

INVESTIGATIONS INTO THE DIAZOKETONE
SYNTHESIS OF 3-METHYL-2-CYCLOPENTENONE

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A thesis presented to the Department of Chemistry of
Union College in partial fulfillment of the requirements for the
degree of Bachelor of Science with a Major in Chemistry.

By Robert A. English

Approved by H. E. Slaffer

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Acknowledgment

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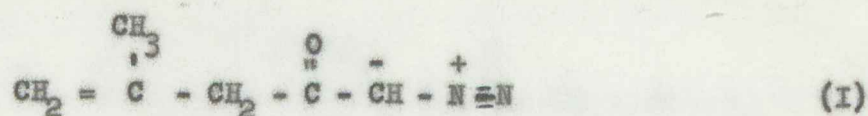
I wish also to acknowledge the assistance given by the Chemistry Staff as a whole, and my fellow seniors, all of whom have contributed through the seminars, and many of whom have given outside help as well. Special thanks to Donald Hoster and William Thielking with whom my close association in the field of diazoketone research has been a pleasure.

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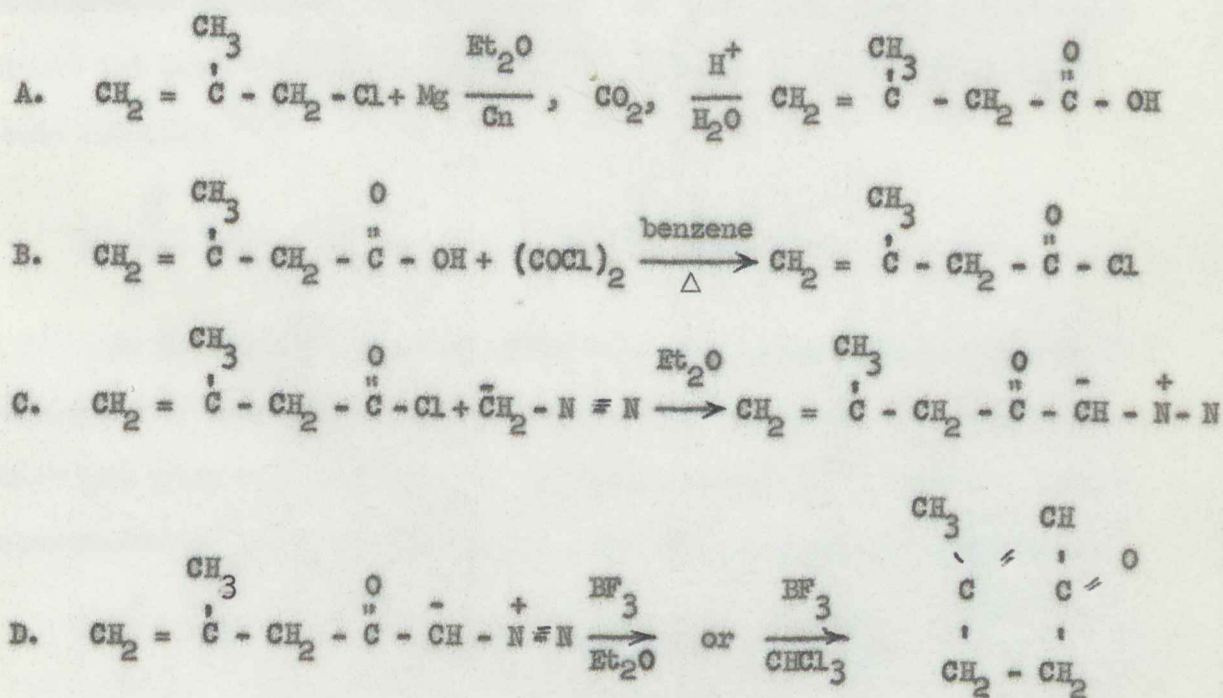
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Introduction

This research was carried out in order to determine the effects of both the etherate and anhydrous forms of BF_3 catalyst upon 1-diazo-4-methyl-4-penten-2-one (I).



