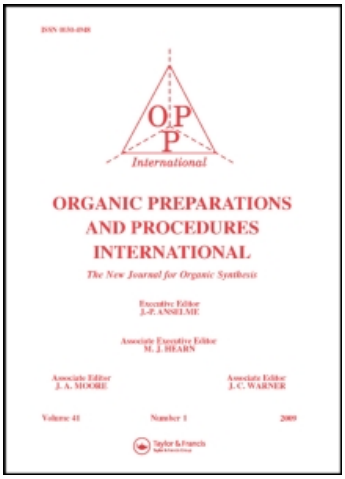


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# IMPROVED PREPARATION OF 2,5-DIMETHYL-1,4-CYCLOHEXANEDIONE

Maria-Joao Queiroz[ab]; Delphine Joseph[a]; Gilbert Kirsch[a]
[a] Laboratoire de Chimie Organique, Universitéde Metz, Metz Cedex, FRANCE [b] Dept. of Chemistry Campus de Gualtar, University of Minho, School of Science, Braga, PORTUGAL

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11. At this point the compound was 98% pure by HPLC [Rainin Microsorb C18 4.6 x 250 mm column, eluent-gradient (0.1% TFA in MECN) in (0.1% TFA in $H_2O$) from 10% to 75% in 20 min; UV detection at 220 and 254 nm], $t_r$ = 10.1 min.



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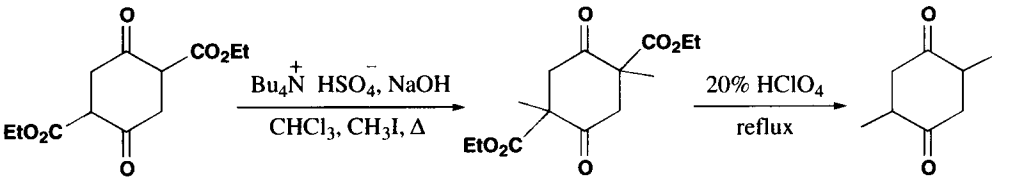
## IMPROVED PREPARATION OF 2,5-DIMETHYL-1,4-CYCLOHEXANEDIONE

*Submitted by* (07/29/94) Maria-Joao Queiroz†, Delphine Joseph and Gilbert Kirsch*

*Laboratoire de Chimie Organique, Université de Metz*
*Ile du Saulcy, 57045 Metz Cedex, FRANCE*

Dione **1**, a very useful compound in synthetic organic chemistry, was needed in our group for the preparation of oxotetrahydrocarbazoles by the Fischer indole synthesis. While the compound has been reported in the literature,[1] the experimental conditions are not reproducible. The problem in its synthesis lies in the dialkylation of diester **2**.[2] Several methods have been attempted but the yields were poor (*e. g. t*-BuOK/DMSO, MeI) or the methods were not reproducible (*e. g.* NaH/DMF, MeI).




**2** **3** **1**

Based on the monomethylation of cyclic β-oxophosphonates using phase-transfer catalysis,[3] we attempted the same procedure on compound **2** for its dimethylation. The phase-transfer reagent, tetrabutylammonium hydroxide, was generated *in situ* from tetrabutylammonium hydrogen sulfate

and sodium hydroxide. Several proportions of these reagents were tested but the best yield for compound **3** (86%) was obtained using one equiv. of tetrabutylammonium hydrogen sulfate and 4 equiv. of a 2N solution of sodium hydroxide. The reaction was carried out in chloroform and with methyl iodide (2.5 eq.) as the alkylating agent. The crude orange oil obtained was hydrolized and decarboxylated using 20% aq. perchloric acid leading to the desired dione **1** in quantitative yield.

## EXPERIMENTAL SECTION

Melting points were determined from Kofler bench and are uncorrected. NMR spectra were recorded at 250 MHz with $CHCl_3$ as an internal standard. Low-resolution electron-impact mass spectra were obtained at 70 eV by GC separation on a WCOT fused silica 0.25 mm x 25 m capillary column.

