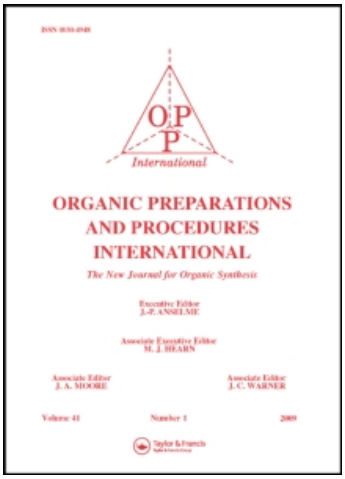

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PRACTICAL SYNTHESIS OF 3,3,4,4-TETRAMETHYLCYCLOPENTANONE

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OPPI BRIEFS

PRACTICAL SYNTHESIS OF 3,3,4,4-TETRAMETHYLCYCLOPENTANONE

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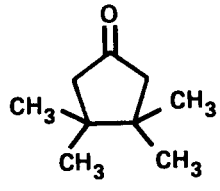
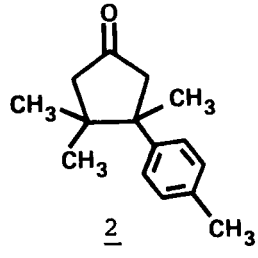
During the course of some recent synthetic studies we required 3,3,4,4-tetramethylcyclopentanone (1) as starting material. This highly symmetrical compound has considerable theoretical interest due to the steric strain generated by four adjacent methyl groups in a rigid cyclopentanone ring. Furthermore, this compound represents an ideal substrate for investigating alkylation and annulation reactions in sterically congested cyclopentane systems. The importance of natural products containing five membered rings is demonstrated by the recent intense synthetic activity in this area.



1

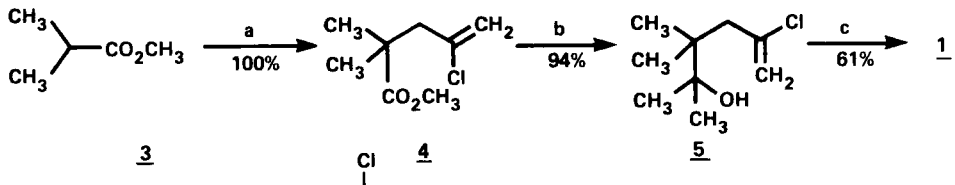


2

To our knowledge there is only one synthesis of 3,3,4,4-tetramethylcyclopentanone reported in the literature.[1] This synthesis involves ultimately a ring expansion of the spiro-epoxide formed from tetramethylcyclobutanone. While few experimental details are given (and no physical data is described which adequately characterizes compound 1), it is apparent that this multi-step process is not easily adaptable to scale-up. We describe in this communication a simple preparation of

the title compound which utilizes inexpensive starting materials, proceeds in good overall yield, requires only a single purification (at the final step), and is amenable to large scale.

SCHEME I



3 4 5

[a]1 equiv. LDA, THF/1.5 equiv. $ClCH_2\overset{Cl}{\overset{|}{C}}=CH_2$, -70°→0°. [b]3.5 equiv. CH_3Li, Et_2O, 0°. [c]H_2SO_4, −20°/H_2O.

Our synthesis, which is patterned after the synthesis of β-cuparenone (2) by Lansbury and Hilfiker,[2] is shown in Scheme I. Treatment of methyl isobutyrate (3) with one equivalent of lithium diisopropylamide followed by quenching with an excess (1.5 equivalent) of 2,3-dichloropropene furnished the crude ester 4 in quantitative yield. Without further purification, ester 4 was treated with an excess (3.5 equivalents) of methyllithium. The resulting crude tertiary alcohol 5 (obtained in essentially quantitative yield) was stirred for 30 minutes in neat sulfuric acid at -20° then quenched with ice to give, after chromatography on alumina, a 61% yield of 3,3,4,4-tetramethylcyclopentanone (1), m.p. 125-127 . The identity of the compound was determined by high resolution mass and infrared spectra ($\nu_{C=O}$ 1745 cm^{-1}) as well as its extremely simple proton (two singlets) and carbon-13 (four singlets) NMR spectra.

