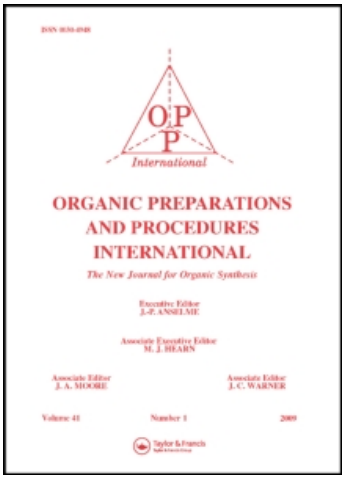

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AN EFFICIENT AND SCALABLE SYNTHESIS OF METHYL 3-HYDROXYMETHYLBENZOATE

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(05/01/00)

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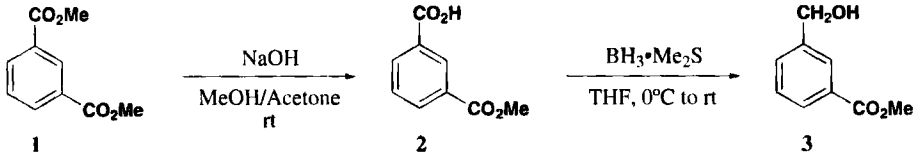
The preparation of the large quantities (from a few to several hundred grams or even kilograms) of biologically active compounds required by the pharmaceutical industry for both animal and human testing still represents, in many cases, a formidable challenge for the synthetic organic chemist. The procedures employed for the synthesis of small amounts of compounds are not always scalable due to technical difficulties (size of equipment, toxicity of starting materials and intermediates, safety issues, etc) or the cost of chemicals. Therefore, the necessity for short, high-yielding routes at a reasonable cost and where the intermediates are easy to isolate and purify is of paramount importance for successfully synthesizing the target molecule.

In an important anti-HIV project currently underway in our laboratories related to the synthesis of antagonists for the CCR5 co-receptor, the need for large quantities of the important intermediate methyl 3-hydroxymethylbenzoate (**3**) arose. In addition, we were interested in a methodology that allowed a simple isolation and the avoidance of time-consuming purification processes such as chromatography. This reagent is not commercially available and, to our surprise, a thorough bibliographic search revealed that it has been hardly cited in the past and, in most cases, included in the patent literature.[1] The use of the conditions previously reported, applied to our case in order to obtain large quantities of this intermediate, led to either incomplete reactions or crude materials that required additional purification. Therefore, an improvement of the existing methodology was needed. The synthetic route followed to prepare methyl 3-hydroxymethylbenzoate (**3**) is given below:



1 2 3

The most straightforward route leading to this hydroxy ester starts from commercially available and inexpensive dimethyl isophthalate (**1**), which after treatment with sodium hydroxyde in a methanol/acetone mixture, yields the monomethyl ester of isophthalic acid (**2**). Selective reduction of the carboxylic acid functionality with borane-dimethyl sulfide complex in THF gives the desired product.[2]

When the partial hydrolysis of the diester was attempted following the procedure reported by Achiwa *et al*,[3] using one equivalent of $Ba(OH)_2$ in methanol, the reaction was incomplete, even after prolonged reaction times (up to two days at ambient temperature) and the addition of more base increased the amount of diacid. Other conditions such as NaOH in methanol gave incomplete reaction as well. Interestingly, when NaOH was used with other solvents such as ethanol or isopropanol, the monoethyl or monoisopropyl ester of isophthalic acid was obtained, respectively. We found that the best conditions to prepare the desired intermediate consist of the addition of a NaOH (1.15 equivalents) methanolic solution to a solution of the diester in acetone at room temperature. No diacid formation was detected. The addition of NaOH in methanol to a refluxing solution of the diester in acetone gave rise to more by-products.[4] The monoacid can be further purified by recrystallization from hexanes/ethyl acetate if desired.

As far as the second step is concerned, the borane-dimethyl sulfide reduction worked best in our hands. The crude hydroxy ester **3** is sufficiently pure to be used further without any additional purification. If necessary, the product may be purified further by distillation. For this step, we also tried the procedure by Periasamy *et al.*,[5] where $NaBH_4$ is used in the presence of I_2. Even though the yields were excellent (90-95%), after a few days, the pale yellow oil first obtained turned dark brown, revealing the existence of some residual iodide which, perhaps upon contact with air, was slowly oxidized to iodine. Even after thoroughly washing an ethereal solution of the product with saturated aqueous $NaHSO_3$, the color reappeared after a few days. When an ethanolic silver nitrate test was run on this product, we obtained a positive test (a thick, yellow precipitate appeared after a few seconds) which most likely indicates the presence of methyl 3-iodomethylbenzoate as a by-product of the reaction. An alternative approach reported by Yamada *et al.*,[6] that involves the formation of a mixed anhydride and subsequent reduction with $NaBH_4$, was not attempted due to the more cumbersome experimental procedure, which included the filtration of highly moisture sensitive material.

