A New Improved Synthesis of Diethyl-3-Hydroxy-4-Methyl-5- Methoxyphenylmalonate

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(Received 5th November, 1989, revised 31st March, 1990)

Introdunction

Diethyl-3-hydroxy-4-methyl-5-methoxyphenylmalonate (6) is an important intermediate towards 3,5-dihydroxy-4-methylphenylacetic acid, leading to (±)-6,8-dihydroxy-3-isopropyl-7-methylisochroman possibly related to the model of rotiorin, one of the fungal metabolites of the sclerotiorin group [1]. We had already reported [2] the synthesis of title compound (6) by Michael addition of sodio-diethylmalonate on 6-acetoxy-5-methoxy-6-methyl methoxy-6-methyl-2,4-cyclohexadienone [3] (1). In this article, we wish to report an improved synthesis of the title compound (6) by a similar type of addition of diethylethoxymagnesiomalonate [4,5] (2) on (1) through the probable intermediate (3). It may be pointed out that (3) was identified by the absence of aromaticity in the infra-red absorption spectra of the reaction mixture in the initial stage of the reaction. At this stage addition of a five-fold excess of (2), followed by decomposition of the reaction mixture with excess of 5N hydrochloric acid yielded (6) in 87.0% yield. This yield is much higher as compared to that obtained previously by use of sodium diethylmalonate [2]. A probable route from (3) to (6) is suggested in the synthetic scheme. The mesomeric malonate moiety (4), resulting by the reaction of (3) with excess of (2), stablizes by the loss of proton and acetate ion to give the aromatized complex (5). On acidification this complex (5) decomposed to yield (6).

Experimental

Diethyl-3-Hydroxy-4-Methyl-5-Methoxyphenylmalonate (6)

Nitrogen was passed through magnesium turnings (5.0 g, 0.2g- atom), absolute ethanol (5 ml), carbon tetrachloride (0.2 ml) and 6 ml of a mixture of diethylmalonate (30.2 ml, 0.2 mol) and absolute ethanol (16 ml). The reaction started vigorously after 3-5 minutes on addition of an iodine crystal. The remainder of the diethylmalonate solution was added dropwise with occasional cooling. When most of the magnesium had disappeared, the reaction mixture was cooled to room temperature and anhydrous ether (60 ml) was added. After consumption of magnesium turnings completely ethanol and ether were evaporated in *in vacuo*. Anhydrous benzene (60 ml) was added to the partially crystalline product (2), and again the solvents were evaporated *in vacuo*. The residue was dissolved in anhydrous ether (60 ml).

A solution of 6-acetoxy-5-methoxy-6-methyl-2,4-cyclohexa-dienone (1) (7.84 g, 0.04 mol) in anhydrous ether (100 ml) was added to the flask containing an ethereal solution of (2) with stirring over 1 h, while cooling externally at 0°C. The reaction mixture was allowed to warm to ambient temperature and stirring was continued for forty eight hours. The progress of the reaction was constantly followed by recording IR spectra and performing TLC of the reaction mixture.

The resulting light green mixture was cooled to 0°C and decomposed by addition of ice cold 5N hydrochloric acid (100 ml) The organic and aqueous phases were separated and the latter extracted with ether (3 x 75 ml). All the ether extracts were combined, dried over anhydrous sodium sulphate and solvent evaporated to give an orange red oil which on chromatography (silica gel 60) from ether :light petroleum (1:10) afforded diethyl-3-hydroxy-4-methyl-5-methoxyphenylmalonate (6), as colourless prismatic crystals: Yield: 10.3g (87.0%) m.p. 66-67°C (Lit. [2] m.p. 66°C). I.R. (KBr): ν_{max}

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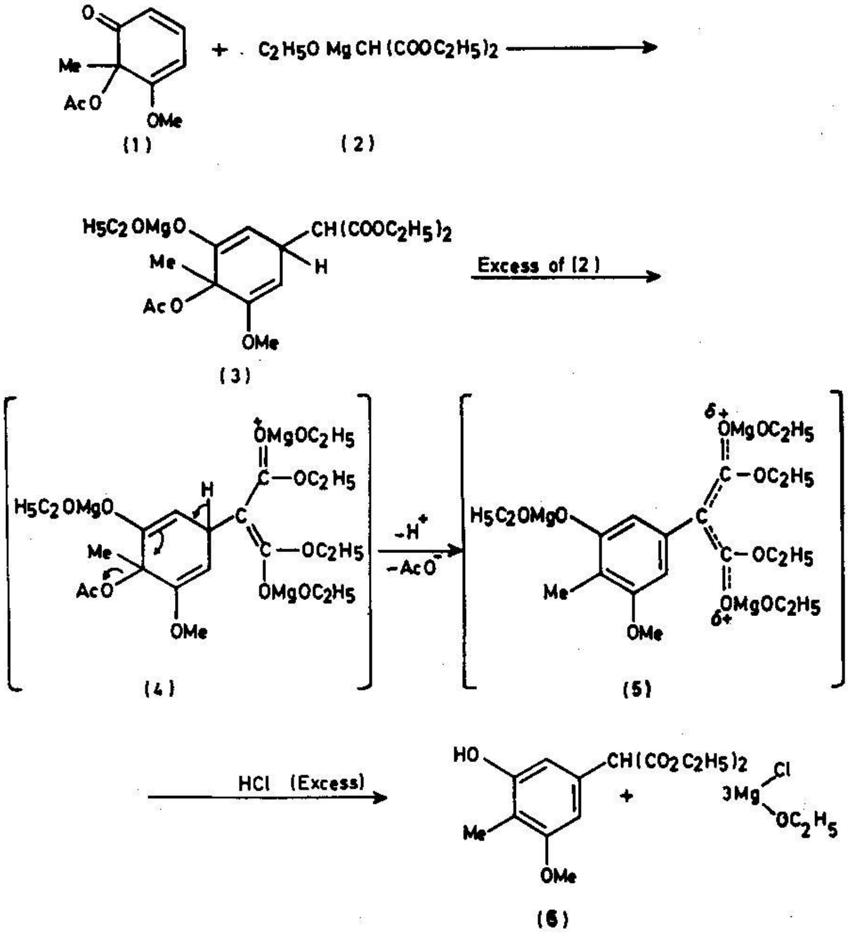

SYNTHETIC SCHEME

= 3466, 1737, 1602, 1512, 1470, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 1.2 (t, 6H $-CH_2$-$\underline{CH_3}$x2); 2.0 (s, 3H, Ar-$\underline{CH_3}$); 3.7 (s, 3H, Ar-O$\underline{CH_3}$); 4.2 (q, 4H, -$\underline{CH_2}$ - CH_3 x 2); 4.5 (s, 1H, Ar-$\underline{CH}$); 6.3 (s, D_2O exchangeable Ar-$\underline{OH}$); 6.4 (s, 1H, Ar-$\underline{H}$); 6.5 (s, 1H, Ar-$\underline{H}$).

Mass spectrum: m/z = 296 (M^+), 195, 167.

References

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