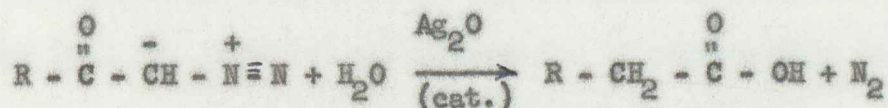
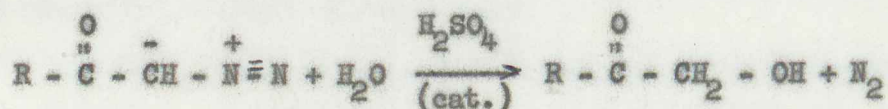
It was hoped that cyclization could be induced to occur due to the presence of the neighboring olefinic bond. Our proposed synthesis of the cyclic product, 3-methyl-2-cyclopentenone, included the following steps:



3-Methyl-2-cyclopentenone, itself has been synthesized by a much more direct method than proposed here. (1)

Historical

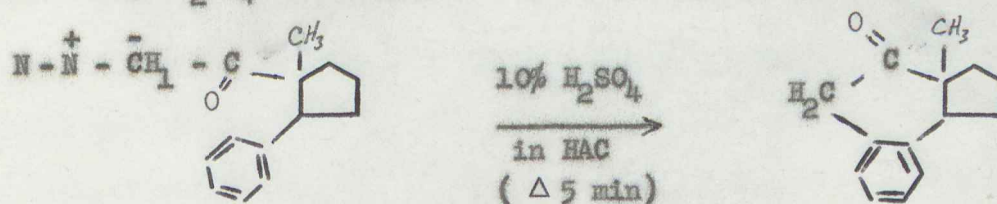
A German chemist, Ludwig Wolff⁽¹¹⁾, is the first known to have investigated diazoketone reactions. Wolff found that diazoketones underwent either replacement or rearrangement, depending on the type of catalyst used, i.e.



It was the year 1935 before a really practical method of diazoketone synthesis was developed. At that time, Arndt and Elstert found the most effective method to be addition of diazomethane to an acid chloride.⁽¹²⁾



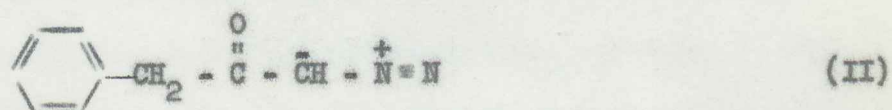
A. L. Wilds⁽⁸⁾ found in 1948 that the rearrangement reaction of diazoketones occurred without catalyst in the presence of alcohols at high temperatures. In 1953, M. S. Newman, et.al.,⁽⁴⁾ obtained a ring closure using H_2SO_4 as catalyst. No rearrangement was reported.



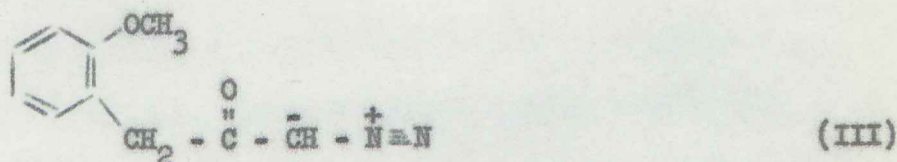
At Columbia in 1961, Stork and Ficinni⁽⁶⁾ successfully obtained the non-aromatic bicycloheptanone-2 (4-1-0) with eleven hour's refluxing in the presence of copper-bronze catalyst.

A. L. Wilds and associates⁽¹⁰⁾ effected ring closure of 1-diazo-3,3,3 triphenyl-2-propanone in 1962. Rearrangement occurred in the presence of γ -collidine, but in the presence of BF_3 etherate, closure was completed without rearrangement.

In 1962, Sheffer and Moore showed the effectiveness of BF_3 etherate in intramolecular cyclization. In contrast to Brønsted acids, the Lewis acid BF_3 furnishes no nucleophile to compete with neighboring nucleophilic groups present on the parent diazoketone. In the systems studied by Wilds, the presence of six ortho positions was an apparently favorable probability factor in determining the type of product. Sheffer and Moore, however, were unable to close a less probable (2 ortho-position) aromatic system (II), although they were



highly successful with a methoxy group present in the ortho-position of the ring (III).



Experimental

Preparation of 3-methyl-3-butenoic acid

The method of synthesis was that described by R. B. Wagner⁽⁷⁾ for 3-methyl-3-butenoic acid.

Equal molar quantities of 3-chloro-3-methylpropene and magnesium were reacted in dry ether for ten hours at room temperature with stirring. The reaction was carried out twice with no catalyst, and a third time with two grams of fine copper wire present. Copper was added due to low yields on the first and second trials. Wagner had used a copper vessel rather than glass. With copper present, the reaction was vigorous and an ice bath was necessary to bring the temperature below 30°C. In each run, a five-liter flask was used, equipped with stirrer, thermometer, and reflux condenser.

