

## METHODS OF CYCLIZATION OF SOME $\delta$ -DIKETONES<sup>1</sup>

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**Abstract:** Three methods of cyclizing  $\delta$ -diketones where the  $\beta$ - and  $\gamma$ -carbons form part of a ring system were studied: 1) strong base in protic media; 2) strong aqueous acid biphasic with apolar solvent; 3) alumina with saturated hydrocarbons. General limits were established for each method and a system validated for preparative scale cyclization without isomerization of an external double bond.

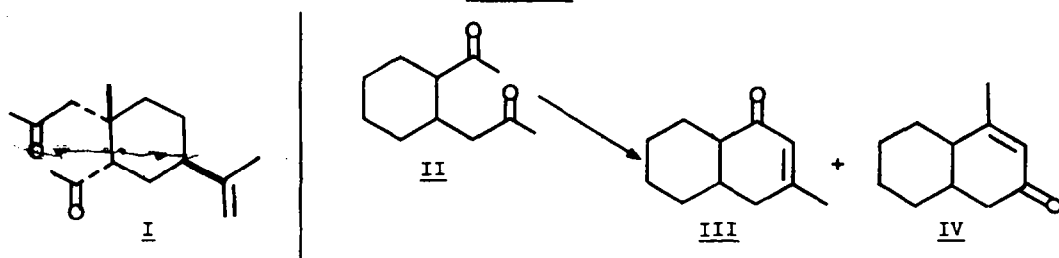
Pursuing a long-held interest<sup>2</sup> in the De Mayo reaction<sup>3</sup> and its synthetic potential, we studied the photoaddition of acetylacetone to limonene as a potential route to sesquiterpenes<sup>4</sup>. In the course of this work a certain difficulty was encountered in applying De Mayo's cyclization technique (hydrochloric acid in ethanol) to the photoaddition products because of the rapid rearrangement of the remaining double bond. For example, cyclization of (1S,2S,4R)-1-methyl-1-acetyl-4-isopropenyl-cyclohexane (I) in 2% HCl/EtOH led to the formation of at least 22 products (GC analysis).

We initially considered three different solutions to this problem. First, the use of strongly basic solution to promote the cyclization; second the use of phase transfer between an aprotic organic medium and aqueous acid; and third, the utilization of aluminum oxide in contact with aprotic solvents in order to promote cyclization and dehydration.

The first system, KOtBu/tBuOH<sup>5</sup> being generically already well known we decided to develop the latter two ideas in a model system and chose the original  $\delta$ -diketone of De Mayo<sup>3</sup>, 1-acetyl-2-acetyl-cyclohexane (II) in order to discover suitable cyclization conditions before applying the three systems to I.

The reaction as reported by De Mayo<sup>3</sup> leads to the formation in 2% HCl/EtOH of two ketones, III and IV in ratio of 1.6 to 1 and in global yield of 95%. We encountered no difficulty in separating the ketones on silica gel for use in other studies<sup>6</sup>.

SCHEME I



Liquid-Liquid Biphasic Conditions:

When we examined the possibility of using phase transfer conditions we were suprised to find that our initial biphasic control systems led to cyclization without the addition of phase transfer agents and so we examined only the aqueous hydrochloric acid-non-miscible organic solvent system.

It was found that when the organic phase was carbon tetrachloride or hexane we could obtain excellent conversions to products. With respect to the aqueous phase it was found that 10N HCl led to loss of material due to intermolecular condensations, but that the cyclization is observed to occur with efficiency when the aqueous phase contained 1N to 4.4N hydrochloric acid. We found that the rate of the cyclizations was proportional to the acidity<sup>8</sup> and for this reason our studies of the effect of the change in organic solvent and of temperature were realized with 4.4N HCl. The reactions were carried out with 1.5 ml of aqueous medium to 1.5 ml of organic solvent. The results are reported in table I.

TABLE I

Cyclizations of 1-Acetyl-2-Acetyl-cyclohexane (II) in Biphasic Systems

<u>Solvent</u> <sup>a</sup>	<u>wt. of II(mg)</u>	<u>T (°C)</u>	<u>Time (h)</u>	<u>Conv. of II(%)</u>	<u>III/IV</u>
Hexane	30	32	17	98	1.9
Hexane	20	reflux	2	100	2.4
CCl <sub>4</sub>	27	32	17	100	2.8
CCl <sub>4</sub>	20	reflux	2	100	1.4
CHCl <sub>3</sub>	27	32	17	0	-
CHCl <sub>3</sub>	20	reflux	2	0	-
CH <sub>2</sub> Cl <sub>2</sub>	20	reflux	2	0	-

