

A new system for the reduction of 4-hydroxymandelic acids

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Summary — We describe a new reduction of 4-hydroxymandelic acids which is easy to perform with available, cheap and environmentally clean reagents. The reduction of these acids is an important method for the synthesis of (4-hydroxyphenyl)-acetic acids. The new reducing system is constituted of sodium bisulfite or dithionite in catalytic quantities and formic acid in slight excess.

4-hydroxymandelic acid / reduction / sodium bisulfite / sodium dithionite / formic acid

Résumé — Nouveau système de réduction des acides 4-hydroxymandéliques. Nous décrivons un nouveau système de réduction des acides 4-hydroxymandéliques, relativement aisé à mettre en œuvre avec des réactifs disponibles, peu coûteux et non polluants pour l'environnement. La réduction de ces acides constitue une voie importante de synthèse des acides (4-hydroxyphényl)acétiques. Ce nouveau système de réduction est constitué de bisulfite de sodium ou de dithionite de sodium en quantité catalytique, et d'acide formique en léger excès.

acide 4-hydroxymandélique / réduction / bisulfite de sodium / dithionite de sodium / acide formique

Hydroxymandelic acids are obtained by condensation of the corresponding phenols with glyoxylic acid in basic medium to give essentially the 4-hydroxy isomer which has been isolated in some cases as a sodium salt (scheme 1) [1, 2]. The reduction of these acids gives (4-hydroxyphenyl)acetic acids, which are used in the synthesis of pharmaceutical drugs such as atenolol, betaxolol or buprenorphine.

There exist a certain number of methods for the reduction of these acids, for example, with stannous chloride in hydrochloric acid [3], with red phosphorus in hydroiodic acid [4], with phosphorous acid in the presence of catalytic quantities of iodine [5], or by hydrogenation catalysts such as palladium deposited on charcoal [6]. These processes present disadvantages due to a significant rejection of salts, or to the high cost of reagents or catalysts.

We propose here a new reductive system for hydroxymandelic acids which also functions with the corresponding salts and gives good results only with 4-hydroxy isomers [7]. The reaction is run in aqueous medium with very common reagents. The optimized operating conditions of the reductive system involve sodium bisulfite or sodium dithionite in catalytic quantities and formic acid in slight excess. The reaction is run in a closed reactor at a constant pressure of 5 bar and at a temperature of 100 °C (scheme 2). The results obtained with sodium 4-hydroxymandelate acidified in situ with phosphoric acid are given in table I.

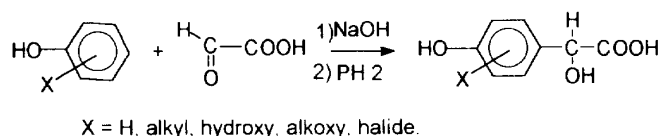
Table I. Reaction of sodium 4-hydroxymandelate with sodium bisulfite and formic acid.

Run	Sodium bisulfite (% mol)	Phosphoric acid ^a (mol)	Formic acid ^a (mol)	Yield (%) ^b (9 h)
1	8	1	1.1	91
2	4	1	1.1	28 ^c
3	12	1	1.1	93
4	12	1	1.25	87
5	12	1	1.5	73
6	0	1	1.1	0
7	100	1	0	0 ^d
8	8	0	1.1	62
9	8	0.25	1.1	73

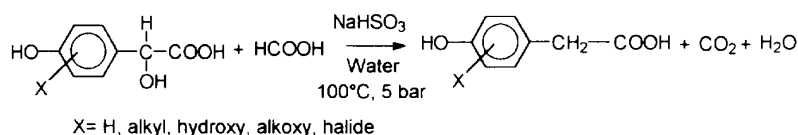
^a For 1 mol of sodium 4-hydroxymandelate; ^b determined by HPLC in the medium; calibration by means of an external reference; ^c supplementary formation of a dimer of (4-hydroxyphenyl)acetic acid identified by MS and ¹H NMR; ^d formation of sodium 2-sulfo-2-(4-hydroxyphenyl)acetic acid identified with an authentic sample [8] by HPLC retention time.

The reaction is sensitive to the acidity of the medium (runs 1, 8 and 9). It is also sensitive to the quantity of catalyst used. When the percentage of sodium bisulfite is low (run 2) the yield drops in a significant manner with the formation of a dimer of (4-hydroxyphenyl)acetic acid 1.