Carbonations of the Grignards were performed by pouring the Grignards over crushed dry ice (20-fold excess) with stirring. The reaction was carried out over a four hour period in a ten-liter pyrex water bath, and stirred by hand with a large porcelain stirrer. When the dry ice was gone, excess hydrochloric acid was added (to pH 1.5) to hydrolyze the complex to the acid.

Ether layer separation was performed by first saturating the aqueous layer with NaCl, then using a two-liter separatory funnel. In some cases, the ether layer was treated with numerous portions of 10% NaOH, then the alkaline layer acidified, salted, and extracted

again with cold ether. In other cases, the original ether layer was merely stripped leaving crude acid (later distilled) as residue.

Distillation of crude acids were performed under vacuum using a 100 ml capacity, six-inch Vigreux column with ground-glass connections. Fractions were collected in a rotating "cow-". Literature gave the boiling point of 3-methyl-3-butenic acid at 5 mm as 68° . This was calculated to be approximately 84° at 15 mm.

The following table summarizes conditions and yields for the three runs.

Notebook No.	0-1	0-2	0-3
3-chloro-2-methylpropene	100 g.	300 g.	300 g.
Magnesium	27 g.	81 g.	81 g.
Ether (Liters)	1	3	3
Temperature	$20-30^{\circ}$	$20-30^{\circ}$	$20-35^{\circ}$
Catalyst	-	-	cn
Carbon dioxide	3 lb.	10 lb.	10 lb.
Extraction	basic	strip	strip
Crude yield of acid	4.5%	5.5%	14%

The 3-methyl-3-butenic acid (N.E. calc. 100) from the above three runs were combined and redistilled to give two fractions as follows:

Fraction	B ₁₅	wt.	N.E.	Purity by N.E.	gms Acid	Moles
1-1	80-83°	33.5 g	160	62%	21	0.21
1-2	83-85°	35.29	112	89%	31.5	0.32

Preparation of 3-Methyl-3-Butenoyl Chloride

Oxalyl chloride was used in preparing the olefinic acid chloride according to the method described by Wilds⁽⁹⁾ and the original work of R. Adams⁽²⁾.

Oxalyl chloride (50 gm) was added to acid fraction 1-1 in 200 ml of benzene, and allowed to stand in a 500 ml reaction flask (equipped with thermometer and reflux condenser) for two hours. Excess oxalyl chloride and benzene (2-8) were distilled from the mixture at atmospheric pressure. The fraction boiling above oxalyl chloride and benzene (82°) was distilled under vacuum to give 3-methyl-3-butenoyl chloride (2-5; b₇₅ 50-54°) and excess acid (2-6; b₁₅ 80-95°). Fraction 2-5 was saved, and the recovered acid (2-6) was combined with acid fraction 1-2. The combined acids were then refluxed at 55-65° for three hours with 50 gm of fresh oxalyl chloride plus the recovered acid chloride-benzene fraction (2-8). The fraction of this run boiling between 49° and 56° at 75 mm. (2-2) was combined with fraction 2-5 to give 24.0 gm. 3-methyl-3-butenoyl acid boiling between 49° and 56° at 75 mm.

Preparation of Diazomethane

To a mixture of 600 ml 30% NaOH, 450 ml 2-(2 ethoxyethoxy)-

ethanol and two liters of ether (at 5°C), was added 180 gms N, N-dinitroso -N, N- dimethyl terephthalamide. The mixture was then shaken and the flask heated by use of a heating mantle. The five-liter flask was equipped with a ground glass neck leading to a water condenser. At the end of the condenser a lengthened adaptor led below the surface of a small amount of ether in another five-liter flask, cooled in ice. The adaptor was equipped with a bleed valve to avoid backpressure at the end of the run. Since diazomethane is both toxic and explosive, all work was done in the hood.

Preparation of 1-Diazo-4-Methyl-4-Penten-2-One

The solution of diazomethane in ether was filtered, and 24 gms (0.2 moles) of 3-methyl-3-butenoyl chloride added at room temperature. Evolution of gas occurred, indicating reaction. The reaction mixture was left in the hood overnight.

