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FACILE SYNTHESIS OF 1,3-DIACETYL-2-METHYLCYCLOPENTENE A VERSATILE SYNTHETIC INTERMEDIATE.

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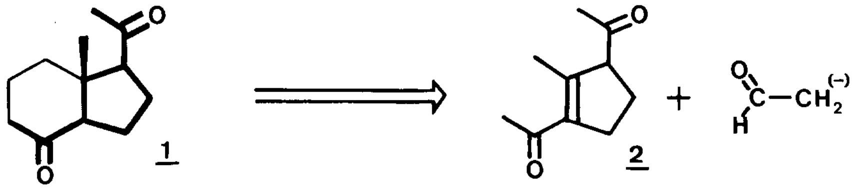
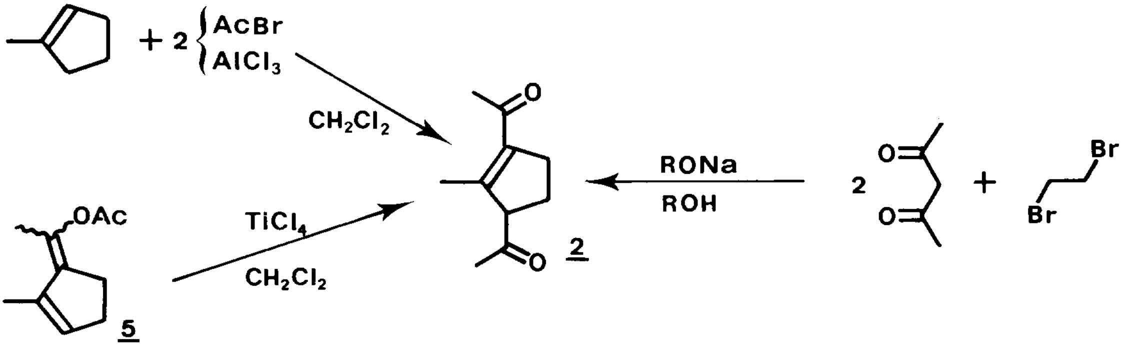
Summary : Convenient access to 1,3-diacetyl-2-methylcyclopentene 2 is reported by three routes : acetylation of methylcyclopentene (or cyclohexane), condensation of acetylacetone with 1,2-dibromoethane, and the isomerisation of O-acetylated dienolate of 1-acetyl-2-methylcyclopentene. The process of isomerisation provides best results and its mechanism is discussed.

Hydrindanone 1 is an important product because of the widespread occurrence of its derivatives in natural products as vitamins D (1). Our synthetic strategy entails the attachment of a suitable equivalent of the acetaldehyde enolate (acetaldehyde d^2 reagents (2)) to a 1,3-diacetyl-1-methylcyclopentene 2 followed by subsequent cyclisation.

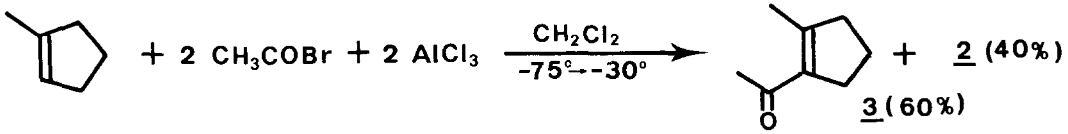


We wish to report three methods to obtain 2 (to our knowledge, 2 was not previously reported (3)).

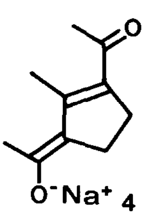


A - Diacetylation of methylcyclopentene or cyclohexane :

Diacetylation of acyclic olefins or paraffins leads to the formation of δ-diketones which cyclise to pyrylium salts (6,7). Reaction of methylcyclopentene with acetyl bromide (2 mol. equiv.) in the presence of $AlCl_3$ (2 mol. equiv.) gives a mixture of 1-acetyl-2-methylcyclopentene 3 and 2 (overall yield 50-55 %)(8,9).