a) aqueous phase 4.4N HCl

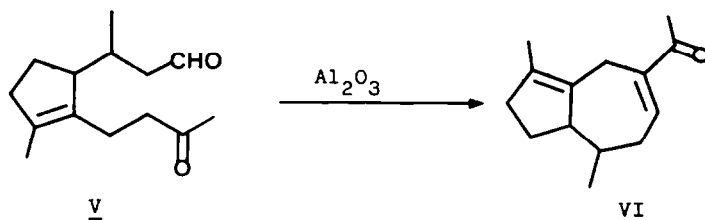
Our data indicate that there is a variation in ratio of ketones with the nature of the organic solvent and the temperature. Since our principle interest is the potential synthetic utilization of the products from the De Mayo reaction we sought to scale-up the procedure and found that in many cases the scale-up led to lower yields due to intermolecular condensations. We were able to establish a reproducible preparative procedure (vide infra) to produce five gram quantities of mixture of III and IV (in ratio of 2:1).

Liquid-Solid Biphasic Conditions:

Utilization of aluminum oxide in reactions of elimination and rearrangement has been reported in literature<sup>9-12</sup>. It is "common" knowledge that acetone should not be use as an eluent when aluminum oxide functions as the solid phase in column chromatography due to the formation of condensation products<sup>13</sup>. Thus it seemed reasonable to test aluminum oxide in the intramolecular aldol condensation to form cyclohexenones. A literature search showed that there exists already a close analogy in the formation of a cycloheptenone by Hoffman and Seigel (Scheme II)<sup>14</sup>. Three examples of intermolecular condensation were also discovered in

the literature<sup>15-17</sup>

SCHEME II



We examined the cyclization of diketone II using 10 mg of this substance in two ml of solvent and stirring with 250 mg of different types of  $\text{Al}_2\text{O}_3$ , for the time and temperature indicated in table II.

TABLE II

Cyclizations of 1-Acetyl-2-Acetyl-Cyclohexane of Aluminum Oxide

<u>Solvent (type of <math>\text{Al}_2\text{O}_3</math>)*</u>	<u>T(°C)</u>	<u>Time(h)</u>	<u>Conv.(%)</u>	<u>III/IV</u>
Hexane (b)	reflux	3	100	3.0
Hexane (b)	30	16	51	1.3
Hexane (b)	30	37	81	1.3
Hexane (a)	reflux	3	94	2.0
Hexane (a)	30	37	100	2.7
Hexane (n)	reflux	3	100	4.5
Hexane (n)	25	16	96	1.6
THF (a)	reflux	3	0	-
THF (b)	reflux	3	0	-
THF (n)	reflux	3	0	-
$\text{CHCl}_3$ (a)	reflux	1	45	1.0
$\text{CHCl}_3$ (b)	reflux	1	91	1.1
$\text{CHCl}_3$ (n)	reflux	1	0	-

\* a=acid, b=basic, n=neutral

Examination of Table II leads to the general impression that best conditions for this conversion would be found at reflux in a saturated hydrocarbon. The data appear to suggest that there is a temperature effect on the selectivity between the two modes of cyclization, with ketone III being favored at higher temperatures.

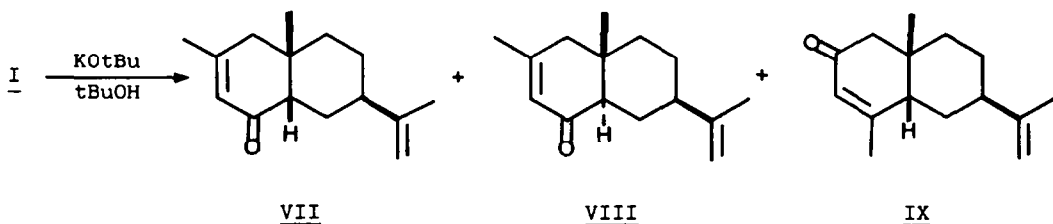
Using the initial studies as a guide, we developed a large scale procedure which resulted in obtaining the two ketones in quantities of three to four grams each. In this scale-up (x 1000) a much smaller proportion of  $\text{Al}_2\text{O}_3$  was used and we found that the ratio of III to IV fell to 2:3 making it clear that surface effects are also involved.

Cyclization of I:

The application of all three methods to the cyclization of I was not entirely satisfactory. Cyclization of I with an equimolar quantity of potassium

t-butoxide, 0.04M in t-butanol under nitrogen stirred at room temperature for 150 minutes led to the isolation of a solid in 98% yield. This solid was fractionated by thin-layer chromatography and found to contain three components identified as VII, VIII and IX. (Scheme III).

