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A Convenient Access to Dihydroxybenzenethiols via Reduction of Iso-Thiouronium Salts with Sodium Borohydride

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A CONVENIENT ACCESS TO DIHYDROXYBENZENETHIOLS *VIA* REDUCTION OF *ISO*-THIOURONIUM SALTS WITH SODIUM BOROHYDRIDE.

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Abstract: An improved procedure for the preparation of unstable dihydroxybenzenethiols in high yields is reported, involving mild reduction of the corresponding *iso*-thiouronium salts with sodium borohydride.

In the course of a research program aimed at developing new phenolic compounds with a potential as antimelanoma agents[1,2], we have recently been faced with the problem of preparing 3,4-dihydroxybenzenethiol and some related aromatic thiols as convenient precursors for a series of alkylthiodiphenols[3]. From a survey of the literature[4]

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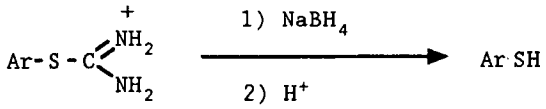
it appeared that the target thiols could readily be obtained from the appropriate *iso*-thiouronium salts by prolonged hydrolysis with refluxing concentrated NaOH under conditions of rigorous exclusion of oxygen[5,6]. In some cases, the product could preferably be isolated as the acetyl derivative. Other methods of conversion of iso-thiouronium salts into thiols include thermal decomposition with bicarbonate ion[7], for heat-stable aromatic derivatives, and treatment with a highly boiling amine, i.e. tetraethylenepentamine in ethylene glycol, adopted in the *S*-alkyl series[8].

In our hands, the alkaline hydrolysis of *S*-3,4-dihydroxyphenyl-*iso*-thiouronium acetate proved to be largely unsatisfactory, in spite of carefully controlled experimental conditions: the compound suffered from extensive degradation and the product was difficult to separate from tarry materials. Attempts to optimize the reaction conditions to increase the yield did not reach much finality.

To overcome these problems, we reasoned that a reductive cleavage of the labile *S*-3,4-dihydroxybenzene-*iso*-thiouronium salt could be a viable route. Under these conditions, a diaminomethylarylthioether intermediate would

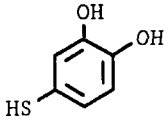
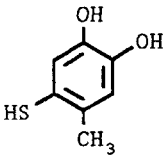
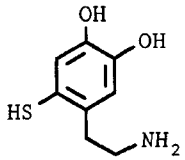
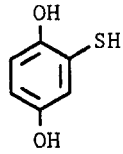
conceivably form, which can safely release the free sulphydryl group by acid hydrolysis. In searching for a handy reducing agent, we found that $NaBH_4$ can effect a mild, yet very efficient reduction of the *iso*-thiouronium group, affording the desired thiol in more than 90% isolated yield after acidic work up.



Main advantages of the method include simple experimental conditions, with brief reaction times and no need of oxygen-free atmosphere; no significant formation of polymeric materials; and very good yields of highly autoxidizable dihydroxybenzenethiols.

The results from the reduction of some representative *S*-dihydroxyphenyl-*iso*-thiouronium salts are shown in the table. It is worthwhile noting the quantitative preparation of the biologically relevant catecholamine 6-mercaptodopamine (**3**), versus a 66% reported yield with a similar procedure[9]. Attempts to prepare other dihydroxybenzenethiols bearing nitro or carboxylic substituents by the same route were defeated, due to difficulties to obtain the precursor S-aryl-*iso*-thiouronium salts.

Table

Compound	Yield[a] [%]	Lit. Yield [%]	(ref.)	^{1}H-NMR (methanol-d_4)
 1	98	81	(5)	6.84 (1H, d, J=2.0 Hz), 6.74 (1H, d, J=8.1 Hz), 6.68 (1H, dd, J= 8.1, 2.0 Hz)
 2	94	86	(5)	6.76 (1H, s), 6.61 (1H, s), 2.17 (3H, s).
 3	99	66	(9)	7.04 (1H, s), 6.76 (1H, s), 3.13 (2H, t, J=7 Hz), 2.64 (2H, t, J=7 Hz).
 4	95	--	(6)	6.64 (1H, d, J=2.8 Hz), 6.53 (1H, d, J=8.6 Hz), 6.26 (1H, dd, J=8.6,2.8 Hz).

In conclusion, mild reduction of dihydroxyaryl-*iso*-thiouronium salts with aqueous sodium borohydride provides ready access to a synthetically useful class of aromatic thiols which

is not available from common commercial suppliers. Work is in progress to clarify the mechanistic aspects of the reaction, and to assess its scope and limitations.

Experimental.

The *iso*-thiouronium salts were prepared by reaction of thiourea with the appropriate quinones according to classical literature methods[10,11]. ^{1}H-NMR spectra were recorded on a Bruker WH-270 spectrometer using TMS as internal standard. EI-MS spectra were carried out on a Kratos MS 80 apparatus. All reagents were purchased from Aldrich and were used without further purification.

General procedure for reductive conversion of iso-thiouronium salts to thiols: A large excess of sodium borohydride was added in portions to a stirred suspension of the *iso*-thiouronium salt in water at room temperature. The resulting mixture was stirred for an additional 15 min. The mixture was then acidified to about pH 2 with 6 M HCl and, only in the case of compounds **1** and **2**, heated for some 20 min to complete hydrolysis of boric intermediates formed during the reduction. After cooling, the mixture was

exhaustively extracted with ethyl acetate, the organic phase was dried over Na_2SO_4 and carefully evaporated. In the case of compound **3**, the acidified mixture was concentrated to a small volume and the white residue which precipitated was recrystallized with 0.5 M HCl. As obtained, the products were virtually pure, as checked by ^{1}H-NMR spectroscopy, and gave satisfactory mass spectra. TLC was carried out on silica gel plates using a mixture of chloroform-methanol-water 80:18:12 v/v as the eluant. The products were revealed by spraying the plates with $FeCl_3$ or with a solution of the Ellman's reagent[12], to selectively localize the bands corresponding to the desired thiols. The artifactual formation of oxidation products during development of the chromatogram was often observed. Significant contamination by disulphides was observed when the work-up of the reaction mixture was not sufficiently rapid, or when the compounds, even in the solid state, were stored without exclusion of oxygen and protection from light.

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