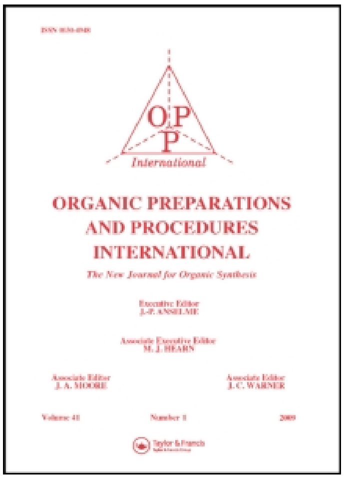

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SYNTHESIS OF 4,4-bis(2-METHOXYETHYL)CYCLOHEXANONE AND OF 4,4-bis(2-METHOXYETHYL)-2-CYCLOHEXEN-1-ONE

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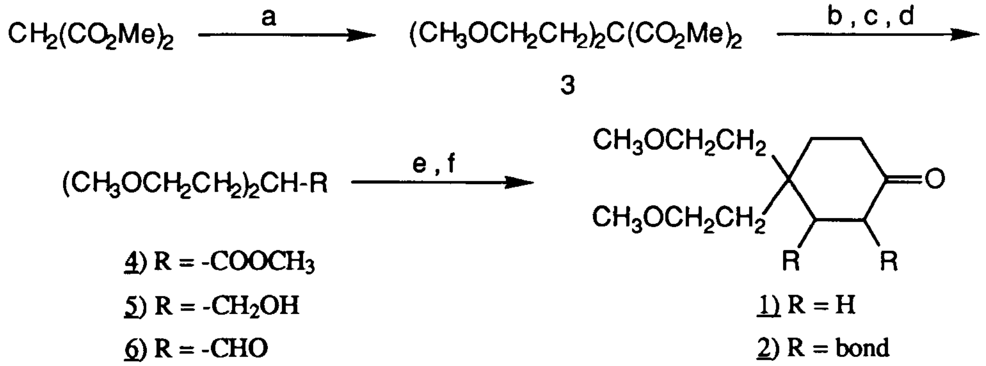
4,4-Disubstituted cyclohexanones are used as intermediates in the synthesis of 8,8-disubstituted 2-azaspiro[4.5]decanes which are compounds recently shown to have antiarthritic and immunoregulatory activity.[1] The literature provides no examples of 4,4-bis(alkoxyalkyl)cyclohexanones or of the corresponding 2-cyclohexen-1-ones. As part of an effort to obtain a variety of substituted cyclohexanones, the synthesis of 4,4-bis(2-methoxyethyl)cyclohexanone and cyclohexenone (1 and 2) was undertaken and is now being reported.



4) R = -$COOCH_3$

5) R = -CH_2OH

6) R = -CHO

1) R = H

2) R = bond

a) 2-Bromoethyl methyl ether, NaOMe b) LiCl, aq. DMSO c) LAH, Et_2O
d) PCC, CH_2Cl_2 e) MVK, H_2SO_4, benzene f) H_2, Pd/C, EtOAc

Dimethyl malonate was alkylated[2] with 2-bromoethyl methyl ether using sodium methoxide in methanol. The resulting mixture of mono- and dialkylated products was realkylated in the same manner to afford a 72% yield of the desired dialkylated 3. This compound was partially saponified and decarboxylated using LiCl[3] in wet DMSO to give the monoester 4. Reduction with LAH gave the alcohol 5 which was oxidized with PCC[4] to the aldehyde 6. The aldehyde was subjected to an acid-catalyzed Robinson annulation[5] to yield the 4,4-disubstituted cyclohexenone 2 which was hydrogenated to cyclohexanone 1.

EXPERIMENTAL SECTION

Gas chromatography was carried out on a Hewlett-Packard 5890 instrument with an Alltech RSL-150m x 0.3 μm polydimethylsiloxane capillary column. IRs were recorded on a Perkin Elmer 598 Infrared Spectrophotometer. ^1H NMRs were obtained in $CDCl_3$, with TMS as an internal reference, on an IBM NR/80 mHz FT NMR. Elemental Analyses were performed by

Atlantic Microlabs Inc.

Dimethyl bis(2-Methoxyethyl)malonate (3)[2].- Sodium (12.1 g, 0.53 mol) was cautiously added to dry MeOH (150 mL). After the reaction was completed, dimethyl malonate (19.8 g, 0.15 mol) was slowly added, refluxed for 15 min and cooled. 2-Bromoethyl methyl ether (104 g, 0.75 mol) was added slowly and the resulting solution was refluxed for 3 hrs, then cooled, concentrated, diluted with water, extracted three times with ether, washed with brine, dried with anhydrous $MgSO_4$ and concentrated to give 26 g (87%) of product. The product, shown by GC analysis to be a 2:3 mixture of mono/dialkylated malonates, was realkylated in the same manner to give 27 g (72% overall, 96% dialkylation). This was used without further purification in the next step.

IR (neat): 1735 (ester), 1115 (ether) cm^{-1}; ^1H NMR: δ 3.70 (s, 6H, -COOC$\underline{H}_3$), 3.40 (t, 4H,
-OC$\underline{H}_2$-), 3.25 (s, 6H, C$\underline{H}_3$O-) and 2.23 (t, 4H, -OCH$_2$C$\underline{H}_2$-).

