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A Convenient Synthesis of *o*- and *p*-Hydroxy Substituted Phenylacetonitriles and Phenethylamines

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During the course of work in isoquinoline alkaloid synthesis,[1] we required relatively large quantities of phenolic β-phenethylamines. The most direct route to these compounds is by high-pressure catalytic hydrogenation[2] or lithium aluminum hydride reduction[3] of the corresponding phenolic β-nitrostyrenes, but both of these procedures gave very variable results in our hands. Since nitriles can be smoothly reduced to amines, we sought a method for preparing phenolic phenylacetonitriles without the usual necessity of blocking the phenolic hydroxyl groups.

Ours and co-workers[4] have reported the conversion of phenolic benzylamines to the corresponding phenolic phenylacetonitriles by direct displacement with cyanide ion, presumably by way of quinone methide intermediates. Based on our previous success in using 4-hydroxybenzyl alcohols as incipient quinone methides,[5] it seemed to us that the more readily available benzyl alcohols would constitute even more convenient precursors to the desired nitriles.

As indicated by the results summarized in Table I, 2- and 4-hydroxybenzyl alcohols were smoothly converted to the nitriles by treatment with sodium cyanide in hot dimethylformamide. The 2-hydroxybenzyl case is particularly noteworthy in view of the poor results previously obtained with the analogous 2-hydroxybenzylamines.[4] Both 3-hydroxy-4-methoxybenzyl alcohol and 3,4,5-trimethoxybenzyl alcohol were recovered unchanged under these conditions and under a variety of more vigorous conditions, results that are in consonance with the postulated intermediacy of quinone methides in the substitution reaction.

A similar procedure applied to 2- and 4-acetoxybenzyl acetate has been recently reported.[6]

Table I. Preparation of Phenylacetonitriles and Phenethylamines

$$\underset{\mathbf{1}}{ArCH_2OH} \xrightarrow[DMF,\ 110\ ^\circ C]{NaCN} \underset{\mathbf{2}}{ArCH_2C{\equiv}N} \xrightarrow[HCl]{H_2,\ Pd/C} \underset{\mathbf{3}}{ArCH_2CH_2NH_2{\cdot}HCl}$$

1	2		3	
Ar	Yield, %	Mp, °C	Yield, %	Mp, °C
4-Hydroxyphenyl	67	69–71[a]		
2-Hydroxyphenyl	60	115–118[b]	87	152–154[c]
4-Hydroxy-3-methoxyphenyl	79	53–56[d]	91	213–216[e]
3-Hydroxy-4-methoxyphenyl	0			
3,4,5-Trimethoxyphenyl	0			

[a] Lit.[6] mp 70–71.5 °C. [b] Lit.[6] mp 120–122 °C. [c] Lit.[7] mp 152 °C. [d] Bp 135–140 °C (0.05 mm) [lit.[4] bp 140–144 °C (0.1 mm)]; a melting point for this compound has apparently not been previously reported. [e] Lit.[2,4] mp 212–214 °C.

Experimental Section

Melting points were measured on a Kofler hot stage and are uncorrected. The benzyl alcohols were obtained from Aldrich Chemical Co., or were prepared by $NaBH_4$ reduction of the corresponding benzaldehydes. See Table I for melting points of the products and comparisons with literature values.

4-Hydroxyphenylacetonitrile. A mixture of 2.02 g (16.3 mmol) of 4-hydroxybenzyl alcohol and 965 mg (19.7 mmol) of NaCN in 50 ml of DMF was stirred under nitrogen at 110–130 °C (oil bath) for 20 h. The solution was cooled to room temperature, 10 ml of water was added, and the mixture was basicified with solid NaOH to pH ~10. The solvent was evaporated under vacuum, 25 ml of water was added, and the solution was neutralized with glacial acetic acid (*Caution*—HCN). The mixture was extracted with $CHCl_3$, and the combined organic extracts were washed with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residual orange oil was subjected to molecular distillation at 75–80 °C (0.04 mm) to afford 1.46 g (11.0 mmol) of the nitrile as a white solid.

2-Hydroxyphenylacetonitrile. The same procedure was followed using 1.01 g (8.15 mmol) of 2-hydroxybenzyl alcohol, 483 mg (9.86 mmol) of NaCN, and 25 ml of DMF, with heating for 7 h. Molecular distillation of the crude product at 75–80 °C (0.02 mm) yielded 647 mg (4.86 mmol) of the nitrile as an off-white solid.

4-Hydroxy-3-methoxyphenylacetonitrile. The same procedure was followed using 30.8 g (0.200 mol) of 4-hydroxy-3-methoxybenzyl alcohol, 11.8 g (0.241 mol) of NaCN, and 500 ml of DMF, with heating for 6 h. Vacuum distillation of the crude product afforded 25.7 g (0.158 mol) of the nitrile as a colorless oil which solidified upon standing in the refrigerator.

2-Hydroxyphenethylamine Hydrochloride. To a solution of 717 mg (5.39 mmol) of 2-hydroxyphenylacetonitrile in 25 ml of 95% ethanol and 1 ml of concentrated HCl was added 275 mg of 10% Pd/C, and the mixture was hydrogenated at 40 psi in a Parr shaker apparatus for 10 h at room temperature. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The residual yellow oil was crystallized from ethanol–ether to give 815 mg (4.71 mmol) of the amine hydrochloride as off-white crystals.

4-Hydroxy-3-methoxyphenethylamine Hydrochloride. The above procedure was followed using 10.0 g (0.0613 mol) of 4-hydroxy-3-methoxyphenylacetonitrile, 10 ml of concentrated HCl, 2.0 g of 10% Pd/C, and 150 ml of 95% ethanol. The residual solid was re-

crystallized from methanol–ethyl acetate to afford 11.3 g (0.0557 mol) of amine salt as off-white crystals.