In summary, we have developed an efficient and scalable synthesis of methyl 3-hydroxymethylbenzoate, which provides access to this hydroxy ester in large amounts and in a straightforward manner.

EXPERIMENTAL SECTION

Dimethyl isophthalate, borane-methylsulfide complex and acetone were obtained from Aldrich Chemical Co. and used as received. Sodium hydroxide and methanol were obtained from Mallinckrodt. THF was obtained from Burdick & Jackson and freshly distilled from sodium. Melting points were determined with a Thomas Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian-Gemini-400 in $CDCl_3$ as both solvent and internal standard.

Monomethyl Isophthalate (2).- In a 3-necked, 5-liter round-bottomed flask equipped with a mechanical stirrer was placed dimethyl isophthalate (200.00 g, 1.03 mol) dissolved in 2 liters of acetone. To this mixture was added dropwise over 20 minutes a solution of NaOH (43.26 g, 1.08 mol) in methanol (400 mL). The resulting milky suspension was stirred at ambient temperature for 20 h. TLC analysis showed that the reaction was not complete and 4.32 g of NaOH (0.11 mol) was added and the suspension stirred for another 4 h. Then, the solvent was removed under vacuum and the white precipitate thus obtained was dissolved in water (4 liters). Concentrated HCl was added dropwise until pH 1 and the resulting precipitate collected , washed with water (4 x 1 liter) and dried in a vacuum oven for 48 h at 65° to give 182.20 g (98%) of the monomethyl isophthalate as a white solid, mp: 188-190° (*lit.*[7] 190-191°). ^{1}H NMR (d^6-DMSO): δ 3.83 (s, 3H), 7.59 (t, 1H, J = 7.8 Hz), 8.11 (dd, 2H, J = 7.8 Hz), 8.41 (s, 1H).

Methyl 3-Hydroxymethylbenzoate (3).- In a 3-necked, 2-liter round-bottomed flask equipped with a magnetic stirrer and a low temperature thermometer under a nitrogen atmosphere was placed monomethyl isophthalate (20.00 g, 0.11 mol) dissolved in 500 mL of dry THF. This solution was placed in an ice-water bath and a 2 M solution of BH_3-Me_2S in THF (280 mL, 0.55 mol) was added dropwise over 40 minutes while the temperature inside of the flask was kept below 5°.[8] After 15 minutes, the cooling bath was removed and the solution allowed to reach ambient temperature. After 4 hours, the reaction was carefully quenched (strong gas evolution) with small pieces of ice while cooling it in an ice-water bath. When the gas evolution had ceased, brine (200 mL) was added and the resulting mixture extracted with diethyl ether[9] (3 x 200 mL). The combined organic extracts were washed with dilute bleach (200 mL) [in order to remove the excess of dimethyl sulfide], with brine (100 mL) and dried over $MgSO_4$. The solvent was removed under vacuum to give an oil which contained a small amount of a white precipitate. Diethyl ether was added (50 mL), the solid removed by filtration and washed with fresh diethyl ether (2 x 20 mL). Removal of the solvent from the filtrate under vacuum yielded 18.40 g (100% yield) of a pale yellow oil, which was used in the next step of our synthesis without any further purification. The product can be further purified by distillation, bp. 125-127° / 0.04 mm Hg; *lit.*[6] 166-167° / 13 mm Hg, to give analytically pure hydroxy ester as a colorless oil, even though the yield decreases considerably (from quantitative to 61%).[10] ^{1}H NMR ($CDCl_3$): δ 3.05 (s, 1H), 3.83 (s, 3H), 4.63 (s, 2H), 7.34 (t, 1H, J = 7.6 Hz), 7.47 (d, 1H, J = 7.6 Hz), 7.86 (d, 1H, J = 7.8 Hz), 7.93 (s, 1H).

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8. This reaction should be run in a well ventilated hood due to the foul smell of dimethyl sulfide.

9. Methyl *tert*-butyl ether (MTBE) can also be used instead of diethyl ether without affecting the result of the extraction. MTBE is less flammable and less likely to form peroxides than diethyl ether.

10. A thick oil, that solidified upon cooling, remained in the flask after the distillation was over.

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