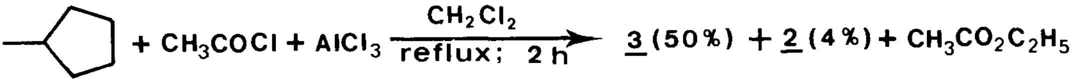


Using more drastic conditions, a similar result is observed with cyclohexane (10) (Acetyl chloride is the oxidative reagent,reduced to ethyl acetate (11)).


4

Purification of 2 was simplified by treating the crude distillate with 20 % aqueous sodium hydroxide giving a suspension of the yellow salt 4 of 2.

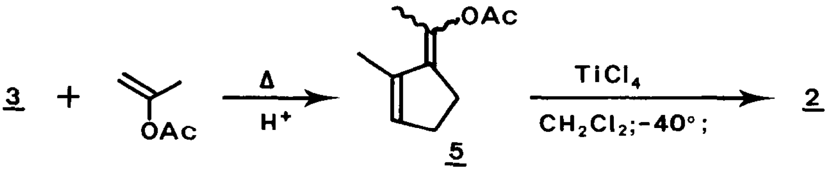
In contrast, poor yield was obtained during the diacylation of methylcyclopentane, but with an equi. molecular amount of acetyl chloride, a very clean reaction occurs and 3 is the major product (12).



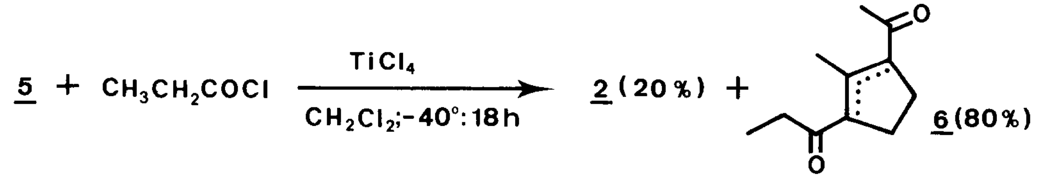
This strikingly simple reaction affords a convenient and very cheap preparative route to 3 (*vide infra*).

B - Rearrangement of *O*-acetylated dienolate of 3 :

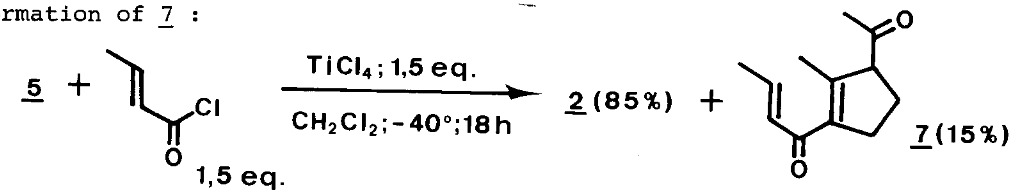
Rearrangement of the *O*-acetylated dienolate 5 in presence of $TiCl_4$ in CH_2Cl_2 at low temperature takes place very cleanly to give diketone 2 (overall yield from 3, 90-95 %). *O*-Acetylated dienolate 5 is easily obtained from 3 and isopropenyl acetate (13). (The overall efficiency for this sequence (*i.e.* methylcyclopentane → 2) is 45 %).



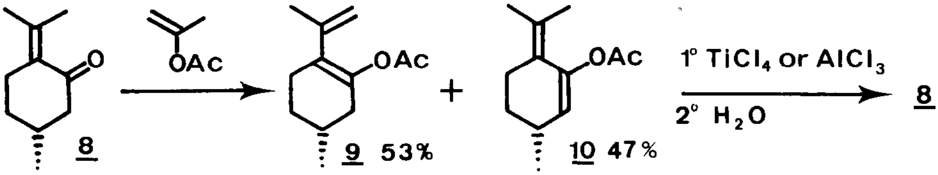
Because of the intriguing nature of this reaction, we wish to explore its mechanism. There is increasing evidence that unsaturated groups undergo particularly easy 1,5-sigmatropy (14). Furthermore, the 1,5-acyl shift is subjected to catalysis by LEWIS acids (15). But the possibility of an intramolecular process being involved was conclusively ruled out by a cross-over experiment with propionyl chloride (overall yield 85-90 %)(16).



