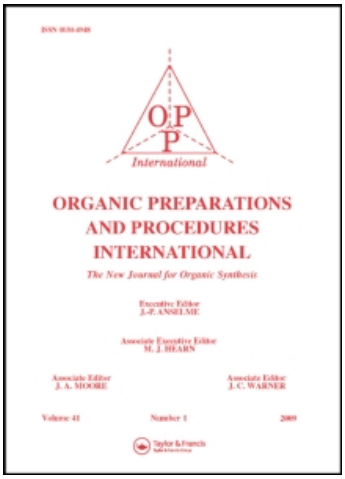

Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN IMPROVED SYNTHESIS OF 2,4-DIMETHOXYPHENYLACETIC ACID

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To cite this Article Alesso, E. N. , Aguirre, J. M. and Lglesias, G. Y. Moltrasio(1992) 'AN IMPROVED SYNTHESIS OF 2,4-DIMETHOXYPHENYLACETIC ACID', Organic Preparations and Procedures International, 24: 6, 690 — 692
To link to this Article: DOI: 10.1080/00304949209356249
URL: http://dx.doi.org/10.1080/00304949209356249

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AN IMPROVED SYNTHESIS OF 2,4-DIMETHOXYPHENYLACETIC ACID

Submitted by (05/08/92)

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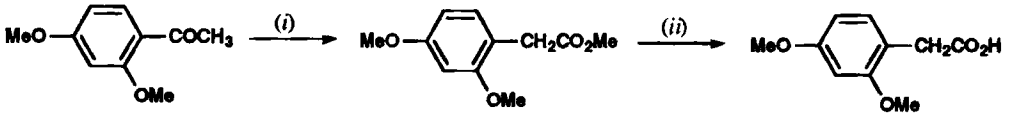
Our need for 2,4-dimethoxyphenylacetic acid (2,4-DMPA, **3**) revealed the absence of a convenient preparation and spectroscopic data for this compound in the literature. Indeed, the procedure of Snook[1] always gave **3** in yields ranging from trace amounts to 20% and when the reaction was repeated following Buess' conditions[1e] a mixture of 2,4- and 2,6-DMPA was obtained. An attempt to prepare the title compound following the Prevost conditions[2] by treatment of 2,4-dimethoxyacetophenone (**1**) with iodine and silver nitrate in refluxing methanol gave an 80% yield of 2,4-dimethoxy-5-iodoacetophenone. The Kindler modification of the Willgerodt reaction[3] afforded a mixture of 2,5-*bis*-(2,4-dimethoxyphenyl)thiophene (56% yield) and 2,4-DMPA (30% yield). We now describe the

direct oxidation of 2,4-dimethoxyacetophenone (1) with thallium(III) nitrate,[2,4] using methanol and perchloric acid to give methyl 2,4-dimethoxyphenylacetate (2) which was hydrolyzed to 3 in 63% overall yield (from 1).



1 2 3

i) $Tl(NO_3)_3$, MeOH, H^+ *ii*) 1. OH^-, EtOH; 2. H_3O^+.

EXPERIMENTAL SECTION

The ^1H and ^{13}C NMR spectra were recorded on a Bruker WO 80 SYFT or Varian FT 80A spectrometer in deuteriochloroform; chemical shifts are reported in part per million downfield from internal TMS. Elemental analyses were carried out in our laboratories using a Coleman analyzer. Melting points (uncorrected) were obtained on a Thomas Hoover apparatus.

Thallium(III) Nitrate Trihydrate was prepared by treatment of 14.5 g (57.5 mmol) of thallium(III) oxide with 34 mL of warm conc. nitric acid and cooling the pale yellow solution to 0°. The crystals of thallium(III) nitrate trihydrate were collected and dried *in vacuo* over phosphorus pentoxide to yield 23.5 g (92%), mp. 102-103°. ***(CAUTION: Thallium compounds are highly toxic).***

