Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Facile Synthesis of Anhydromevalonolactone from Ethyl Acetoacetate

A. Nangia [a] , B. Madhusudan Rao [a] & G. Prasuna [a]
[a] School of Chemistry, University of Hyderabad, Hyderabad, 500 134, INDIA
Version of record first published: 24 Sep 2006.

To cite this article: A. Nangia , B. Madhusudan Rao & G. Prasuna (1992): Facile Synthesis of Anhydromevalonolactone from Ethyl Acetoacetate, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:4, 593-602

To link to this article: http://dx.doi.org/10.1080/00397919208019258

SYNTHETIC COMMUNICATIONS, 22(4), 593-602 (1992)

FACILE SYNTHESIS OF ANHYDROMEVALONOLACTONE FROM ETHYL ACETOACETATE

A. Nangia,* B. Madhusudan Rao and G. Prasuna
School of Chemistry, University of Hyderabad
Hyderabad 500 134, INDIA.

ABSTRACT: Ethyl acetoacetate was transformed to 3-methylglutaconic anhydride, which upon LAH reduction and Jones oxidation afforded anhydromevalonolactone.

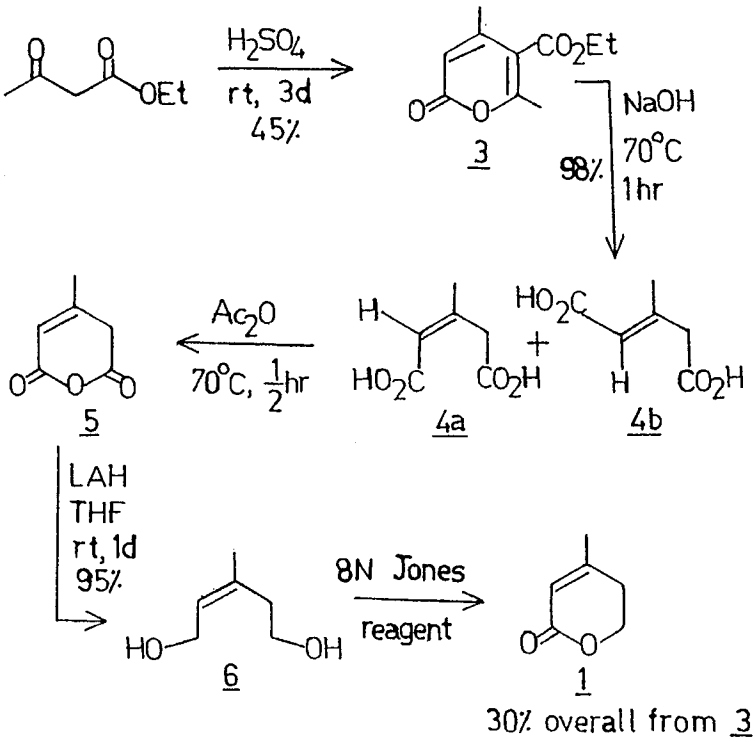
Anhydromevalonolactone (5,6-dihydro-4-methyl-2H-pyran-2-one) is an important and versatile intermediate in the synthesis of natural products.[1] Several methods of preparation of anhydromevalonolactone have been reported in the literature.[2-5] A major drawback of the early procedure of Cornforth,[2] which was subsequently modified by White,[3] is the large number of steps and the low yield in the preparation of 4-hydroxy-2-butanone[6] (23% after fractional distillation). Tamm's[4] two step sequence also suffers from low overall yield (15%), whereas pyridinium chlorochromate

oxidation of 5,6-dihydro-4-methyl-2H-pyran to anhydromevalonolactone (85%)[5] is not viable because the pyran is no longer commercially available.

In connection with an ongoing project in our laboratory, we required gram quantities of anhydromevalonolactone (1) for the preparation of (Z)-3-methyl-5-bromo-2-penten-1-ol (2). We were able to procure lactone 1 in 15% overall yield by Jones oxidation of 3-methyl-3-buten-1-ol to the corresponding acid followed by Prins reaction with formaldehyde in AcOH solvent.[4] However, 3-methyl-3-buten-1-ol is some what expensive and also large amounts of AcOH have to be fractionally distilled after the Prins reaction prior to work-up.

In this *Communication* we describe a five step synthesis of anhydromevalonolactone (1) from ethyl acetoacetate via the protocol delineated in Scheme.

