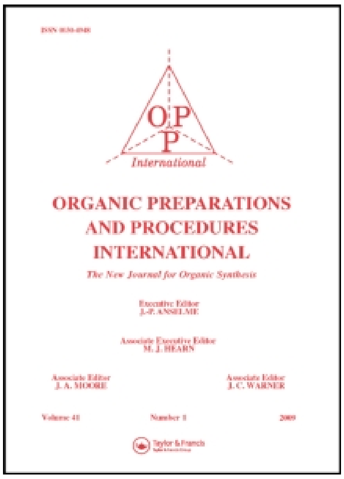

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AN IMPROVED SYNTHESIS OF DIMETHYL (*E*)-5-METHOXYCARBONYL-2-ENEDIOATE AND DIMETHYL (*E*)-6-METHOXYCARBONYL-2-ENEDIOATE

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AN IMPROVED SYNTHESIS OF DIMETHYL (*E*)-5-METHOXYCARBONYL-2-HEXENEDIOATE AND DIMETHYL (*E*)-6-METHOXYCARBONYL-2-HEPTENEDIOATE

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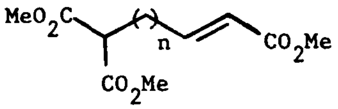
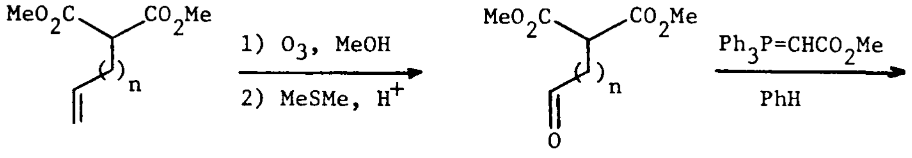
The recently described tandem Michael addition procedure[1] for five- and six-ring annulations required large quantities of dimethyl (*E*)-5-methoxycarbonyl-2-hexenedioate (**1**) and dimethyl (*E*)-6-methoxycarbonyl-2-heptenedioate (**2**).



1 n = 1
2 n = 2

There are currently two known preparations of **1** (ethyl ester), both of which are inadequate for the production of this compound in 20-30 g quantities. The first method[2] which involves alkylation of sodium diethyl malonate with ethyl (*E*)-4-bromo-2-butenoate, at best, gives a 20-30% yield and is, therefore, unsatisfactory. An alternative approach[3] introduces the malonate fragment by nucleophilic attack of the malonate anion on di-μ-chlorobis[1-3-η-(1-ethoxycarbonylallyl)palladium(II)]. While this procedure is reported to afford a quantitative yield of **1**, the low yield in the preparation of the palladium complex[4] coupled with the cost factor makes this route unfeasible. Triester **2**, on the other hand, has not been previously reported but its synthesis would be subject to the same problems by direct alkylation and would require the use of the difficulty accessible methyl (*E*)-5-bromo-2-pentenoate.[5] Secondly, by virtue of its extended carbon chain, this second target molecule does not lend itself to preparation by nucleophilic substitution of the malonate anion to a π-allylpalladium complex.[3] We, therefore, found it necessary to develop our own approach to these useful compounds and now report, a simple, low-cost, two-step procedure for the preparation of 1 and 2 on a large scale.



1
2

3 n = 1
4 n = 2

5
6

The synthesis employed is illustrated in the scheme and begins with dimethyl allyl malonate (3) and dimethyl 3-butenylmalonate (4).[6] Treatment of 3 and 4 with ozone followed by reductive workup with dimethyl sulfide[7] yielded the diester aldehydes 5 and 6, respectively, in 90% yield. After purification, these aldehydes were reacted with methyl (triphenylphosphoranylidene)acetate in refluxing benzene to generate 1 and 2 in 70-75% yield.

The current approach to the synthesis of 1 and 2 constitutes a substantial improvement over the previously described methods. Surprisingly, it is only the malonate derived compounds which are difficult to prepare by the direct alkylation procedure with (E)-4-bromo-2-butenoate; other activated methylene compounds give respectable yields (60-90%) using these conditions.[2,3] Thus, our method complements this established route giving us access to a variety of substrates useful for ring synthesis by the tandem Michael reaction.

EXPERIMENTAL SECTION

All reagents and solvents were used as received from commercial suppliers. Ozonolyses were performed using a Welsbach T-23 laboratory ozonizer. IR spectra were recorded with a PE-681 instrument and are referenced to polystyrene. ^{1}H-NMR spectra were recorded at 60 MHz using a Hitachi Perkin-Elmer R24-B instrument or at 300 MHz using a Varian XL-300 superconducting FT instrument; chemical shifts are reported in δ units relative to internal tetramethylsilane. High resolution mass spectra were obtained at 70 eV using a CEC double focusing mass spectrometer.