SCHEME III



Analysis (GC) showed under the conditions listed above that we obtained VII (28%), VIII(57%) and IX (15%). It should be noted that a control study showed that pure samples of VII and VIII both suffered extensive interconversion by epimerization under the cyclization conditions. The application of the 4.4N aq. HCl/hexane cyclization system furnished no result! The reagent was recovered unchanged.

Finally, the  $Al_2O_3$ /hexane system after 21h of reflux did not lead to any significant cyclization. We decided to use a higher temperature with decalin as the solvent. At reflux in decalin the cyclization was completed in 5 minutes with only VII and VIII being formed in a 40:60 ratio. This cyclization in which there is only attack by the nucleophilic group localized on the acetyl methyl followed by epimerization at the ring junction could be a case of selective absorption by the basic sites in the  $Al_2O_3$ .

In summary our studies strongly recommend the utilization of  $Al_2O_3$  to promote intramolecular condensation in systems sensitive to strong acid or strong base and especially in the case of acid-sensitive isopropenyl groups often found in terpenes and sesquiterpenes.

EXPERIMENTAL

The melting points and boiling points are uncorrected. Gas Chromatography unless otherwise stated was done on a Perkin-Elmer 900 with a column of SE-54 5% on chromosorb W (60-80 mesh) 2m x 3.2 mm at 180°C. Other instruments used: Perkin-Elmer 467 IR spectrometer; Hewlett-Packard, 5985-A GC/MS and Varian XL-100 for  $^1H$  and  $^{13}C$  NMR.

Cyclization of 1-Acetyl-2-Acetonyl-Cyclohexane (II):

A)  $Al_2O_3$ /Hexane: In a 500 ml roundbottomed flask were placed 37g of acidic aluminum oxide (activation grade I<sup>18</sup>) and 150 ml of hexane(dried over sodium) A solution of 10g (40 mmoles) of 1-acetyl-2-acetonyl-cyclohexane(II<sup>19</sup>) in 50ml(0.2M) of dry hexane was added and the reaction mixture was stirred under reflux for two hours. The system was cooled to 40°C, filtered to remove the aluminum oxide which was washed with 20 ml of hot hexane, and the combined filtrates were evaporated in a rotatory evaporator. The residual liquid was distilled, giving a fraction at

106-8°C (3 torr) weighing 8.6g (95% yield) which contained ketones III and IV in a 2:3 ratio (glc).

B) Aq.HCl/Hexane: To a 500 ml roundbottomed flask were added 150 ml of 4.4N hydrochloric acid and a solution of 6.0g of 1-acetyl-2-acetyl-cyclohexane (II) in 200 ml of hexane. The system was stirred and refluxed for 2h. After cooling, the organic layer was separated and washed with 100 ml portions of 10% sodium bicarbonate and water, and then dried over sodium sulfate. After solvent evaporation the residual oil was distilled, 106-8°C (3 torr), to give 5.30 g (98%) of the mixture of ketones (2:1). The ketones were separated by column chromatography on silica.

Cyclization of (1S,2S,4R)-1-Methyl-1-Acetyl-2-Acetyl-4-Isopropenyl-Cyclohexane(I)