**Diethyl 1,4-Dimethyl-2,5-dioxocyclohexane-1,4-dicarboxylate (3).**- To a solution of tetrabutylammonium hydrogen sulfate (13.26 g, 0.039 mol) in 2N NaOH (78 mL, 0.156 mol) a mixture of MeI (14 g, 0.0985 mol) and diester **2** (10 g, 0.039 mol) in $CHCl_3$ (50 mL), was added. The reaction mixture was refluxed for 15 hrs. The organic layer was separated and the solvent removed under reduced pressure. Ether was then added and the precipitated tetrabutylammonium iodide was filtered off and washed with ether. The ethereal extracts were dried ($Na_2SO_4$), filtered and concentrated to give an orange oil (9.5 g, 86%) whose $^1H$ NMR showed it to be compound **3**. Crystallization from i-PrOH gave colorless crystals, mp. 71-72°. $^1H$ NMR ($CDCl_3$, 250 MHz): δ 1.24 (6H, t, J = 7 Hz, 2 x $CO_2CH_2CH_3$), 1.44 (6H, s, 2 x $CH_3$) 2.82 (2H, d, J = 15 Hz, 2 x CH), 3.14 (2H, d, J = 15 Hz, 2 x CH), 4.18 (4H, q, J = 7 Hz, 2 x $CO_2CH_2CH_3$). $^{13}C$ NMR ($CDCl_3$, 250 MHz): δ (ppm) 13.67 ($CH_3$), 20.44 ($CO_2CH_2CH_3$), 47.81 ($CH_2$), 57.14 ($C(CH_3)(CO_2Et)$), 67.17 ($CO_2CH_2CH_3$), 170.58 ($CO_2$), 201.06 (CO). EIMS *m/z* (%): 211 (48), 164 (100), 137 (60), 69 (74), 41 (64).

*Anal.* Calcd for $C_{12}H_{15}O_6$: C, 59.14; H, 7.09. Found: C, 59.21; H, 7.24

**2,5-Dimethyl-1,4-cyclohexanedione (1).**- To compound **3** (9.5 g, 0.033 mol) was added 20% aq. $HClO_4$ (200g, 0.33 mol). The mixture was refluxed for 15 hrs. After cooling, solid $Na_2CO_3$ was added to neutralize to pH 7. The aqueous phase was extracted with $CHCl_3$ (5 x 250 mL) and the organic extract was dried ($Na_2SO_4$) and the solvent removed to give a solid, mp. 73-75°, which was shown by $^1H$ NMR to be dione **1** (4.6 g, 100%). Crystallization from ether gave (4.3 g, 93%) of colorless crystals, mp. 90-92°, lit.[4] 93°. $^1H$ ($CDCl_3$, 250 MHz): δ 1.14 (6H, d, J = 6.5 Hz, 2 X $CH_3$), 2.40-2.55 (2H, m), 2.70-2.80 (4H, m). $^{13}C$ NMR ($CDCl_3$, 250 MHz): δ (ppm) 15.36 ($CH_3$), 42.75 (CH), 43.57 ($CH_2$), 208.86 (CO). EIMS *m/z* (%): 140 (100), 70 (50), 42 (100).

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† Present address: University of Minho, School of Science, Dept. of Chemistry, Campus de Gualtar, 4700 Braga, PORTUGAL

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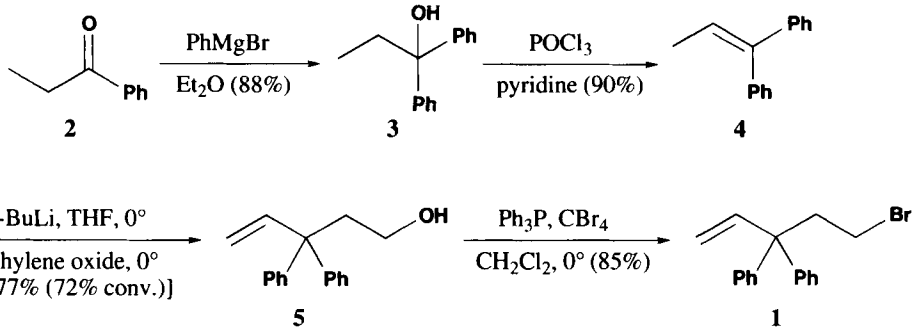
## SYNTHESIS OF 5-BROMO-3,3-DIPHENYL-1-PENTENE

Submitted by (8/16/94) Richard A. Bunce* and R. Shawn Childress

*Department of Chemistry*
*Oklahoma State University*
*Stillwater, OK 74078-0447*



A current synthetic study required the use of 5-bromo-3,3-diphenyl-1-pentene (**1**). A review of the literature revealed that neither **1** nor its alcohol precursor 3,3-diphenyl-4-penten-1-ol (**5**) had been previously reported. Earlier work[1] on alkylations of 1,1-diphenylallyllithium demonstrated that reaction occurs predominantly at the diphenyl substituted carbon (C-1) of the allylic system. Thus, it was expected that reaction of this lithium compound with ethylene oxide would afford **5** which could then be easily converted to the title compound. This report describes the successful application of this strategy to the synthesis of **1** in four steps with an overall yield of 52% (see Scheme).




**2** **3** **4** **5** **1**

The synthesis of 1,1-diphenyl-1-propene (**4**) was carried out by Grignard synthesis of 1,1-diphenyl-1-propanol (**3**) followed by dehydration using phosphorous oxychloride in pyridine. The best yield in the Grignard reaction (88%) was realized by addition of phenylmagnesium bromide to propiophenone (**2**) while dehydration proceeded in 90%. Treatment of **4** with *n*-butyllithium at 0°