Anal. Calcd. for $C_{11}H_{20}O_6$: C, 53.22; H, 8.12. Found: C, 53.28; H, 8.13

Methyl bis(2-Methoxyethyl)acetate (4).- A mixture of 3 (29.9 g, 0.121 mol), LiCl[3] (5.85 g, 0.14 mol), DMSO (230 mL) and H_2O (2.5 g, 0.14 mol) was heated at 185° for 3.5 hrs, cooled and poured into 500 mL of ice water. The solution was extracted with hexane (3 x 100 mL), washed with brine, dried over anhydrous $MgSO_4$, concentrated and distilled to give 14.8 g (64%) of the ester as a colorless liquid, bp. 89-91°/20 mm Hg.

IR (neat): 1740 (ester), 1115 (ether) cm^{-1}; ^1H NMR: δ 3.68 (s, 3H, -COOC$\underline{H}_3$), 3.38 (t, 4H, -OC$\underline{H}_2$-), 3.30 (s, 6H, C$\underline{H}_3$O-), 2.66 (m, 1H, -C$\underline{H}$COOCH$_3$), 1.86 (m, 4H, -OCH$_2$C$\underline{H}_2$-).

Anal. Calcd. for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 56.88; H, 9.55

2-bis(2-Methoxyethyl)ethanol (5).- To a cooled (5°) mixture of LAH (6.0 g, 0.16 mol) and ether (500 mL), ester 4 (12.9 g, 0.063 mol) in ether (100 mL) was slowly added and the temperature was allowed to rise to 25°. After the mixture was stirred for 2 hrs, the unreacted LAH was quenched with solid $Na_2SO_4.10H_2O$. It was then filtered and concentrated to give 10.0 g (98%) of the desired alcohol, pure enough to be used without purification.

IR (neat): 3430 (alcohol), 1115 (ether) cm^{-1}; ^1H NMR: δ 3.45 (m, 6H, -OC$\underline{H}_2$- and -C$\underline{H}_2$ OH), 3.34 (s, 6H, C$\underline{H}_3$O-), 1.66 (m, 5H, (C$\underline{H}_2$)$_2$-C$\underline{H}$-).

Anal. Calcd. for $C_8H_{18}O_3$: C, 59.23; H, 11.18. Found: C, 59.36; H, 11.17

bis(2-Methoxyethyl)acetaldehyde (6).- To a stirred mixture of pyridium chlorochromate[4] (50.7 g, 0.24 mol) and anhydrous CH_2Cl_2 (260 mL) was slowly added a solution of 5 (9.8 g, 0.06 mol) in CH_2Cl_2 (40 mL) at 25°. After 2 hrs, ether (300 mL) was added. The solution was passed through a short florisil column, then concentrated to give 8.6 g (89%) of the aldehyde as a liquid. The product was used without further purification in the next step.

IR (neat): 1725 (aldehyde), 1115 (ether cm^{-1}; ^{1}H NMR: δ 9.6 (d, 1H, -C$\underline{H}$O), 3.41 (t, 4H, -OC$\underline{H}_2$-), 3.30 (s, 6H, C$\underline{H}_3$O-), 2.56 (m, 1H, -C$\underline{H}$CHO), 1.90 (m, 4H, -OCH$_2$C$\underline{H}_2$).

4,4-bis(2-Methoxyethyl)-2-cyclohexen-1-one (2).- A mixture of 6 (9.0 g, 0.056 mol), methyl vinyl ketone (6.7 g, 0.095 mol), conc. H_2SO_4 (0.4 mL) and benzene[5] (45 mL) was refluxed overnight using a Dean-Stark trap. The resulting solution was washed with satd. $NaHCO_3$, then brine. It was then dried over anhydrous $MgSO_4$, concentrated and kugelrohr distilled to give 5.5 g (46%) of 2, bp. 93-96°/0.2mm Hg.

IR (neat): 1680 (ketone), 1620 (alkene), 1115 (ether) cm^{-1}; ^{1}H NMR: δ 6.80 (d, 1H,-C$\underline{H}$CO-), 5.90 (d, 1H, -C$\underline{H}$CH$_2$CHO-), 3.46 (t, 4H, -OC$\underline{H}_2$-), 3.31 (s, 6H, C$\underline{H}_3$O-), 2.47 (t, 2H, -C$\underline{H}_2$CO-), 2.1-1.7 (m, 6H, rest.)

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.68; H, 9.48

4,4-bis(2-Methoxyethyl)cyclohexanone (1).- A mixture of 2 (5.3 g, 0.025 mol), 10% Pd/C (0.2 g), and EtOAc (50 mL) was hydrogenated until the uptake of hydrogen had ceased. The resulting mixture was filtered through Celite and concentrated to give a quantitative yield of the saturated ketone 1.

IR (neat): 1710 (ketone, 1115 (ether) cm^{-1}; ^{1}H NMR: δ 3.47 (t, 4H, -OC$\underline{H}_2$-), 3.33 (s, 6H, C$\underline{H}_3$O-), 2.37 (t, 4H, -(C$\underline{H}_2$)$_2$CO), 1.66 (t,8H, rest).

Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.28; H, 10.37

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