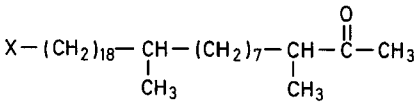
# Phase-Transfer Methylation of Benzyl 3-Oxobutanoate as a Route to 3-Methyl-2-alkanones. Improved Syntheses of Two Female Sex Pheromones of the German Cockroach[1]

Albert W. BURGSTAHLER*, Mark E. SANDERS, Craig G. SHAFFER, Leland O. WEIGEL

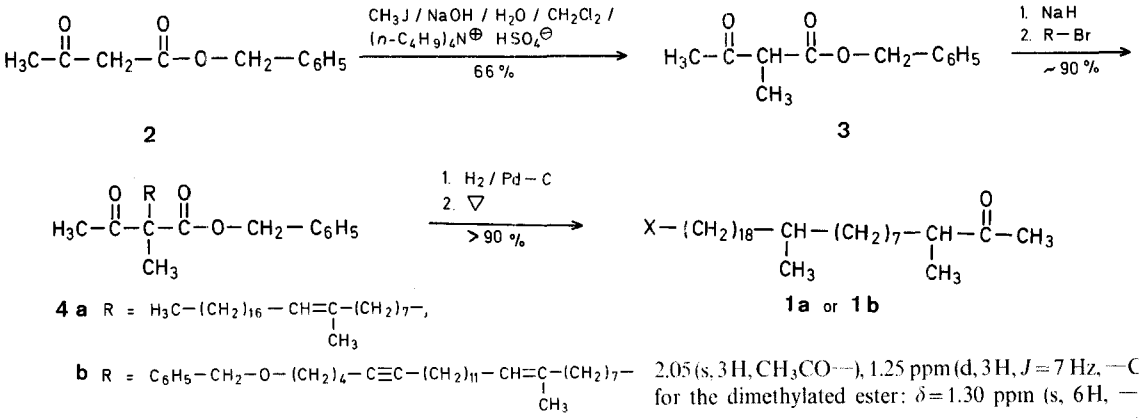
Department of Chemistry, The University of Kansas, Lawrence, Kansas 66045, U.S.A.

Although widely applicable to the preparation of unsubstituted 2-alkanones, the acetoacetic ester synthesis is not always satisfactory as a route to 3-methyl- and other 3-alkyl-2-alkanones. The initial alkylation is generally difficult to carry to completion; moreover, hydrolysis of the hindered ester function after introduction of the second alkyl group is sometimes complicated. Under alkaline conditions the hydrolysis is frequently accompanied by acyl cleavage[2], whereas under acidic conditions it tends to be quite slow, at least in our experience. Other reported methods of hydrolysis-decarboxylation are generally less convenient or are unsatisfactory for dialkylated $\beta$-keto esters[3].



**1a** X = H
**b** X = OH

Here, in work designed to improve our recent syntheses[4,5] of the two methyl ketone female sex pheromones **1a**[6] and **1b**[7] of the German cockroach *(Blattella germanica)*, we were able to circumvent these problems by an extension of the benzyl acylmalonic ester hydrogenolysis developed by Bowman[8]. For this purpose we employed a phase-transfer methylation[9] of benzyl acetoacetate (benzyl 3-oxobutanoate, **2**)[10,11] to give the *C*-methyl derivative **3**, followed by further alkylation to produce the keto ester **4a** and **4b**. Hydrogenation-hydrogenolysis and decarboxylation of **4a** and **4b** then furnished the desired 3-methyl-2-alkanones **1a** and **1b**.




After finding that conventional methods of methylation invariably led to recovery of at least 8–10% of **2**, which could not be separated readily from **3**, we turned to a phase-transfer catalyzed procedure[9] that enabled us to limit the amount of unmethylated **2** to less than 2% of the 93% yield of reaction product. Although the need to use an excess of the methylating agent produced a considerable amount (33%) of dimethylated ester, the presence of the latter did not interfere with the further alkylation of **3** and was therefore of no consequence.

With the availability of **3**, our[4,5] and Ishii's[6,7] syntheses of the German cockroach pheromones **1a** and **1b** (as biologically active diastereoisomeric mixtures) are substantially shortened, and the overall yields significantly improved. In view of these favorable results, other synthetic applications of **3** can be anticipated.

**Benzyl 3-Oxobutanoate (2):**

Although available by other methods[10,11], ester **2** is prepared conveniently by reaction of freshly distilled diketene (0.40 mol) with benzyl alcohol (0.39 mol) in ether at 25° for 24 h with pyridine (1.5 ml) as catalyst[12]; yield: 56.9 g (76%); b.p. 85–87°/0.15 torr (Lit.[10,11]: b.p. 162–164°/16 torr).

$^1$H-N.M.R. (30% in $CCl_4$) $\delta = 7.3$ (s, $5H_{arom}$), 5.09 (s, 2H, $-OCH_2C_6H_5$), 3.33 (s, 2H, $-COCH_2CO-$), 2.15 ppm (s, 3H, $CH_3CO-$).

