, G. A.; Hutchings, G. J. *Top. Catal.* **2004**, *27*, 131–136.
10. Representative oxidation procedure. A solution of TA (98%; 120 mg, 1 mmol) and NaBr (6.78 mg, 6.6 mol%) in 25 mL of distilled water immersed in an ice bath was added with NaOCl (~13% w/w, 0.55 mL, 1.2 mmol) in 20% molar excess previously brought at pH 10 with 4 M HCl. Prior to the bleach addition, the pH of the reaction mixture was adjusted to 10 by preliminary titration of the acid controlled by an automatic titrator (Mettler-Toledo DL50) and kept at this value throughout the oxidation by the addition of 0.5 M NaOH. The reaction started immediately after the addition of TEMPO (10.36 mg, 0.065 mmol), and the oxidation was followed by consumption of NaOH as a function of time and by HPLC detecting products at 215 nm in reaction samples eluted at 60 °C over a column for organic acids (Alltech IOA 1000) with H_2SO_4 0.005 M as mobile phase. When reaction was complete (no more acid formation), the reaction product was precipitated with cold ethanol (50 mL, −20 °C), filtered and extensively washed with EtOH (80%, v/v), prior to drying at 40 °C and analysis of the resulting white powder by NMR. An analogous procedure was followed for the oxidation of DHA (a dimer, 97%; 90.1 mg, 1 mmol) using 2.20 mL of NaOCl. In case of large scale applications, the excess NaCl co-precipitated upon the addition of ethanol can easily be removed, for instance by using suitable membranes. Yields were calculated by the calibration curves obtained using authentic reagents (external standard method). The NMR spectra in D_2O were recorded on a Bruker spectrometer working at a proton resonating frequency of 250 MHz.