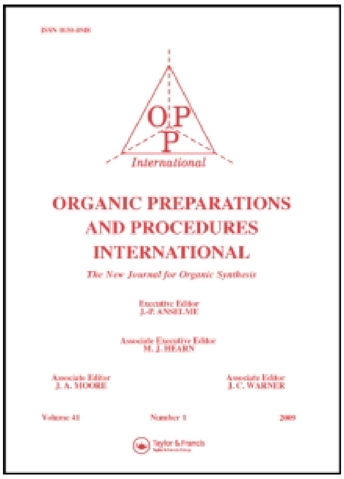

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# SIMPLE AND PRACTICAL SYNTHESES OF DIBENZYL, BENZYL ETHYL AND BENZYL METHYL MALONATES

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# SIMPLE AND PRACTICAL SYNTHESES OF DIBENZYL, BENZYL ETHYL AND BENZYL METHYL MALONATES

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The classical malonic ester synthesis is a widely used method to prepare homologous carboxylic acids and/or esters from alkyl halides, but in some cases has the disadvantage of the strongly basic conditions required for the conversion of alkylated malonate to monocarboxylic acid. It is known that benzyl esters can release the corresponding carboxylic acids by hydrogenolysis under essentially neutral conditions. Hence, a simple modification to circumvent this problem is the use of benzyl malonates such as **1-3** which are however, very expensive chemicals.[1]

**1**, $R = C_6H_5$ **2**, $R = CH_3$ **3**, $R = H$ $RCH_2O_2CCH_2CO_2CH_2C_6H_5$

Compounds **1-3** have been obtained by many methods including the base-catalyzed transesterification of cheap dimethyl or diethyl malonates with benzyl alcohol (44-74%).[2] We have found that substantial amounts of **1-3** can be conveniently prepared by thermal transesterification (without catalyst) of diethyl and dimethyl malonates with benzyl alcohol. Although extensively applied to β-keto esters,[3] this method has been rarely employed for malonates as substrates.[4]

The method involves heating a stirred mixture of the malonate and benzyl alcohol in the appropriate ratios at 165-170°, while nitrogen or argon is bubbled through the solution. The amount of the limiting reactant used in all our experiments was 0.1 mol, and the nearly theoretical amount of EtOH or MeOH was collected in ~ 90-120 min. Excess reactant and product were then separated by fractional distillation at reduced pressure. The thermal monobenzylation of diethyl and dimethyl malonates was first investigated in detail, in molar ratios of 1:1.5, 1:3, and 1:5 (benzyl alcohol/malonate); the results are presented in the following Table. As expected, the best yields of **2** and **3** are obtained with the highest ratio of reactants (5:1) but even so the formation of **1** could not be completely avoided.

**TABLE.** Thermal Monobenzyl Transesterification of $CH_2(CO_2R')_2$

| Molar ratio (benzyl alcohol/malonate) | | Yields* | | |
|---|---|---|---|---|
| | | **2** | **3** | **1** |
| 1 : 1.5 | R' = Et | 50 – 55 | | 26 – 28 |
| | R' = Me | | 48 - 53 | 25 – 30 |
| 1 : 3 | R' = Et | 71 – 76 | | 14 – 18 |
| | R' = Me | | 76 - 78 | 15 – 18 |
| 1 : 5 | R' = Et | 84 – 87 | | 10 – 12 |
| | R' = Me | | 81 - 86 | 9 – 11 |

*Average values for at least 2 runs.

The recovered malonates in the above experiments are pure enough to be recycled. Actually, we have also performed a series of consecutive experiments in which we started from 0.1 mol of benzyl alcohol and 0.5 mol of malonate (methyl or ethyl) and after isolation of **2** or **3**, to the recovered malonate (usually 90-95% of theory) fresh benzyl alcohol was added to reach again the 1:5 ratio of benzyl alcohol/malonate and the process repeated again up to 10 runs without any significant variation in the yields.

For the practical synthesis of **1** an excess of benzyl alcohol was now required, but an unexpected problem arose. Under the standard conditions which were effective for the monobenzyl transesterification reaction, substantial amounts of dibenzyl ether were simultaneously produced. Although dibenzyl ether can be easily separated from **1** by fractional distillation at reduced pressure, this side-reaction which consumes benzyl alcohol decreases the yield of **1**. Based on the assumption that acidic by-products formed from the malonate were acting as catalysts for the etherification reaction, the thermal transesterification was then performed in the presence of 2 drops of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[5] No dibenzyl ether was detected and good yields of **1** were obtained (66-72% for the 1:3 and 76-81% for the 1:5 molar ratios of malonate/benzyl alcohol, respectively). About 10-15% of monobenzyl malonates (**2** or **3**) can also be isolated in the forerun.

