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Dimethyl β-Ketoadipate

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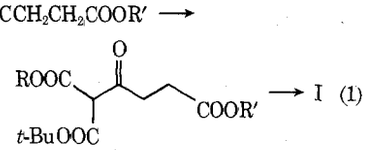
Several years ago there was reported a new and improved synthesis of several esters of the important biomolecule β-ketoadipic acid (I).[1] The starting materials employed were alkyl *tert*-butyl malonate and β-carboalkoxypropionyl chloride (eq 1). We report here an improvement

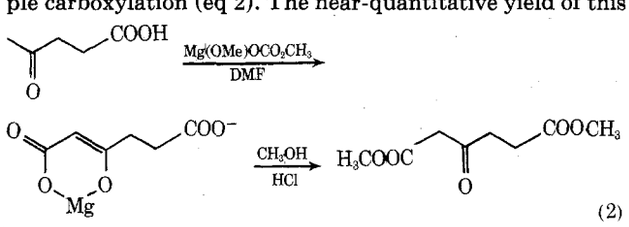
$$ROOCCH_2COO\text{-}t\text{-}Bu + ClOCCH_2CH_2COOR' \longrightarrow$$



$$\longrightarrow I \quad (1)$$

in the preparation that (a) avoids the problem of synthesis of the starting materials above and (b) employs cheap levulinic acid as starting material.

Carboxylation of levulinic acid by the procedure of Finkbeiner and Wagner[2] followed by Fischer esterification of the crude product affords a 92% isolated yield of dimethyl β-ketoadipate. There was no evidence for formation of the isomeric dimethyl acetylsuccinate or products from multiple carboxylation (eq 2). The near-quantitative yield of this



(2)

preparation requires use of a large (tenfold) excess of the carboxylating agent methylmagnesium carbonate. The regioselective nature of this reaction is consistent with the findings of Crombie, *et al.*, in an analogous case.[3]

Dimethyl β-Ketoadipate. A solution of 10.6 g (91.4 mmol) of levulinic acid (Eastman Technical) in 360 ml (920 mmol) of 2.56 *M* methylmagnesium carbonate in dimethylformamide (DMF)[2] was heated at 135° for 24 hr. The DMF was removed by distillation under vacuum at 60°. Trituration of the residue with ether gave after filtration and air drying of 136 g of yellow solid. The solid was suspended in 820 ml of methanol in a 3-l., three-necked, round-bottom flask equipped with a mechanical stirrer, a condenser, and a gas inlet tube. After cooling to −10°, hydrogen chloride was passed over the mixture until saturation had occurred. After standing overnight and warming to 25°, the mixture was concentrated at 40° under reduced pressure. The syrupy residue was poured on ice and the aqueous solution was extracted four times with chloroform. The organic extracts were washed with saturated bicarbonate solution and water and dried over anhydrous sodium sulfate. Distillation through an 1-in. Vigreux column gave 15.8 g (92% yield) of dimethyl β-ketoadipate as a colorless liquid: bp 94–96° (0.35 mm) [lit.[1] bp 110–111° (0.25 mm)]; nmr ($CDCl_3$) δ 2.70 (4 H, A_2B_2 multiplet), 3.49 (2 H, singlet), 3.62 (3 H, singlet), and 3.67 (3 H, singlet).

Registry No.—Dimethyl β-ketoadipate, 5457-44-3; levulinic acid, 123-76-2.

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Phenacyl Kojate Compared with Crown Ethers

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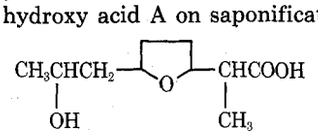
Crown ethers are of interest because of their ability to form complexes with sodium chloride and related salts. Following Pedersen's papers[1] there has been considerable development of this area. A comprehensive summary[2] has appeared recently. It lists 107 references, most of which are selected from the past decade. The area is diverse, and includes carbohydrates, for example. One obtains $C_{12}H_{22}O_{11} \cdot 2CH_3COOK$ when ether is added to a 0.02 *M* solution of sucrose[3] in ethanol that contains 0.4 *M* potassium acetate. Again, Sidgwick and Brewer[4] reported that the dihydrate of sodio-1-phenyl-1,3-butanedione was soluble in toluene whereas the anhydrous sodio derivative was insoluble. This observation was confirmed and extended by Bright, Milburn, and Truter.[4]

Nonactin is a neutral antibiotic, $C_{40}H_{64}O_{12}$, obtainable from *actinomyces*. It is a macrocyclic ester that yields four molecules of hydroxy acid A on saponification. Nonactin[5]



A

binds KCNS to form a complex wherein K^+ is surrounded by eight oxygens, four coming from the four ether oxygens and four from the four ester carbonyls. Also there are acidic