The acid catalysed dimerisation of ethyl acetoacetate to pyrone 3 proceeded in 45% yield as reported in the literature.[7] Base hydrolysis of pyrone 3 afforded a 2:1 mixture of *trans-cis* 3-methylglutaconic acid 4 in near quantitative yield. The assignment of olefin geometry and ratio of isomers was determined in the following manner:



SCHEME

It is known that in trisubstituted olefins bearing an α,β-unsaturated carbonyl, the CH_3 protons *cis* to the carbonyl resonate 0.1-0.2 ppm downfield relative to the CH_3 group *trans* to the carbonyl.[8] Based on the above anology, protons on the γ carbon *cis* to the vinyl CO_2H will be deshielded. Hence, CH_2 protons in *cis* isomer **4a** and CH_3 protons in *trans* isomer **4b** are deshielded relative to the corresponding signals in the other

isomer. The peaks corresponding to CH_2 and CH_3 groups in *cis* isomer **4a** appear at δ 3.76 and 2.04, respectively, wheras in *trans* isomer **4b** they resonate at δ 3.24 and 2.28, respectively. Integration of methylene and methyl signals furnished a ratio of 2:1 which is in agreement with the NMR data reported by Wiley and Jackson[9] (1958). A *cis-trans* ratio of 2:1 was incorrectly assigned by Payne[10] (1968) and went unnoticed by Jung *et. al.*[7] (1984). The crude mixture of diacids was converged to the desired *cis* geometry by cyclisation to 3-methylglutaconic anhydride 5[7] prior to reduction.

The unsymmetrical anhydride 5 can, in principle, be transformed to lactone 1 by two methods.

1) Selective and controlled reduction of saturated carbonyl of anhydride 5 to lactone 1. This was attempted with $NaBH_4$/THF,[11] but was unsuccessful.

2) Reduction of anhydride 5 to diol 6, and selective oxidation of allylic over homoallylic alcohol to provide lactone 1. Efforts in this direction were more encouraging.

The crude anhydride 5 was reduced with lithium aluminium hydride in THF[12] (0 °C--->rt, 24h) to obtain (Z)-3-methyl-2-penten-1,5-diol (6)[13] in 90% yield after work-up. The crude diol 6 was reoxidised to lactone 1

with 8N Jones reagent[14] (2 equi.) at 0°C; if excess Jones reagent was used, over-oxidation products (such as diacid 4) were observed on TLC. Purification of crude lactone 1 on silica gel afforded pure anhydromevalonolactone (1) in 30% overall yield from pyrone 3.

The advantages of our synthetic protocol over those reported in the literature are that:

1) Starting material is inexpensive and commercially available in bulk.

2) No purification of intermediates is required, except pyrone 3 which is easily distillable.

3) Reaction conditions are mild and simple reagents are employed.

4) The entire sequence is amenable to scale-up and excuted in less than a week.

In conclusion, we have synthesised anhydromevalonolactone from ethyl acetoacetate in 12% overall yield in five steps.

EXPERIMENTAL:

Melting points are uncorrected. IR spectra were recorded on Perkin-Elmer model 1310 or 297 spectrophotometers. ^1H NMR spectra were recorded at 100 MHz on JOEL-FX-100 spectrometer. All spectra were run in $CDCl_3$ (except diacid 4 which was dissolved in

$CDCl_3$+DMSO-d_6) using TMS (δ 0.00) as internal reference. All reagents and solvents were purified and distilled according to standared methods.[15] Work-up means drying organic extracts over anhydrous $MgSO_4$, filtration and concentration under reduced pressure.

ETHYLISODEHYDROACETATE (3)

Pyrone 3 was isolated in 45% yield after work-up and distillation as a yellow liquid (b.p 100-110^{o}C/1.0 torr) whose ^{1}H NMR and IR spectra were in agreement with literature values.[7]

3-METHYLGLUTACONIC ACID (4)

A solution of ethylisodehydroacetate (3) (6.0 g, 30 mmol) in 5N NaOH (30 mL, 150 mmol) was heated at 70^{o}C for 1h. The reaction mixture was cooled to room temperature and extracted with ether (1X30 mL). The aqueous layer was cooled to 0^{o}C, acidified with 14 mL of conc. HCl (160 mmol) to pH 2, saturated with solid NaCl and extracted in ether (4X20 mL) and washed with brine. Work-up afforded 4.33g (98%) of an off-white solid (m.p. 113-115^{o}C). The crude diacid was obtained as a 2:1 mixture of *trans-cis* isomers as determined by integration of methylene and methyl signals. IR (Neat, cm^{-1}): 3000(br), 2800(br), 1700, 1460, 1390, 1280, 1230, 1180, 980. ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 5.88 (m, 1H, vinyl H); 3.24 and 3.76 (pair of singlets, 2H, CH_2);

2.04 and 2.28 (pair of doublets, J=1Hz, 3H, CH_3). The ratio of peaks at δ 3.24 and 3.76 and at δ 2.28 and 2.04 was 2:1, respectively. The peak at δ 4.7[10] (CO_2H) could not be located up to δ ~ 15 ppm.