Reaction of 1-Diazo-4-Methyl-4-Penten-2-One in Ether

The following day, 29 gms. of BF_3 etherate was added to the diazoketone in ether. Immediate reaction occurred with evolution of nitrogen. Collection of nitrogen (3.3 l) gave 70% of the volume expected for 0.2 moles. When the gas evolution diminished (about 1 hr.) the mixture was washed with 150 ml of water and 200 ml of NaHCO_3 to remove BF_3 . These aqueous extractions were washed with ether several times to reclaim any water-soluble ketones. The total

ether layer was then stripped under vacuum (0° - 10° C) to a volume of around 75 ml .

A total of six fractions (5-1 to 5-6; 14.3 gms) were collected between the range of 28° at 50 mm. and 82° at 18 mm. The fractions boiling between 78° and 80° (5-4 and 5-5) corresponded to the literature value for 3-methyl-2-cyclopentenone ($b_{15} 74^{\circ}$). Chromatography of all high-boiling fractions (5-2 through 5-6) on a Perkin-Elmer 154 Vapor Fractometer (column type R_x, 1 meter by 1/8", propylene glycol-UCON LB-550-X) showed four major constituents present in nearly equal proportions. The lowest boiling fraction (5-1) appeared also as an azeotrope in fraction 5-2, appearing to be essentially pure (96% by V.P.C.).

Fractions 5-2 to 5-6 were redistilled using a 75 theoretical plate insulated column, equipped with a solenoid-controlled vapor take-off. Due to unnoticed contamination of the column, however, about fifty percent of the product was lost in handling. Five fractions (7-1 to 7-5) were finally obtained, boiling between 75° and 82° at 18 mm. An attempt had been made to form semicarbazones of 5-1 and 5-3, but without success (lit. for 3-methyl-2-cyclopentenone m. 220° C). So little product was left after distillation (4.32 g), that it was decided to go through the synthesis once more and combine products for final analysis.

3-Methyl-3-Butenoic Acid (Fourth Run)

The Grignard reaction was carried out as before; in the presence of copper catalyst. Instead of carbonating the mixture with dry ice itself, gas was generated over ether, dried, and bubbled through the Grignard in the original reaction flask. Ten pounds of CO_2 were used over a five-hour period with mechanical stirring. Work-up of the product by the base extraction method yielded no acid. Upon standing for more than a week over concentrated HCl, the previously extracted ether yielded a crystalline solid (8-1) when evaporated. The solid appeared in approximately 40% yield (70 gm.). Recrystallization from methanol gave a solid (8-3) melting at $64.5\text{-}65^\circ$ (V.P.C. shows only 75% purity, however). Immediate work-ups of other runs had given no such solid, but gave high yields of an olefin (b. $110\text{-}112^\circ$) proposed as 2-5-dimethyl 1-5-hexadiene (lit. b $113\text{-}114^\circ$). This olefin was also present in the mother liquor yielding the above solid. Infra-red analysis of the liquor showed peaks corresponding to 2-5 dimethyl-1-5-hexadiene given in the literature (6.9μ , 7.2μ , 11.2μ)⁽³⁾, of which the 11.2μ peak was found missing in the spectrum of the solid. Since the 11.2μ peak corresponds to the end vinyl grouping, it has been proposed that the solid be of cyclic structure.

3-Methyl-3-Butenoic Acid (Fifth Run)

This time solid CO_2 was used as well as copper catalyst as in the third run (0-3). From 300 g. of 3-chloro-3-methyl propene was produced

34.9 gm. of crude acid (Nos. 12-1 to 12-4, N.E. 193). Calculated 52% pure, the actual yield was 6.1%.

3-Methyl-3-Butenoyl Chloride (Second Run)

The crude 3-methyl-3-butenic acid, 100 ml of benzene, 50 gm. of oxalyl chloride, and 22.6 gm. of oxalyl chloride left over from the first run (2-3) were refluxed for six hours at 60-70°C. After distilling off the benzene at atmospheric pressure, the remainder was distilled in the Vigreux column. Volatilization of the acid chloride from the receiver flasks at low pressure resulted in a yield of only 3.7 g. (No. 14-2; b 36-46°, 22-14 mm.) Having N.E. = 87 (calc. 45), the 3-methyl-3-butenoyl chloride was 52% pure. The manometer trap yielded 20 gms. of a product which was redistilled to give 10 gms. boiling 50-52° at 70 mm. (No. 16-2; N.E. 200; 20% pure).

1-Diazo-4-Methyl-4-Penten-2-One (Second Run)

Fraction 14-2 was added to diazomethane in ether (prepared as before), and allowed to stand for two days. On the second day, fraction 16-2 was added. Reaction was noted with each addition.

