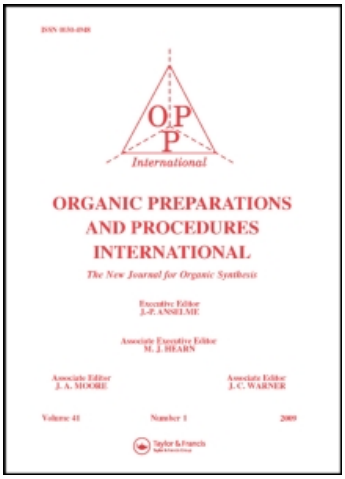

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FACILE SYNTHESIS OF α-SUBSTITUTED MALONATES

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FACILE SYNTHESIS OF α-SUBSTITUTED MALONATES

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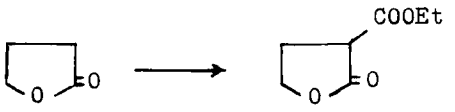
In the course of our studies on 4-substituted 3,5-dihydroxyisoxazole derivatives[1-3] we found it necessary to develop new procedures for the preparation of α-aryl derivatives of malonic esters. Aliphatic substituents are generally introduced into the α-position by alkylation of the malonate anion, a method which is not applicable for most of the aromatic substituents. Direct carbethoxylation of phenylacetic acid esters[4-6] or nitriles[7,8] are general routes for aromatic derivatives of malonates. Either diethyl oxalate or diethyl carbonate is thus used in a two- step synthesis <u>via</u> oxaloacetic esters catalyzed by either ethanol free sodium ethoxide[4,5,8] or freshly prepared sodamide.[6,7] The yields of the condensation step both with sodium ethoxide and sodamide, were 10-64% and the procedures were long and tedious. We now report a general and facile method for direct carbethoxylation of esters in the α-position in 70-92% yield by using diethyl carbonate, with sodium metal, by simple heating of the reagents for about 65 min. In this fashion, excellent yields of

$$ArCH_2COOEt + (EtO)_2CO \xrightarrow{Na} ArCH(COOEt)_2 \qquad I$$

a) Ar = 1-naphthyl
b) Ar = 2-naphthyl
c) Ar = 4-chlorophenyl
d) Ar = anisyl

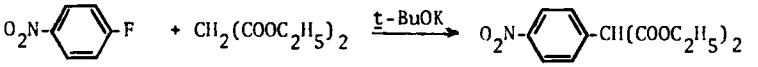
α-phenyl-, α-anisyl-, α-(1-naphthyl)-, α-(2-naphthyl)- and α-(4-chlorophenyl)malonates (I) were obtained.

This method also proved to be a general method for aliphatic malonates, e.g. converting ethyl propionate to ethyl α-methylmalonate in 70% yield and γ-butyrolactone to α-carbethoxy-γ-butyrolactone (II), in almost quantitative yield. Compound II, a potential precursor for γ-substituted amino acids, has been described by Traube and Lehman.[9]



An attempt to react ethyl succinate with diethyl carbonate in the same conditions resulted in the formation of diethyl 1,4-dihydroxy-cyclohexa-1,4-diene-2,5-dicarboxylate (III).[10]

In an attempt to carbethoxylate ethyl (4-nitrophenyl)acetate, we were unable to isolate any pure product. However, we obtained very pure IV in 67% yield by arylation of the potassium salt of ethyl malonate with 4-nitrofluorobenzene in t-butanol.



IV

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were taken with a Varian T-60 in CCl_4 with tetramethylsilane as internal reference.

Ethyl α-(1-naphthyl)malonate (Ia).- Ethyl (1-naphthyl)acetate (21.4g, 0.1 mole) was dissolved in diethyl carbonate (150ml) and sodium (2.3g, 0.1 mole) was added in small pieces. The mixture was heated close to the

boiling point, when the reaction became exothermic. The reaction was allowed to proceed without heating and after the reaction subsided the mixture was refluxed for additional 65 min. The diethyl carbonate was then removed in vacuum and the residue was added to "ice-cold" water (100ml) and neutralized with acetic acid (40ml). The ester was extracted with three portions of ether and dried over Na_2SO_4. On evaporation of the ether in vacuum, ethyl α-(1-naphthyl)malonate deposited. Upon recrystallization from ethanol, white crystals were obtained (24.6g, 80.5%) mp.62°, lit.[4] mp.62°, lit.[5] mp.62-63°. The product was also identified by elemental analysis and by NMR (δ): 1.10t(6H); 4.05q(4H); 5.21s(1H); 7.0-7.8m(7H).