EXPERIMENTAL SECTION

IR spectra were obtained on neat samples (oils) or on Nujol mulls (crystalline samples). The mass spectrum was recorded at high resolution at 70 eV. The ^1H NMR spectra of chloroform-d solutions were obtained on a Varian EM-390 spectrometer operating at 90 MHz. Chemical shifts are reported in (parts per million) relative to internal tetramethylsilane. The C-13 NMR spectrum was obtained of a chloroform-d solution on a Varian CFT-20 spectrometer operating at 20 MHz. Chemical shifts are reported in δ (parts per million) relative to internal tetramethylsilane. Brine refers to a saturated aqueous solution of NaCl. All solvents were reagent grade or reagent grade distilled from glass (Burdick and Jackson). All reagents were used as purchased and were reagent grade where available. All reactions were done under an inert atmosphere. Thin layer chromatograph (TLC) was conducted with Analtech (Uniplates) precoated with silica gel GF (250 nm).

3,3,4,4-tetramethylcyclopentanone (1).-A solution of 3.7 mL (26.4 mmol) of diisopropylamine in 40 mL of tetrahydrofuran at -40° was treated with 16.4 mL (26.4 mmol) of 1.61 M n-butyllithium in hexane. The resulting solution was stirred for 15 minutes at -40° and then five minutes at 0°, cooled to -70°, treated with a solution of 3.0 mL (26.2 mmol) of methyl isobutyrate (3) in 12 mL of tetrahydrofuran, stirred at -70° for 75 minutes, and then treated with a solution of 3.7 mL (40 mmol) of 2,3-dichloropropene in 10 mL of tetrahydrofuran. The resulting solution was allowed to warm to -40° over 35 minutes, then stirred at 0° for 30 minutes, added to water and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine and dried (Na_2SO_4). The solvents were removed under reduced pressure to give 4.64 g (100%) of methyl 4-chloro-2,2-dimethyl-4-pentenoate (4) as a yellow liquid (which was used without further purification).

NMR: δ 1.26 (s, 6H), 2.65 (s, 2H), 3.66 (s, 3H), 5.14 (s, 1H), 5.26 (s, 1H); IR (film) 1730, 1630, 1240, 1190, 1150, 890 cm^{-1}.

A solution of 48 mL (67 mmol) of 1.4 M ethereal methyllithium-lithium bromide complex in 100 mL of ether at 0° was treated dropwise with 3.4 g (19 mmol) of crude ester 4 using 30 mL of anhydrous ether for the transfer. The resulting solution was stirred at 0° for 1.75 hour and then carefully quenched with 100 mL of 10% aqueous ammonium chloride solution. The layers were separated and the aqueous portion extracted with 100 mL of ether. The combined ethereal extracts were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 3.2 g (94%) of 2-chloro-5-hydroxy-4,4,5-trimethyl-1-hexene (5) as a yellow liquid (which was used without further purification).

NMR: δ 1.03 (s, 6H), 1.21 (s, 6H), 1.55 (bs, 1H), 2.48 (s, 2H), 5.12 (s, 1H), 5.31 (s, 1H); IR (film): 3450 (broad), 1625, 1470, 1370, 1150, 1120, 945, 890 cm^{-1}.

A total of 1.8 g (10.8 mmol) of crude alcohol 5 was added dropwise over 5 minutes into a stirred solution of 130 mL of concentrated sulfuric acid maintained at -20°. After another 25 minutes at -20°, the resulting orange solution was added

all at once to 500 g of ice. The aqueous solution was extracted with two 300 mL portions of ether. The combined ethereal extracts were washed with brine, saturated aqueous sodium bicarbonate solution, brine and were dried ($MgSO_4$). Removal of the solvent afforded 1.6 g of an orange oil which was chromatographed on 140 g of Alcoa neutral alumina eluting with 5:1 pentane-diethyl ether to give 0.87 g (61%) of 3,3,4,4-tetramethylcyclopentanone (1)[1] as a white solid, mp. 125-127°; R_f 0.47 (in 5:1 pentane-diethyl ether).

NMR: δ 1.05 (s, 12H), 2.21 (s, 4H); C-13-NMR: δ 24.02, 40.32, 52.61, 190.73 (very small, C=0); IR (mull) 1745 cm^{-1}; mass spectrum, Calcd. for $C_9H_{16}O$ m/e 140.1201, found m/e 140.1198.

REFERENCES

1. M.-L. Leriverend and P. Leriverend, Compt. Rend., Ser. C., 280, 791 (1975).
2. P. T. Lansbury and F. R. Hilfiker, Chem. Commun., 619 (1969).

PREPARATION OF MONOALLYL ETHYLENE GLYCOLS

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Difficulties with the procedure of Riemschneider and Kotzsch [Monatsh. Chem., 90, 787 (1959)] for the synthesis of monoallyl ethylene glycols were immediately apparent. Preparation of the sodium salt of the glycol was accomplished by addition of sodium to excess glycol under toluene. Removal of the toluene required repeated triturations with ether.