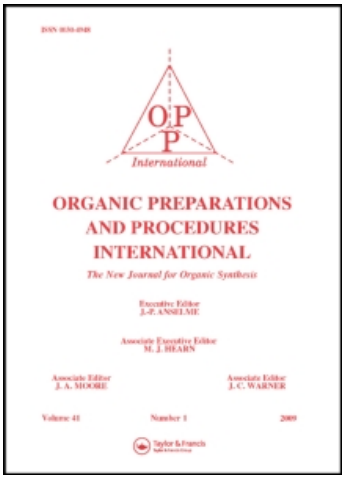

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IMPROVED PREPARTION OF 2,5-DIMETHYL-1,3-CYCLOHEXANEDIONE

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IMPROVED PREPARATION OF 2,5-DIMETHYL-1,3-CYCLOHEXANEDIONE

Submitted by (12/19/94)
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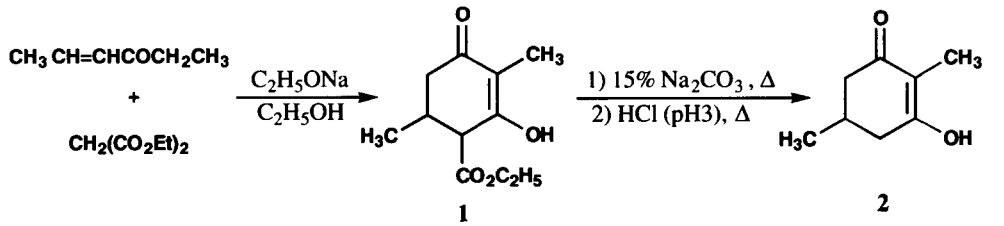
As part of our continuing interest in cyclohexanedione chemistry,[1] we have devised a new approach of the synthesis of 2,5-dimethyl-1,3-cyclohexanedione. Compound **2** has previously been prepared in 50-70% yield by alkylation of 5-methyl dihydroresorcinol,[2] obtained by the procedure of Crossly and Renouf,[3] with methyl iodide in the presence of 4N sodium hydroxide. We now describe an improved preparation (80% overall yield) of **2** which avoids the alkylation step; only 2,5-diphenyl-1,3-cyclohexanedione[4] had been made in a similar way before.

Compound **1** was obtained in 84% yield by the Michael addition of diethyl malonate to hex-2-en-4-one. Alkaline hydrolysis of **1** afforded the corresponding carboxylic acid which underwent decarboxylation by refluxing for 4 hrs in acidic media (pH 3) in 95% yield.



1 **2**

EXPERIMENTAL SECTION

Melting points were determined from Kofler bench and are uncorrected. ^{1}H NMR spectra were recorded using 250 MHz Brucker spectrometer. The solvent is quoted in parenthesis before the chemical shift values.

Ethyl 2,4-Dioxo-3,6-dimethylcyclohexanecarboxylate (1).- To sodium (4.9 g, 0.213 mol) dissolved in dry ethanol (100 mL) was added diethyl malonate (32.64 g, 0.203 mol), followed after 20 minutes by hex-2-en-4-one (20 g, 0.203 mol) in dry ethanol (400 mL). The mixture was stirred at room temperature for 24 hrs. The solution was then evaporated under reduced pressure and the residue was dissolved in water (500 mL) and filtered. Acidification of the filtrate with conc. hydrochloric acid afforded **1** (36.2 g, 84%) as a colorless solid, mp.116-118°. ^{1}H NMR ($CDCl_3$): δ 1.07 (3H, d, J 6.3 Hz, CH_3), 1.28 (3H, t, J 7.1 Hz, $CO_2CH_2\mathit{CH_3}$), 1.71 (3H, s, CH_3), 2.21-2.35 (1H, m), 2.49-2.67 (2H, m), 3.06 (1H, d, J 10.4 Hz), 4.22 (2H, q, J 7.1 Hz, $CO_2\mathit{CH_2}$ CH_3).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.53; H, 7.70

2,5-Dimethyl-1,3-cyclohexanedione (2).- The diketoester **1** (36 g, 0.171 mol) was refluxed for 15 hrs with sodium carbonate (45.2 g, 0.425 mol) in water (300mL). The solution was allowed to cool to

room temperature and then acidified to pH 3 with conc. hydrochloric acid. The mixture was refluxed for 4 hrs. Upon cooling, the dione **2** precipitated and was collected. The solid was crystallized from water to give 21.8 g (95%) of colorless needles, mp. 174-176°, lit.[5] 175-176°. ^{1}H NMR ($CDCl_3$-DMSO): δ 0.89 (3H, d, J 4.9 Hz, CH_3), 1.54 (3H, s, CH_3), 1.92-1.99(3H, m), 2.29 (1H, d, J 13.5 Hz), 9.28 (1H, brs).

Anal. Calcd. for $C_8H_6O_2$: C, 68.57; H, 8.57. Found: C, 68.73; H, 8.85

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AN IMPROVED SYNTHESIS OF 4'-HYDROXY AND 4'-METHOXYBIPHENYL-2-CARBOXYLIC ACIDS

Submitted by (10/20/94)

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Biphenyl derivatives of type **1** were needed as part of our research on non peptidic AII antagonists.[1] Previously these compounds had been synthesized by radical coupling[2] of diazonium salts or by the Ullmann reaction.[3,4] Compound **1a** had been obtained previously in low yield (10%) by the Gomberg-Bachman reaction between *o*-anisidine and methyl benzoate;[5] this route, however, led to a mixture of products. Over the past ten years, new coupling methodologies based on the use of palladium or nickel,[6-8] have been found to be very convenient because of the mild conditions and the yields are frequently quite high. Furthermore, these techniques are often more regioselective, a valuable feature in the synthesis of unsymmetrical biphenyls. In general the syntheses are realized with palla-