**Benzyl 2-Methyl-3-oxobutanoate (3):**

To a magnetically stirred mixture of dichloromethane (20 ml) and 2.62 molar aqueous sodium hydroxide[13] (36.5 ml, 95.6 mmol) is added tetra-*n*-butylammonium hydrogen sulfate (13.5 g, 39.8 mmol). After dissolution of the salt, ester **2** (7.7 g, 40 mmol) and then methyl iodide (4.5 ml, 72 mmol) are introduced at 5–10°, and the two-phase system is stirred (~300 rpm) for 16 h at 20–25°. The organic layer is then separated and washed successively with water, 10% sodium hydrogen sulfite, 10% sodium hydrogen carbonate, and brine. Afterwards it is dried with magnesium sulfate and concentrated at 20 torr. Dry ether (20 ml) is added to precipitate tetra-*n*-butylammonium iodide, and after cooling to −15° the mixture is filtered and rinsed with ether through a 2-cm pad of Florisil. Evaporation of the ether furnishes **3** sufficiently pure for further alkylation; yield: 7.7 g (93%).

Analysis by G.L.C. (5 m × 6 mm column of 10% DEGS on 100–120 mesh Gas-Chrom W) of the product of hydrogenolysis (30% Pd/C in dioxan) showed (by direct comparison with 2-butanone, acetone, and 3-methyl-2-butanone) that the methylation product contained 66% of **3**, 1.2% of **2**, and 33% of dimethylated **2**.

These figures also corresponded to those determined by $^1$H-N.M.R. spectral analysis (in $CCl_4$) of **3**: $\delta = 7.3$ (s, $5H_{arom}$), 5.08 (s, 2H, $-OCH_2C_6H_5$), 3.43 (q, $J = 7$ Hz, 1H, $-COCH(CH_3)CO-$), 2.05 (s, 3H, $CH_3CO-$), 1.25 ppm (d, 3H, $J = 7$ Hz, $-CH(CH_3)-$); for the dimethylated ester: $\delta = 1.30$ ppm (s, 6H, $-C(CH_3)_2-$).

A sample prepared by short-path distillation (b.p. ~90°/0.15 torr) gave the following combustion analysis:

| $C_{12}H_{14}O_3$ (66%), (206.2) | | $C_{11}H_{12}O_3$ (1.2%), (192.2) | $C_{13}H_{16}O_3$ (33%) (220.3) |
|---|---|---|---|
| calc. | C 70.21 | H 7.00 | |
| found | 70.00 | 6.70 | |

**Pheromones 1a and 1b from 3 via Keto Esters 4a and 4b:**

1-Bromo-8-methyl-8-hexacosene (as a mixture of *Z* and *E* isomers) is prepared in 62% yield by reaction[6] of the ylid of octadecyltriphenylphosphonium bromide[4,6] with 9-bromo-2-nonanone[5,6] in ether for 30 min at 0°. (At higher temperature or after extended reaction time significant amounts of terminal olefin are formed.) This bromoolefin (376 mg, 0.822 mmol) in benzene (1 ml) is added to the sodium hydride-generated enolate (1.6 mmol) of **3** in benzene (4 ml) and dimethylformamide (1 ml), and the mixture is stirred at 45° under argon for 48 h, after which it is poured into water, extracted with ether, and the ether solution dried with magnesium sulfate, and evaporated. The crude keto ester **4a** (having all the expected $^1$H-N.M.R. spectral features) is dissolved in peroxide-free dioxan (10 ml) and is stirred under hydrogen at 1 atm with 30% Pd/C (100 mg) for 3 h. Although hydrogen uptake appears to cease after 10 min, the end-point is obscured by the evolution of carbon dioxide[14]. After removal of the catalyst and evaporation of the solvent the residue is heated to 90° for 15 min and then chromatographed on a 35 × 1.5 cm column of silica gel (Silicar CC-4). Crystallization from pentane at −20° of the fraction eluted by hexane/ether (20:1) affords 3,11-dimethyl-2-nonacosanone (**1a**); yield: 301 mg (81% from the Wittig product); m.p. 28–30°, raised by one recrystallization to 29–31° as recorded[4,6]; I.R. and $^1$H-N.M.R. spectra are as reported previously[4,6].

In the same manner, but with the reaction time at 0° extended to 1 h, a mixture of (*Z*)- and (*E*)-26-benzyloxy-1-bromo-8-methyl-8-hexacosen-21-yne (homogeneous by T.L.C.) is obtained in 61% yield by reaction of the appropriate phosphorane ylid[5] with 9-bromo-2-nonanone[5,7]. Reaction of this bromo-ether (133 mg, 0.238 mmol) with the sodium enolate of **3** (0.55 mmol) in 4:1 benzene/dimethylformamide (2 ml) furnishes, after elution from ethyl acetate/deactivated Florisil, **4b** (homogeneous by T.L.C. and exhibiting all the expected $^1$H-N.M.R. spectral features); yield: 145 mg (89%). Hydrogenolysis of this product in dioxan (3 ml), followed by heating to 90°, and then preparative layer chromato-

graphy of the residue as described previously[5], gives 29-hydroxy-3,11-dimethyl-2-nonacosanone (**1b**); yield: 91 mg (92%); m.p. 39–40° as recorded[5,7]; I.R. and $^1$H-N.M.R. spectra as reported[5,7].

| | | | |
|---|---|---|---|
| $C_{31}H_{62}O_2$ | calc. | C 79.76 | H 13.39 |
| (466.8) | found | 79.60 | 13.47 |

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