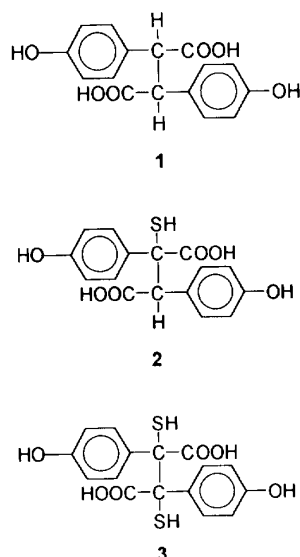
* Correspondance et tirés à part



Scheme 1



Scheme 2



When the quantity of formic acid increased (runs 4 and 5) a lower yield is observed and two secondary products are obtained. Coupled HPLC/MS analysis suggests the following formulation: $\text{C}_{16}\text{H}_{14}\text{O}_6\text{S}$ **2** and $\text{C}_{16}\text{H}_{14}\text{O}_6\text{S}_2$ **3**. There is no reduction with formic acid alone (run 6). When only sodium bisulfite is used (run 7), sodium 2-sulfo-2-(4-hydroxyphenyl)acetic acid **4** is obtained (scheme 3) [8]. This product gives no reaction with formic acid.

Identical results are obtained with the reaction catalyzed by sodium dithionite and formic acid. With sodium dithionite alone there is very small quantity of (4-hydroxyphenyl)acetic acid (3% yield) and formation of product **4**, as with sodium bisulfite alone.

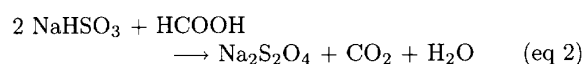
This reaction has been extended to other mandelic acids. The results obtained are recorded in table II.

The results show that this reaction is very specific for 4-hydroxymandelic acids (runs 3, 11 and 12) provided that they do not possess electroattracting groups on the aromatic ring (run 10). Under these conditions, although no examples are given, 4-hydroxymandelic acids with alkyl groups on the phenolic ring should also be reduced. The reaction gives poor results with 2-hydroxymandelic acid (run 13). The starting product is not completely transformed and the reduction also gives unidentified secondary products. This reductive system does not function with other mandelic acids (run 14).

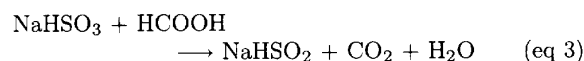
The mechanism of the reaction probably involves sodium sulfoxylate formed by the dismutation of sodium dithionite [9].



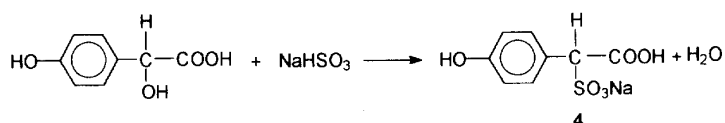
The sodium dithionite is obtained by reduction of the sodium bisulfite with formic acid [10].



These two reactions give sodium sulfoxylate by reaction of sodium bisulfite with formic acid.



The reactivity of 4-hydroxymandelic acids in this reaction is in favor of an α -carboxy quinonemethide structure to which the sulfoxylate anion is added to give the reduction product with liberation of SO_2 (scheme 4).

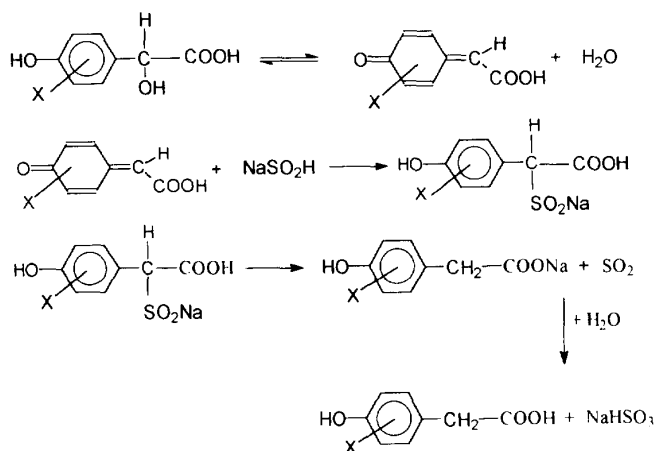


Scheme 3

Table II. Reduction^a of mandelic acids with substituents X1 and X2 on the aromatic ring.

Run	X1	X2	Yield (%) ^b (9 h)	Isolated product		
				Yield (%)	Acidimetric purity (%) ^c	HPLC purity (%) ^d
3	4-Hydroxy		93	73	99.7	99.9
10	4-Hydroxy	3-Chloro	30			
11	4-Hydroxy	3-Hydroxy	95	78	96	100
12	4-Hydroxy	3-Methoxy	85	71	95	100
13	2-Hydroxy		13			
14	4-Methoxy		No reaction			

^a Operative conditions are those of entry 3 (table I); see also *Experimental section*; ^b determined by HPLC in the medium; calibration by means of an external reference; ^c titration of the carboxylic function; ^d internal normalization at 230 nm.