In conclusion, compounds **1**-**3** are now conveniently obtained by a simple and reasonably rapid method. These findings will make them more available as useful starting materials for organic synthesis.

## EXPERIMENTAL SECTION

Diethyl and dimethyl malonates (Aldrich) and benzyl alcohol (Monterrey) were used as received. Some experiments were also performed with diethyl malonate from Merck, but this product was yellow and was first purified by taking it into ether, washed with aqueous saturated $NaHCO_3$ solution, dried ($Na_2SO_4$) and after removal of solvent, distilled at reduced pressure.

GC analyses were conducted in a Varian 3300 instrument equipped with a programmed temperature oven and a flame ionization detector. Data collection was done with an integration system 3390 A (Hewlett-Packard). A fused-silica capillary column (30 m length x 0.25 mm i.d.) coated with a 0.25 µm layer of cross-bounded, 5% phenylmethyl silicone (DB-5, J & W Scientific, Folsom, CA) was used. After 1 min at an initial temperature of 180°, the GC oven was heated to 280° at 10°/min. In all analyses the injector (split relation 1:30) was set at 200° and the detector temperature at 290°. Hydrogen at 1 mL/min was used as the carrier gas. Under the above conditions, retention times for **1**, **2** and **3** were 6.65, 2.46 and 2.12 min respectively.

**Benzyl Ethyl Malonate (2) and Benzyl Methyl Malonate** (3).- A two-necked (14/20 joints), 100 mL round-bottomed flask fitted with a thermometer to check the internal temperature and a small integrated distilling apparatus (length of the column 7 cm), was charged with the malonate (excess) and the benzyl alcohol in the appropriate molar ratio (1.5:1, 3:1 or 5:1). From a long needle introduced through a septum placed in the upper part of the distilling apparatus, nitrogen or argon was bubbled in the stirred solution for ~ 15 min and then the flask was immersed in a preheated heating mantle. The internal temperature rose to 140-150° in ~ 20 min and EtOH or MeOH began to distill. The internal temperature was maintained between 165-170° throughout the distillation (1-1.5 h) and when distillation stops, for an additional 30 min. The whole process took ~ 2-2.5 h.

After cooling, excess reactant malonates were removed at reduced pressure (diethyl malonate, bp 43°/0.5; dimethyl malonate, bp 43°/0.8) and the colorless monobenzyl malonates **2** or **3** were isolated by fractional distillation at reduced presssure using an integrated distilling apparatus with a 6 cm Vigreux column (total length of the column, 11 cm).

From the residue, dibenzyl malonate was recovered by short path distillation (Aldrich Kugelrohr) first at 130-150°/0.2 (to remove some **2** or **3**) and then at 185-190°/0.2.

The purity of the compounds thus obtained was ≥ 95% by GC. IR and $^1$H-NMR spectra were in accord with those recorded in the literature.[7]

**Dibenzyl Malonate** (1).- The same apparatus was used as indicated above, but now with excess benzyl alcohol (molar ratios of 3:1 and 5:1 were used) containing 2 drops of DBU. It was observed in these experiments that the first three fourths of theoretical amount of EtOH (~ 9 mL) or MeOH (~ 7 mL) distilled very rapidly (~ 1 h) and in the next 2 h of heating only 1-2 mL more of the alcohols are collected. Hence, the total time of heating in these experiments was somewhat longer (3-3.5 h).

The isolation of dibenzyl malonate involved the removal by distillation at reduced pressure of excess benzyl alcohol (bp 45°/0.3) and a forerun containing **1** and **2** or **3** (bp 130-150°/0.2). The residue was then short-path distilled at reduced pressure (0.2 Torr) in an Aldrich Kugelrohr apparatus, removing first a forerun (oven temperature 130-150°) before the collection of the product as a viscous, nearly colorless oil (oven temperature 185-190°). In our hands the conventional fractional distillation at reduced pressure of crude **1** using the integrated distilling apparatus described above, was a lengthy (~ 10 h) and tedious process yielding a yellow product and appreciable amounts of an undistillable red-brown residue (15-20% in weight). In striking contrast, the Kugelrohr distillation leaves only a small amount of residue (1-2% in weight).

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