Methyl 2,4-Dimethoxyphenylacetate (2).- To a stirred solution of 2,4-dimethoxyacetophenone (2.5 g, 13.9 mmol) in methanol (31 mL) containing perchloric acid (5 mL, 70% w/w), was slowly added thallium(III) nitrate trihydrate (6.17 g, 13.9 mmol). After 1 hr at room temperature, the precipitate of thallium(I) nitrate was removed by filtration and the filtrate poured into water. The aqueous solution was extracted with methylene chloride (2 x 15 mL), and the organic extract was washed with cold water and dried (sodium sulfate). The solvent was removed and the residual oil was purified by chromatography on alumina using benzene as eluent to afford 2.45 g (84%) of methyl 2,4-dimethoxyphenylacetate (2) as white crystals, mp. 47° (EtOH). ^1H NMR ($CDCl_3$): δ 3.53 (s, 2H, CH_2), 3.65 (s, 3H, OCH_3), 3.77 (s, 6H, OCH_3), 6.45 (m, 2H, Ar-3 and Ar-5) and 7.05 (d, J = 8.0 Hz, 1H, Ar-6).

Anal Calcd. for: $C_{11}H_{14}O_4$: C, 62.91; H, 6.72. Found: C, 63.01; H, 6.70

2,4-Dimethoxyphenylacetic Acid (3).- A solution of methyl 2,4-dimethoxyphenylacetate (2.0 g, 9.52 mmol), NaOH (0.975 g) and ethanol (30 mL) was refluxed for 8 hrs. The ethanol was evaporated and the residue was treated with water. The aqueous solution was washed with chloroform and then was acidified (conc. HCl). The precipitate was collected, washed with cold water and recrystallized from water to yield 1.45 g (78%) of 3 as white crystals, mp. 110° (EtOH), lit.[1a] 107-108°. ^1H NMR ($CDCl_3$): δ 3.5 (s, 2H, CH_2), 3.7 (s, 6H, OCH_3), 6.4 (m, 2H, Ar-3 and Ar-5), 7.0 (d, J = 8.0 Hz, 1H, Ar-2) and 9.45 (br s, 1H, COOH).

2,4-Dimethoxy-5-iodoacetophenone.- Iodine (2.96 g, 11.7 mmol), was added to a suspension of silver nitrate (3.96 g, 23.3 mmol) in a mixture of methanol (50 mL) and trimethyl orthoformate (17 mL) containing 2,4-dimethoxyphenylacetophenone (2 g, 11.1 mmol); the mixture was then heated

under reflux for 1 hr. After the solution had been cooled, the silver salts were filtered off and the filtrate was evaporated. The solid residue was purified by preparative TLC (silica gel, chloroform) to afford 3.2 g (94%) of white crystals, mp. 134-136° (EtOH). ^{1}H NMR: ($CDCl_3$): δ 2.5 (s, 3H, CH_3), 3.90 (s, 6H, OCH_3), 6.35 (s, 1H, Ar-3), 8.20 (s, 1H, Ar-6).

Anal. Calcd. for $C_{10}H_{11}IO_3$: C, 39.23; H, 3.61. Found: C, 40.01, H, 3.70

2,5-*bis*-(2,4-Dimethoxyphenyl)thiophene.- This compound was obtained in 56% yield using the Schwenk[3a] and Vogel[3b] procedures. It was obtained as a brown oil which was purified by preparative TLC (silica gel, benzene). ^{1}H NMR ($CDCl_3$): δ 3.8-3.9 (s, 12H, OCH_3), 6.5 (m, 4H, Ar-3, Ar-5), 7.25 (d, 2H, Ar-6), 7.5 (d, 2H, H-3 and H-4).

Anal. Calcd. for $C_{20}H_{20}O_4S$: C, 67.40; H, 5.66. Found: C, 67.70, H, 5.70

Acknowledgement.- The authors express their gratitude to the SECYT, Universidad de Buenos Aires, and CONICET for support of this study.

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A CONVENIENT SYNTHESIS OF (4-NITROPHENYL) (4-PIPERIDINYL) KETONE

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Recently altanserin (**1a**) labeled with ^{18}F has been described as a potential ligand for the mapping of 5-HT_2 receptors in humans using Positron Emission Tomography (PET).[1] [^{18}F]Altanserin