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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Anthony Hadfield , Harold Schweitzer , Michael P. Trova & Kenneth Green (1994) Practical, Large-Scale Synthesis of 2,2-Dimethyl-5-hydroxy-4-oxo-benzo-1,4-dioxin, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:7, 1025-1028, DOI: 10.1080/00397919408020778

To link to this article: <u>http://dx.doi.org/10.1080/00397919408020778</u>

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PRACTICAL, LARGE-SCALE SYNTHESIS OF 2,2-DIMETHYL-5-HYDROXY-4-OXO-BENZO-1,4-DIOXIN

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Abstract: Modification of a known procedure employing the interaction of thionyl chloride, acetone, and 2,6-dihydroxybenzoic acid was found, to provide the title compound in multikilogram quantities of acceptable yield and purity.

An initial approach to preparing multikilogram quantities of a monoalkylated derivative of 2,6-dihydroxybenzoic acid methyl ester¹ via a selective alkylation procedure proved to be unsatisfactory, because of the accompanying formation of unwanted quantities of the corresponding disubstituted material. In an effort to address this problem, we chose to construct an appropriately protected intermediate which upon elaboration would produce only the desired array of functionality. At the onset, we foresaw no difficulty in obtaining the acetonide 2 from 1, however, subsequent experimentation proved this to be a more substantial problem than had been anticipated. Described herein are our developments which have resulted in a procedure allowing for the straightforward preparation of large quantities of 2c, an intermediate we believe will find use in other areas of synthesis.

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A search of the literature revealed reports for the preparation of **2a** and **2b** using (a) dibromomethane/sodium hydroxide/benzene and (b) benzaldehyde diacetoxyacetal/glacial acetic acid/PTSA respectively ².

Unfortunately, neither of these compounds could be formed in our hands using these approaches. Attempts to extend this chemistry using variations such as (a) acetone/toluene/H₂SO₄(cat.) (b) benzal bromide/MEK/potassium carbonate (c) benzal bromide/DMF/sodium hydride and (d) paraformaldehyde/benzene/PTSA, 2,2-dimethoxypropane/BF₃-Et₂O/THF/-78°C, were not met with success. Recently, for 2,4,6-trihydroxybenzoic acid this problem was addressed using TFA-TFAA/acetone where a 35% yield of the desired benzodioxin was realized³. When this methodology was applied to our system, a yield of 16% was obtained. For the quantities of material we desired, this was not considered a workable solution.



2a: R = R' = H 2b: R = phenyl, R' = H

2c: R = R' = methyl

Another option, employing the use of thionyl chloride and acetone had previously been applied to salicylic acid analogues, and involved temperatures and reagents which appeared attractive from the perspective of scale-up ⁴. Initial attempts, however, at integrating this chemistry into our system produced a complex mixture of byproducts from which the desired material could be isolated in only 20% yield after the application of an arduous purification procedure.

In an effort to understand these results, further literature work was undertaken. A report was subsequently uncovered describing the reaction of neat thionyl chloride with ketones to produce a variety of α -substituted byproducts ⁵. We concluded that the problem of enhanced byproduct formation in our system might be due to such interactions,

and rationalized that the use of an inert solvent could significantly help resolve the problem. Therefore, we modified our initial experimental conditions to incorporate the use of 1,2-dimethoxyethane as a solvent, DMAP as a cataylst and almost equimolar equivalents of the benzoic acid, acetone and thionyl chloride. The thionyl chloride was added in aliquot amounts over a 2 h period, and the reaction temperature was kept below 30 °C.

With respect to the purification procedure we were faced with addressing how to remove large quantities of hydrogen chloride dissolved in the reaction mixture. Earlier attempts to extract the products between methylene chloride and aqueous sodium carbonate caused the formation of emulsions and resulted in loss of product due to significant in situ hydrolysis. A workable solution was achieved by vigorously purging the reaction mixture with nitrogen. We found that after 8 hours of nitrogen purge, the excess hydrogen chloride gas was effectively removed while simultaneously evaporating most of the solvent. The resulting residue was slurried in hexane-methylene chloride (1:1 - v/v) and filtered through silica gel. Evaporation of the filtrate and addition of hexane gave a solution from which the desired product efficiently precipitated upon being stored overnight at 15 °C. Using this procedure, a total of 20 kg of **2c** have been prepared, to date.

Under these new conditions a process amendable to easy scaleup, which represents a dramatic improvement over earlier results. was achieved, affording a product of acceptable quality in about 65 % yield.

Experimental Section

2,2-Dimethyl-5-Hydroxy-4-Oxo-Benzo-1,4-Dioxin (2c)

A 22 L, 3-neck round bottom flask was charged 2,6-dihydroxybenzoic acid (3.25 kg, 21.12 mol), dimethoxyethane (7 L), 4-

dimethylaminopyridine (133 g, 1.1 mol) and acetone (2 L, 28 mol). This solution was cooled to 20 °C and a solution of thionyl chloride (3.6 kg, 30.2 mol) dissolved in dimethoxyethane (1.0 L) was added over 2 h, maintaining the temperature at less than 30 °C. Upon completion of the addition, the resulting solution was allowed to stir for 1 h. At this point, the solution was transferred to a 20 L vacuum bottle where nitrogen was bubbled through the solution with a slight vacuum placed on the system using a water aspirator. After 8 h, the remaining solvent was evaporated and the residue dissolved in a mixture of hexane-methylene chloride (1:1, v/v; 4.0 L) and filtered through a pad of silica gel (1.1 kg). The pad was washed with 8.0 L of the solvent mixture and the filtrate evaporated. To the residue was added hexane

(3.0 L) and the resultant solution cooled to 15 °C and allowed to stand overnight. The desired product was filtered and air dried to produce **2c** (2.71 kg, 14.0 mol), 66%. ¹H-NMR (300 MHz, CDCl₃) δ 10.34 (s, 1H), 7.41 (t, 1H, J = 8.3 Hz), 6.63 (dd, 1H, J = 0.8 Hz, 8.2 Hz), 6.44 (dd, 1H, J = 0.8 Hz, 8.2 Hz), 1.75 (s, 6H); ¹³C NMR (75.5 MHz, CDCl₃) δ 165.46, 161.37, 155.54, 137.90, 110.78, 107.23, 107.10, 99.31, 25.63. Anal. Calcd. for C₁₀H₁₀O₄ : C, 61.85; H, 5.19. Found: C, 61.61; H, 5.14.

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6) We found that 2,6-dihydroxybenzoic acid obtained from various sources invariably had a significant degree of hydration (7 - 12%). If this material was not dried, it would not perform satisfactorily in the procedure. Therefore, we would routinely stir the 1,2-dimethoxyethane solution to be used in the reaction over MgSO₄ (anhydrous) overnight prior to use.

(Received in the USA 16 September 1993)