Ether was stripped on the day following. After the separation of a few milliliters of water, the 1-diazo-4-methyl-4-penten-2-one portion was dried first over Na_2SO_4 , then by benzene azeotrope. A brownish-red oily liquid remained, weighing 2.65 gms. (16-3). No

attempt was made at distillation of the oil due to the chance of decomposition. The product was stored in brown glass at 0°C.

Reaction of 1-Diazo-4-Methyl-4-Penten-2-One in Cyclohexane and Chloroform

It was decided to investigate the effect of BF_3 upon the diazoketone in a solvent other than ether. In ether, the oxygen linkage can compete as a nucleophile, leading to the formation of an ethoxy ketone (Sheffer and Moore, ref. 5). In solvents such as cyclohexane and chloroform, no nucleophilic center is present to offer competition with the olefinic bond.

The reaction mixture consisted of 2.5 gms. 1-diazo-4-methyl-4-penten-2-one (16-3), 5 ml. cyclohexane, and 40 ml. chloroform. Anhydrous BF_3 was bubbled through the mixture contained in a two-foot by one-inch tube. Polymerization with evolution of heat was immediate, the polymer coating the walls of the tube. BF_3 was passed through until no more heat was evolved. An equal volume of water was shaken with the reaction mixture to remove BF_3 , then the water extracted with chloroform to reclaim any water-soluble ketones. Distillation of the acetone-dissolved products yielded no fractions boiling higher than cyclohexane ($b_{760} 80^\circ$). The polymeric residue began to decompose around 150° at one mm. Hg.

Later Analysis

Since no more ketone material was obtained, further analysis was performed on fractions 7-1 to 7-5. A chromatographic preparation column of type "A" (diisodecyl phthalate resin) was tried for separation of products without success. We then returned to the previously-used "R" (polyglycol) column for analysis. A distinct increase in the percentage of fourth component was found with increasing boiling point of the fractions. Fraction 7-5 contained only the fourth component and wash ether as major components. This was run in the I.R. against ether to show peaks at 3μ (hydroxy), 6μ (keto), and 3.2μ , 6.2μ , 10.5μ and 11.3μ (vinyl).

The low-boiling azeotrope (5-1) was water-soluble, but showed no peak enhancement upon addition of water for V.P.C. analysis. It was found to freeze at -20 to -30°C , and showed I.R. peaks as above, with the addition of a strong peak at $9.3-9.8\mu$, tending to signify fluorine (9.6μ).

A sample of crude 3-methyl-3-butenic acid (from combined fractions 12-1 to 12-4) was run on V.P.C. All major components appearing had retention times less than that of ether. Less than one percent of the components had retention times comparable with product fractions 5-1, or 7-1 through 7-5 at comparable temperature and carrier-gas flow (175°C , flow 3). It is believed that the low-

retention components are olefinic decomposition products or olefinic impurities originally present. No major component corresponding to the acid itself was noted over a two-hour period.

Discussion

Due to difficulties with the synthesis of 3-methyl-3-butenic acid, analysis of final products has been limited both by time and by lack of sufficient product yields. Reports by Sheffer and Moore of fluoro, ethoxy, hydroxy and cyclic ketones lead us to speculate that these are present as components of 5-1, and 7-1 through 7-5. Infra-red data tends to support the presence of the fluoro and hydroxy ketones. Proof of such would be dependent upon the isolation and characterization of derivatives. There is also the possibility of isomeric forms accounting for peaks shown on V.P.C.

The reaction of 1-diazo-4-methyl-4-penten-2-one in the presence of anhydrous BF_3 could stand further study. It is proposed that polymerization could be discouraged at low temperatures (below 0°C) in dilute solution of cyclohexane, and that cyclization would be enhanced under these conditions.

Summary

1. Copper catalyst for the Grignard reaction of 3-chloro-2-methylpropene resulted in improved yields of 3-methyl-3-butenic acid.
2. Crystalline solid, proposed to be of cyclic nature, was formed from the hydrolyzed Grignard upon standing over concentrated hydrochloric acid.
3. Boron trifluoride etherate catalyzed 1-diazo-4-methyl-4-penten-2-one to form four components boiling within a seven-degree temperature range. A lower-boiling, immiscible fraction was also present.
4. Anhydrous BF_3 caused immediate polymerization of 1-diazo-4-methyl-4-penten-2-one in cyclohexane and chloroform. No other products were found present.

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