General Procedure for Ozonolysis of Dimethyl Alkenylmalonates 3 and 4.- A 300 ml methanol solution of 0.15 mol of each dimethyl alkenylmalonate was cooled to -78° in a Dry Ice-acetone bath. The solution was then treated with a slow stream of ozone introduced through a fritted inlet until moist starch-iodine paper indicated that ozone was no longer being absorbed (ca. 1.5 hr). While still at -78°, nitrogen was passed through the solution to remove any excess ozone and 14.0 g (16.5 ml, 0.23 mol) of dimethyl sulfide containing 1 ml of glacial acetic acid was added. The reaction was stirred for 2 hrs as the temperature rose to 20° and the crude reaction mixture was concentrated under vacuum at 50° with rotary evaporation. Vacuum distillation afforded a small forerun of dimethyl sulfoxide (bp. 35-40°, 1 mm Hg) followed by the pure diester aldehyde. The properties of these compounds are given below.

3,3-Bis(methoxycarbonyl)propanal (5), 21.6 g (0.135 mol, 89.7%), bp. 71-72° (0.1 mm Hg). IR (thin film): 2860, 2750, 1745 (br) cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$): δ 9.66 (s, 1H), 3.87 (t, J = 6.5 Hz, 1H), 3.72 (s, 6H), 3.06 (d, J = 6.5 Hz, 2H); MS: exact mass calcd for $C_7H_{10}O_5-CH_3O$, m/z 143.0344; found m/z 143.0332.

4,4-Bis(methoxycarbonyl)butanal (6).- 23.5 g (0.135 mol, 90.3%), bp. 98-99° (0.4 mm Hg). IR (thin film): 2850, 2740, 1735 (br) cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) 9.58 (s, 1H), 3.67 (s, 6H), 3.40 (t, J = 6.5 Hz, 1H), 2.52 (m, 2H), 2.21 (m, 2H); MS: exact mass calcd for $C_8H_{12}O_5-CH_3O$, m/z 157.0500; found m/z 157.0446.

General Procedure for Wittig Reaction of Diester Aldehydes 5 and 6.- A 300 ml benzene solution of 0.135 mol of each diester aldehyde and 45.1 g (0.135 mol) of methyl (triphenylphosphoranylidene)acetate was refluxed for 8 hrs with stirring under nitrogen. The mixture was cooled to 20° and concentrated *in vacuo*. The residue was subjected to flash chromatography on a 20 cm x 6 cm column of silica gel eluted with 10% ether in hexane to remove unreacted ylide and triphenylphosphine oxide. The resulting oil was distilled _in vacuo_ to afford the pure triesters. The properties of these compounds are given below.

Dimethyl (E)-5-Methoxycarbonyl-2-hexenedioate (**1**), 22.6 g (0.10 mol, 72.7%), bp. 105-108° (0.05 mm Hg), lit.[2,3] bp. 134° (0.8 mm Hg) and 97-100° (0.02 mm Hg); IR (thin film): 1740 (broad), 1668 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$): δ 6.86 (dt, J = 15, 6 Hz, 1H), 5.86 (t, J = 15 Hz, 1H), 3.72 (s, 6H), 3.69 (s, 3H), 3.32 (t, J = 6 Hz, 1H), 2.78 (t, J = 6 Hz, 2H): MS: exact mass calcd for $C_{10}H_{14}O_6$, m/z 230.0790; found m/z 230.0778.

Dimethyl (E)-6-Methoxycarbonyl-2-heptenedioate (**2**), 24.4 g (0.10 mol, 74.0%), bp. 118-120° (0.05 mm Hg); IR (thin film): 1740 (broad); 1668 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$): δ 6.92 (dt, J = 16, 6.5 Hz, 1H), 5.88 (d, J = Hz, 1H), 3.75 (s, 9H), 3.40 (t, J = 6.5 Hz, 1H), 2.27 (q, J = 6.5 Hz, 2H), 2.09 (q, J = 6.5 Hz, 2H); MS: exact mass calcd for $C_{11}H_{16}O_6$, m/z 244.0945; found m/z 244.0942.

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DIIMIDE REDUCTION OF SUBSTITUTED STYRENES AND OF PHENYL-1,3-BUTADIENES

Submitted by (05/16/86)

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We have studied the synthetic utility of the diimide reductions[1,2] of styrene derivatives (IIa-k) and phenyl-1,3-butadienes. The relative rates of these reductions were also investigated since they relate to the practicability of the procedure. The results are given in Table 1. Similar treatment of styrenes substituted on the side-chains (IIIa-c) gave the corresponding reduced compounds (Table). Interestingly, the reduction of

$$\underset{\text{I}}{KO_2CN{=}NCO_2K} + \underset{\text{II}}{XC_6H_4CH{=}CH_2} \longrightarrow XC_6H_4CH_2CH_3 \qquad (1)$$

a) X = H b) X = 4-CH_3 c) X = 3-CH_3 d) X = 2-CH_3 e) X = 4-t-Bu

f) X = 4-OCH_3 g) X = 3-OCH_3 h) X = 4-Cl i) X = 3-Cl j) X = 4-Br

k) X = 4-NO_2