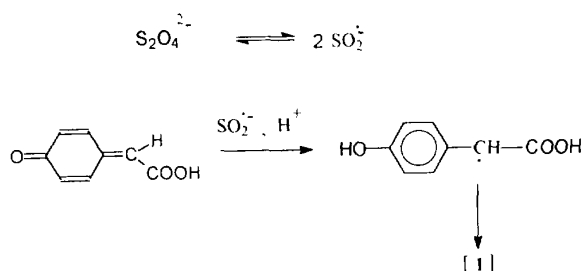
**Scheme 4**

Sodium sulfoxylate is used in the same manner for the reduction of double bond of α,β -unsaturated ketones [11] or in the reduction of aldehydes and ketones by sodium dithionite [12, 13]. Equation 3 and scheme 4 result in the formation of (4-hydroxyphenyl)acetic acids by reduction of 4-hydroxymandelic acids with formic acid and liberation of carbon dioxide.

Another mode of dismutation of sodium dithionite is the formation of the anion radical $\text{SO}_2^{\cdot-}$ [9, 12, 13], which could explain the formation of the dimeric product **1** (scheme 5). $\text{SO}_2^{\cdot-}$ reacts in a similar manner with carbonyl compounds [9].

In the case of **2** and **3**, which are formed starting from two molecules of 4-hydroxymandelic acid, radical reactions are also probably involved. H_2S formed by the decomposition of the sulfoxylate anion [9] could also play a role.

We have described a new reducing system for 4-hydroxymandelic acids with available, cheap and environmentally clean reagents. Similar results have been obtained for the synthesis of (4-hydroxyphenyl)acetic acid starting from sodium 4-hydroxymandelate, catalytic sodium bisulfite and phosphorous acid [14]. A

**Scheme 5**

similar mechanism is probably involved. However, phosphorous acid is much more expensive than formic acid.

Experimental section

4-Hydroxymandelic acids (or the corresponding sodium salts) and sodium 2-sulfo-2-(4-hydroxyphenyl)acetic acid were prepared according to the literature [1, 2 and 8] and 4-methoxymandelic acid by etherification with the dimethyl sulfate of sodium 4-hydroxymandelate by known methods.

2-Hydroxymandelic acid was provided by Société française Hoechst. Sodium metabisulfite, sodium dithionite and formic acid were purchased from Prolabo.

¹H NMR spectra were recorded on a Bruker AC 200 and coupled HPLC/MS on a Fisons Trio 2000. HPLC analyses were performed using a C18 nucleosil column (5 μ , 25 cm; water (0.1% H₃PO₄) 80: acetonitrile (0.1% H₃PO₄) 20; detection at 230 nm). All 4-(hydroxyphenyl)acetic acids isolated were compared with commercially available products for melting point, ¹H NMR, and HPLC retention time.

General procedure

In a Büchi-type glass autoclave, was introduced the mandelic acid (0.5 mol) in 400 mL water, 25.3 g formic acid (0.55 mol) and 11.4 g sodium metabisulfite (0.06 mol) and heated to 100 °C for 9 h at constant pressure to 5 bar (liberation of CO₂). The products were isolated by concentration of the aqueous medium to two-thirds and filtration at room temperature after acidification to pH 2 with dilute phosphoric acid, hydrochloric acid or sulfuric acid. They were washed with water and dried. When the reaction was started from sodium mandelates, 0.5 mol of phosphoric acid (85%), hydrochloric acid (37%) or 0.25 mol of sulfuric acid (50%) was also added.

• Dimer of 4-hydroxyphenylacetic acid 1

After reaction (condition run 2) the mixture filtered with hot and the white precipitate obtained was washed with water and dried.

¹H NMR (D₂O, NaOD, 200 MHz): 3.8 ppm (s, 2H), 6.3 ppm (d, 4H), 7 ppm (d, 4H).

MS (CI, NH₃): one peak at the mass number 284 (anhydride).

Anal calc for C₁₆H₁₄O₆: C, 63.57; H, 4.63. Found: C, 62.9; H, 4.7.

• Identification of secondary products 2 and 3

Coupled HPLC/MS conditions: HPLC: water (0.1% HCOOH) 78: acetonitrile 22.

MS (CI, NH₃): one peak at the mass number 352 (M + 18) for 2 and one peak at the mass number 384 (M + 18) for 3.

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