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Registry No.—4-Hydroxyphenylacetonitrile, 14191-95-8; 4-hydroxybenzyl alcohol, 623-05-2; 2-hydroxyphenylacetonitrile, 14714-50-2; 2-hydroxybenzyl alcohol, 90-01-7; 4-hydroxy-3-methoxyphenylacetonitrile, 4468-59-1; 4-hydroxy-3-methoxybenzyl alcohol, 498-00-0; 2-hydroxyphenethylamine HCl, 5136-97-0; 4-hydroxy-3-methoxyphenethylamine HCl, 1477-68-5; NaCN, 143-33-9.

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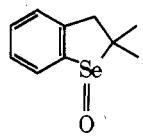
Communications

Organoselenium Chemistry. Intra- and Intermolecular Trapping of Selenenic Acids Formed by Selenoxide Elimination. Formation of a Selenium Ylide

Summary: The thermal decomposition of 3,3-dimethyldihydrobenzoselenophene oxide (**1**) leads to an unstable intermediate selenenic acid, which is trapped intramolecularly to give hydroxyselenides (**2** and **3**) or intermolecularly with diethylamine or benzyl bromide to give a selenenamide or selenoxide.

Sir: We report here the thermolysis of the selenoxide **1**,[1] which exhibits several striking departures from the behavior of related sulfur compounds.[3] Compound **1** decomposes at room temperature, rapidly in organic solvents, slowly in aqueous solution, giving the alcohols **2** and **3**. Similar results are obtained in acidic (acetic acid–dichloromethane, aqueous HCl) or weakly basic (triethylamine– or 1,8-bis(dimethylamino)-naphthalene–dichloromethane, aqueous Na_2CO_3) media.



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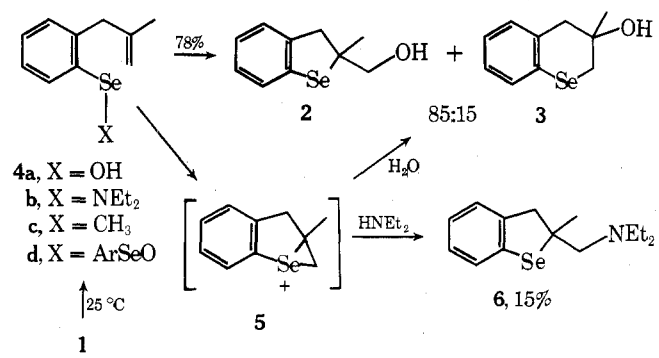
The thermal transformations of **1** are probably initiated by selenoxide syn elimination[4] to selenenic acid **4a**. Evidence for

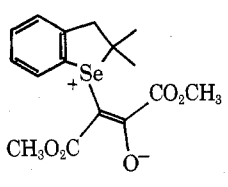


a ring-opened intermediate was obtained by the formation of selenenamide **4b** when **1** was decomposed in the presence of excess diethylamine. The selenenamide was characterized spectroscopically,[5] but could not be isolated in pure form. Reduction ($LiAlH_4$) and methylation of **4b** gave the stable selenide **4c**. *N,N*-Dialkylbenzeneselenenamides have been prepared previously by trapping of selenenic acids with amines.[6] Acyclic products were also obtained when decomposition was carried out with strong base and an alkylating agent present (see below). These results are accommodated by a mechanism in which a reactive intermediate (either **4a** or, more probably, the selenenic anhydride[7] **4d**, RSeOSeR or RSe(O)SeR) is trapped either intramolecularly by the olefin, leading to **2** and **3** via an episelenonium ion (**5**),[8] or intermolecularly by amine, with both of these processes being more rapid than the normal disproportionation to diselenide and seleninic acid. Diisopropylamine is evidently too hindered to compete effectively with olefin, since in its presence **1** decomposes to **2** and **3** giving no selenenamide. The selenenamide **4b** in the presence of excess diethylamine slowly isomerizes to **6** in low yield, presumably by reversible hydrolysis to **4a** or **4d**, cyclization to **5**, and capture by amine.[9]

The behavior of **1** is in sharp contrast to the chemistry observed for related sulfur systems. β-Oxygenated sulfides are formed from sulfenic acids, but only in the presence of electrophiles (typically acetic anhydride or acetic acid).[3c,d] In the present study, products of electrophilic double-bond addition (**2**, **3**, and **6**) are observed even under basic conditions.

When the decomposition of **1** is carried out in acidic or basic D_2O to test for reversibility of the ring opening, no deuterium incorporation in **2** and **3** could be detected. This demonstrates that the *selenenic acid does not revert to selenoxide* competetively with further transformation. A number of sulfoxide syn eliminations have been shown to be highly reversible under neutral conditions.[3b-h] Even intermolecular olefin additions of sulfenic acids to give sulfoxides can frequently be observed.[3b,h] We have carried out the decomposition of **1** in the presence of ethyl propiolate, phenylacetylene, norbornadiene, or dihydropyran, but have seen no indication of intermolecular reaction with **4a**.

Dimethyl acetylenedicarboxylate reacted rapidly with **1**. The adduct was not the vinyl selenoxide expected from addition of selenenic acid,[3h] but, rather, the ylide **7** formed by



7

direct reaction with selenoxide **1**. Similar ylides have been formed from sulfoxides[10] (although at 100 rather than at 0 °C), as well as from phosphine imides.[11] The much greater rate of