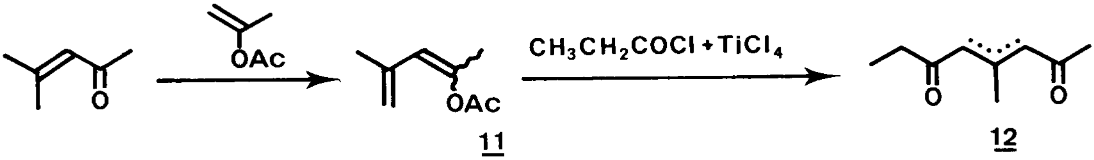
In contrast, even when the above reaction was carried out with 1.5 mol. equiv. of crotonyl chloride, the major product was 2 with slight formation of 7 :



Efforts to expand the scope of the reaction with respect to the *O*-acetylated dienolate did not result in synthetically useful yields. The mixture of *O*-acetylated dienolates of (+)-pulegone 9 and 10, did not rearrange in presence of $TiCl_4$ or $AlCl_3$ (17):



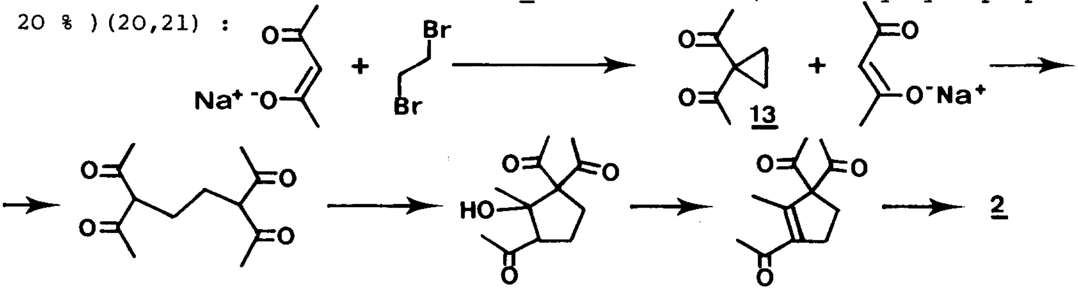
However, the condensation of propionyl chloride and 4-acetoxy-2-methyl-1,3-pentadiene 11 leads to the formation of δ-diketone 12 (18) :



These results lead to the conclusion that rearrangement of 5 into 2 is polar, with the intermediate formation of acylium cation derivatives, like the FRIES rearrangement (19).

C - Condensation of sodium acetonylacetonate with 1,2-dibromoethane :

This reaction leads to 2 (40 %) and 1,1-diacetylcyclopropane 13 (20 %)(20,21) :



References and Notes :

1 C.B. CHAPLEO, P. HALLET, B. LYTHGOE, I. WATERHOUSE and P.W. WRIGHT, *J. Chem. Soc., Perkin I*, 1977, 1211.

2 D. SEEBACH, *Angew. Chem. Int. Ed. Eng.*, 1979, 18, 239.

3 Others derivatives of 1-acetyl-2-methylcyclopentene : 3-isobutenyl see (4); 3-formyl see (5).

4 P.R. BERSTEIN and G. STORK, *Tetrahedron Letters*, 1979, 1967.

5 T.A. BRYSON and C.J. REICHEL, *ibid.*, 1980, 2381.

6 C.D. NENITZESCU and A.T. BALABAN, *Friedel-Crafts and related reactions*, G.A. OLAH Ed., Vol. III part 2, p. 1099, Interscience publ. New York.