5,6-DIHYDRO-4-METHYL-2H-PYRAN-2,6-DIONE (5)

A mixture of crude 3-methylglutaconic acid (4) (6 mmol, 864 mg) and Ac_2O (18 mmol, 1.63 g, 1.5 mL) was heated at 70°C for 30 min. The volatiles were removed at reduced pressure (1-2 torr). The product was immediatly used without further purification. ^1H NMR spectrum showed peaks corresponding to anhydride 5[7] along with traces of undistilled Ac_2O and AcOH at δ 2.24 and 2.05, respectively.

(Z)-3-METHYL-2-PENTEN-1,5-DIOL (6)

To a suspension of LAH (18 mmol, 684 mg) in 10 mL of dry THF at 0°C was slowly added crude anhydride 5 (6 mmol, 800 mg) as a solution in 10 mL of dry THF. The reaction mixture was stirred for 24 hours at ambient temperature, at which point it was quenched with sat. Na_2SO_4 soln. (2.5 mL). Work-up yielded 662 mg (95%) of crude diol 6 which was used in the next step without further purification. A small sample was purified on silica gel to afford analytical data. IR (Neat, cm^{-1}): 3300(br), 2950, 1450, 1390, 1050, 1010, 920, 870. ^1H NMR ($CDCl_3$): δ 5.7 (br t, J=8Hz, 1H, vinyl H), 4.04(d,

J=8Hz, 2H, allylic CH_2O), 3.66 (t, J=6Hz, 2H, CH_2O), 2.76 (br s, 2H, OH), 2.32 (t, J=6Hz, 2H, allylic CH_2), 1.76 (s, 3H, CH_3).

5,6-DIHYDRO-4-METHYL-2H-PYRAN-2-ONE (1)

(Z)-3-Methyl-2-penten-1,5-diol 6 (5.7 mmol, 661 mg) in 8 mL of acetone was taken in a 25 mL RB flask. To it 8N Jones reagent (12 mmol, 1.5 mL) was added slowly dropwise at $0^{o}C$. After completion of the addition, i-PrOH (3-5 drops) was added to destroy excess of Jones reagent. The reaction mixture was extracted with ether (30 mL) and the ether layer was washed with sat. $NaHCO_3$ soln. (20 mL) and brine (20 mL). Work-up afforded 400 mg of crude lactone which was purified by column chromatography (hexane--->20% EtOAc/hexane) to furnish 208 mg (31%) of pure anhydromevalonolactone (1) whose ^1H NMR and IR data were in agreement with literature values.[4]

ACKNOWLEDGEMENTS: We thank DST (New Delhi) for financial assistance and UGC (New Delhi) for SAP and COSIST programmes in School of Chemistry. GP thanks UGC (New Delhi) for a research fellowship.

REFERENCES:

1. a) Thomas, A.F. and Bessiere, Y. in *The Total Synthesis of Natural Products*, vol. 7, Ed. ApSimon, J.; Wiley-Interscience: New York, 1988; p 275. b)

Tse-Lok, H. in *Carbocycle Construction in Terpene Synthesis,* VCH Publishers: New York, 1988; p 533-34.

2. Cornforth, J.W.; Cornforth, R.H.; Popjak, G. *Biochem. J.* **1958** 69 148.

3. White, J.D.; Carter, J.P.; Kezar, H.S. *J. Org. Chem.* **1982** 47 929.

4. Herold, P.; Mohr, P.; Tamm, Ch. *Helv. Chim. Acta.* **1983** 66 744.

5. Bonadies, F.; DiFabio, R. *J. Org. Chem.* **1984** 49 1647.

6. White, T.; Harvard, R.N. *J. Chem. Soc.* **1943** 25.

7. Jung, M.E.; Lowe, J.A.; Lyster, M.A.; Node, M.; Pfluger, R.W.; Brown, R.W. *Tetrahedron* **1984** 40 4751.

8. Jackman, L.M. and Sternhell, S. in *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,* Second ed.; Pergamon: Oxford, 1972; p 171.

9. Jackman L.M.; Wiley, R.H. *Proc. Chem. Soc.* **1958** 196.

10. Payne, G.B. *J. Org. Chem.* **1968** 33 1284.

11. Bailey, D.M.; Johnson, R.E. *J. Org. Chem.* **1970** 35 3574.

12. Bloomfield, J.J.; Lee, S.L. *J. Org. Chem.* **1967** 32 3919.

13. For (E)-diol, see: Schlosser, M.; Hammer, E. *Helv. Chim. Acta.* **1974** 57 2547.

14. Harding, K.E.; May, L.M.; Dick, K.F. *J. Org. Chem.* 1975 40 1664.

15. Perrin, D.D.; Armarego, W.L.F.; Perrin, D.D. in *Purification of Laboratory Chemicals*, Second ed.; Pergamon: London, 1986.

(Received in UK 30 August, 1991)