A) KOtBu/tBuOH: In a 25 ml 3-necked r.b. flask was placed 94.4 mg (0.4 mmoles) of I<sup>2</sup> which was diluted with 5.0 ml of dry t-butanol. Under a flux of N<sub>2</sub> 5.0 ml of 0.08M KOtBu/tBuOH was added using a syringe and septum. The mixture was stirred for 150 min at room temperature. After cooling to 0°C the reaction was neutralized with 10% HCl and products extracted with CH<sub>2</sub>Cl<sub>2</sub>. After drying over MgSO<sub>4</sub> and evaporating, 90 mg of an oil was obtained. Substances with Rf 0.44 and 0.57 were separated on thin layer silicagel plates. The fraction at 0.57 contained two products (VII and VIII) and the fraction at 0.44 one component (IX). IX (5S,7R,10S)-4,10-dimethyl-7-isopropenyl-3-decalen-2-one, IR(film), 2935, 2850, 1668, 1433, 1375, 885 cm<sup>-1</sup>; NMR [<sup>1</sup>H] (CDCl<sub>3</sub>, TMS,  $\delta$ ), 5.97(m,1H), 4.80(m,2H), 2.34(d,J=16Hz,1H), 2.24(d,J=16Hz,1H), 1.98(m,3H), 1.14(s,3H). MS(m/e),%, 218(100), 203(21), 176(52), 161(50), 160(58), 145(16), 134(18), 133(44), 120(28), 119(29), 107(48), 95(84), 93(11), 69(35), 41(6). The two substances with Rf=0.57 were separated by GC in the analytic system to give VII, (5S,7R,10S)-2,10-dimethyl-7-isopropenyl-2-decalen-4-one, IR(film), 2925, 2850, 1660, 1435, 1375, 870 cm<sup>-1</sup>; NMR [<sup>1</sup>H] (CDCl<sub>3</sub>, TMS,  $\delta$ ), 5.88(m,1H), 4.72(m,2H), 2.50-1.88(6H), 1.92(m,3H), 1.72(m,3H), 1.16(s,3H). Irradiation at 5.88 $\delta$  modifies the multiplet at 1.92 $\delta$  and irradiation at 1.92 $\delta$  leaves the multiplet at 5.88 $\delta$  as a doublet, J=2Hz), MS(m/e),%, 218(36), 203(36), 161(42), 147(34), 135(22), 123(100), 121(24), 93(8), 91(14), 82(18), 76(14), 41(11); and VIII (5R,7R,10S)-2,10-dimethyl-7-isopropenyl-2-decalen-4-one, IR(film), 2938, 2865, 1670, 1433, 1380, 885 cm<sup>-1</sup>; NMR [<sup>1</sup>H] (CDCl<sub>3</sub>, TMS,  $\delta$ ), 5.85(broad m,1H), 4.72(m,2H), 2.36(d, J=16Hz,1H), 2.08(d,J=16Hz,1H), 1.92(m,3H), 0.88(s,3H), protons at 5.85 $\delta$  and 1.92 $\delta$  were shown to be coupled by a decoupling experiment. MS(m/e),%, 218(100), 203(98), 161(54), 147(82), 135(36), 121(56), 93(22), 91(22), 82(52), 79(14), 44(6).

B) Al<sub>2</sub>O<sub>3</sub>/Decalin: In a 50 ml r.b. flask was placed 94 mg of I (0.40 mmol), 450 mg of basic alumina, 5 ml of decalin. The mixture was stirred magnetically, at reflux, for 5 minutes. The alumina was removed by filtration and extracted with 5 ml portions of ethyl ether and methanol. The extracts were combined with the original solution and concentrated, then the decalin was removed by distillation (short-path) at 2 torr (45°C) leaving 80 mg of residue. GC analysis of the residue showed presence of only VII and VIII in the ratio of 1:3.

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#### FOOTNOTES

1. The preliminary studies were presented to the 33rd Annual Meeting of the "Sociedade Brasileira para o Progresso da Ciência"(SBPC), Salvador, Brasil, 1981.
2. Communication with F.R.P.Cysne and W.B.Kover to the 25th Annual Meeting of the SBPC, Rio de Janeiro, Brasil, 1973.
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4. a)Preliminary communication with M.L.A.von Holleben, A.B.B.Ferreira and W.B. Kover to the 33rd Annual Meeting of the SBPC, Salvador, Brasil,1981; b) Thesis of M.L.A.von Holleben, Instituto de Química, Universidade Federal do Rio de Janeiro, Brasil, 1985; D.Sc.
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6. The stereochemistry of the two enones is not determined in the literature. See references in footnote 3 and also Corey,E.J. & Boged,D.L., Tetrahedron Lett., 1978, 28:2461-64; and ibid, 47:4457-4600. We can furnish two new pieces of information, 1) We were able to convert III to a known trans-3-methyl-decalone and trans-3,3-dimethyl-decalone' (unpublished work with W.R.Gilbert) and 2) using high resolution GC (capillary, SE-54) indicates that IV is a mixture of two components (isomeric, by mass spectrs).
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19. Prepared according to the method of De Mayo<sup>3</sup>.
20. Spectral data of I: IR(film), 2910, 2850, 1710, 1640, 1445, 1356, 884 cm<sup>-1</sup>, NMR[<sup>1</sup>H](CDCl<sub>3</sub>, TMS, δ) 4.70(m,2H), 3.25(broad s,1H), 2.80 (d,J=16Hz,1H), 2.40(d J=16Hz,1H), 2.18(s,3H), 2.10(s,3H), 1.70(m,3H), 1.08(s,3H), NMR[<sup>13</sup>C](CDCl<sub>3</sub>, TMS ppm) 212.1(s), 209.0(s), 149.4(s), 108.6(t), 52.8(t), 52.6(t), 39.3(d), 35.0(t), 34.2(s), 32.3(s), 30.2(q), 28.3(t), 26.7(t), 23.9(q), 20.9(q); MS(m/e),%, 236(1) 228(13), 135(28), 93(28), 43(100), 41(27), 39(16), 17(40). (vide ref. 4b).