7 M. ARNAUD, A. PEDRA, C. ROUSSEL and J. METZGER, *J. Org. Chem.*, 1979, 44, 2972.

8 For diacylation of 1-methylcyclohexene, see :
M. DUBOIS and M. CAZAUX, *Bull. Soc. Chim. France*, 1975, 274.

9 In a typical exp., anhydrous $AlCl_3$ (13.2 g; 0.1 mol) was stirred with CH_2Cl_2 (75 ml) and acetyl bromide (12.8 g; 0.1 mol) until dissolution. The mixture was cooled to -78 ° and methylcyclopentene (4.1 g; 0.05 mol) was added. The mixture was kept at -78 ° for 3 h, at -30 ° for 2 h, and then hydrolysed. 2 Eb. : 85-90 °/0.5 Torr. NMR : ^1H δ (60 MHz, CCl_4) : 3.57 (1H;t;J=7Hz);2.22 (3H;s); 2.13 (3H;s); 2.0 (3H;broad s). ^{13}C δ (25.159 MHz, $CDCl_3$) : 209.0 (C=O); 198.4 (C=O); 149.9 (C=C); 139.20 (C=C); 65.65 (CH); 33.5 (CH_2); 25.73 (CH_2); 30.49 (CH_3); 28.49 (CH_3); 15.87 (CH_3).

10 In the previous works, only 3 was identified, see:
I. TABUSHI, K. FUJITA and R. ODA, *Tetrahedron Letters*, 1968, 4247.
J. BERTRAM, J.P. COLEMAN, M. FLEISCHMANN and D. PLETCHER, *J. Chem. Soc. Perkin trans* 1973, 2, 374.

In a typical exp., anhydrous $AlCl_3$ (53g; 0.4 mol), CH_2Cl_2 (160 ml), cyclohexane (80 ml) are refluxed for 24 h. After cooling to r.t., acetyl chloride (39g, 0.4 mol) was added and the mixture was allowed to stand at r.t. for 18 h and was hydrolysed. 3 (20 g) and 2 (12 g) are isolated by distillation.

11 D.M. BROUWER and A.A. KIFFEN, *Rec. Trav. Chim. Pays-Bas*, 1973, 92, 689.

12 A solution of $AlCl_3$ (39.75 g; 0.3 mol), CH_2Cl_2 (200 ml), acetyl chloride (23.4 g; 0.3 mol), methylcyclopentane (25.2 g; 0.3 mol) was refluxed for 2 h. Hydrolysis and subsequent distillation yielded 3 (18 g; 0.15 mol) and 2 (2.18 g; 17 mmol). Cyclohexane and ethyl acetate are obtained in the light fractions of the distillation.

13 3 (12.4 g; o.1 mol), isopropylidene acetate (30.1 g; 0.3 mol), p. toluenesulfonic acid (50 mg) was heated and acetone was eliminated by distillation (10 h). Excess of isopropylidene acetate was eliminated by distillation under vacuum (r.t. 10 Torr). The crude product 5 was diluted with CH_2Cl_2 (50 ml), and the solution was added to a mixture of $TiCl_4$ (19 g; 0.1 mol) and CH_2Cl_2 (100 ml) cooled at -40 °. After stirring at -40 ° for 18 h, hydrolysis and subsequent distillation yielded 2 (15 g).

14 R.W. ALDER and W. GRIMME, *Tetrahedron*, 1981, 37, 1809.

15 D.J. FIELD, D.W. JONES and G. KNEEN, *J. Chem. Soc. Chem. Comm.*, 1976, 873.

16 To a solution of $TiCl_4$ (1.9 g; 10 mmol), propionyl chloride (0.93 g; 10 mmol) and CH_2Cl_2 (10 ml), cooled at -40°, was added to crude 5 (13) (1.66 g; 10 mmol). The mixture was kept at -40 ° for 18 h and was hydrolysed. 2 and 6 were isolated by CPV.

17 A similar result is observed from *O*-acetylated dienolates of acetylcyclopentene and mesityl oxide.

18 *O*-silylated dienolates has not given any recognisable products with $CH_3COCl + TiCl_4$, see
I. FLEMING and T.V. LEE, *Tetrahedron Letters*, 1981, 705.

19 R. MARTIN, *Bull. Soc. Chim. France*, 1974, 983.

20 Condensation of sodium acetylacetonate with excess of dibromoethane (without solvent) gives 1,1,4,4-tetracetylbutane in poor yield, see :
G.T. MORGAN and C.J.A. TAYLOR, *J. Amer. Chem. Soc.*, 1926, 48, 43.

21 A solution of sodium acetylacetonate (0.2 mol) and dibromoethane (21.2 g; 0.1 mol), isopropyl alcohol (100 ml) was heated to reflux during 40 h. Acid work-up leads to products.

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