Ethyl α-(2-naphthyl)malonate (Ib).- Ethyl (2-naphthyl)acetate (21.4g, 0.1mole) was treated as above yielding 25.6g (86.5%) of product, mp.102°, lit.[11] mp.101.6-2.4°. The product was also identified by elemental analysis and by NMR (δ): 1.18t(6H); 4.09q(4H); 4.60s(1H); 7.0-7.7m(7H).

Ethyl α-(4-chlorophenyl)malonate (Ic).- Ethyl α-(4-chlorophenyl)acetate (19.8g, 0.1mole) was treated with diethyl carbonate and sodium as above. After evaporation of the etheral extract, the residue was distilled in vacuum. The ethyl α-(4-chlorophenyl)malonate was collected at 154-156° (3mm), 20.6g (76.3%).

Anal. Calcd. for $C_{13}H_{15}ClO_4$: C,57.69; H,5.58; Cl,13.09. Found: C,57.87; H,5.37; Cl,12.96. NMR (δ): 1.12t(6H); 4.15q(4H); 4.46s(1H); 7.2s(7H).

Ethyl α-anisylmalonate (Ic).- Ethyl (4-methoxyphenyl)acetate (19.4g, 0.1mole) was treated as above. The product was collected at 145-148° (1mm), 18.2g (70%), lit.[12] bp. 148-150(1mm). The product was also identified by elemental analysis and NMR (δ): 1.16t(6H); 3.55s(3H); 4.0q(4H); 6.5-7.2q(4H).

α-Carbethoxy-γ-butyrolactone (II).- γ-Butyrolactone (8.6g, 0.1mole) was treated as above. The product was collected at 165-180° (25mm) and further purified by washing with water (to eliminate the water soluble γ-butyrolactone) and dried over Na_2SO_4 (14.6g, 92%).

Anal. Calcd. for $C_7H_{10}O_4$: C,53.16; H,6.37. Found: C,53.43; H,6.38. NMR (δ): 1.25t(3H); 2.0-3.0m(2H); 3.44t(1H, J = 9Hz); 3.9-4m(4H).

Diethyl 1,4-dihydroxy-cyclohexa-1,4-diene-2,5-dicarboxylate (III).- Diethyl succinate (17.4g) was treated with sodium metal in $(EtO)_2CO$. Upon evaporation of the etheral extract, a crystalline solid deposited. It was recrystallized from ethanol (10.5g, 80%) m.p. 129°, lit.[10] mp. 130-131°.

Anal. Calcd for $C_{12}H_{16}O_6$: C,56.25; H,6.29. Found: C,56.04; H,6.13. NMR(δ): 1.15t(6H); 3.05s(4H); 4.15q(4H); 12.0s(2H). IR in KBr (cm^{-1}): 1670 (chelated ester); 1640 (enolic C=C).

Ethyl α-(4-nitrophenyl)malonate (IV).- Potassium (11.7g, 0.3mole) was dissolved in t-butanol (600ml). After all the metal had dissolved, ethyl malonate (48.0g, 0.3mole) was added and the mixture was heated gently with stirring until the reaction became exothermic. The reaction was allowed to proceed on its own and a white cake formed. Then 4-nitrofluorobenzene was added (21.2g, 0.15mole) and the mixture was refluxed with efficient stirring for 90 min. The red mixture which was formed was poured into cold water (0°) (200ml) and neutralized with acetic acid (60ml) with cooling (2°). The light yellow crystals which separated were collected and recrystallized from ethanol (30g, 67%), mp. 54°, lit.[13] mp.56°; NMR (δ): 1.20t(6H); 4.14q(4H); 4.50s(1H); 7.3-8.0q(4H).

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