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CONJUGATE ADDITION OF GRIGNARD REAGENTS TO UNSATURATED KETONES: GC/MS-HPLC STUDY. ISOLATION AND OXIDATION OF E AND Z ENOLS OF A KETONE†

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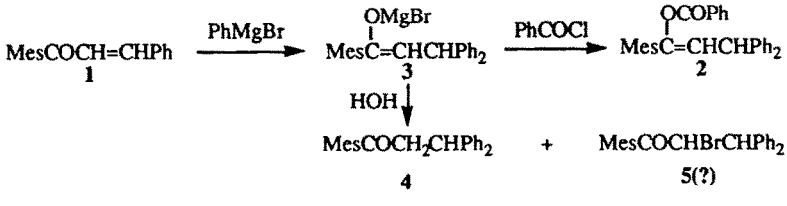
Abstract. The conjugate addition of phenylmagnesium bromide to benzalacetomesitylene (**1**) was studied. The only product resulting from 1,4-addition was Kohler's ketone (**4**) in 84 ± 1% yield based on (**1**) by isolation and analysis. The byproducts from **4** were formed mainly by oxidation of the Z enol of **4** to the α-ketohydroperoxide (**6**) during the hydrolysis and workup of the product followed by subsequent decomposition of **6** to diphenylethanal and a trace of 2,4,6-trimethylphenol. The other byproducts which were formed during the preparation of phenylmagnesium bromide are biphenyl, and trace amounts of phenol and 1-phenyl-1-ethanol. No trace of the previously reported[3] α-bromoketone (**5**) was found under these conditions. The E enol was prepared by the enolization reaction of Kohler's ketone (**4**) with methylmagnesium iodide followed by hydrolysis. The E enol appeared at a retention time of 3.6 compared with that of the Z enol at 4.1 on the HPLC chromatograms. The relative rates of oxidation of the enols as determined by following the disappearance the respective HPLC peaks were approximately 7:1 for Z:E respectively. An explanation is presented for the faster oxidation of the Z enol.

INTRODUCTION

Although the conjugate addition of Grignard reagents to unsaturated ketones was discovered in 1904 by Kohler[1], a satisfactory mechanism which encompasses all of the facts has not yet emerged. Possibly one reason for this is because in most of the reactions a mixture of 1,2- and 1,4-addition products results thus complicating systematic studies.

If the alkyl group attached to the carbonyl is large, then 1,2-addition is hindered and 1,4-addition is favored. An example of this is in the reaction of phenylmagnesium bromide with benzalacetomesitylene (**1**) as reported by Kohler et al.[2] and later by Nesmeyanov et al.[3] Kohler et al.[2] reported a 96% yield of the enol benzoate (**2**) resulting from reaction of the magnesium enolate conjugate addition product (**3**) with benzoyl chloride.

Nesmeyanov et al.[3] reported that a quantitative yield of the conjugate addition product, (2,4,6-trimethylphenyl 2,2-diphenylethyl ketone; Kohler's ketone)(**4**) was obtained by hydrolysis of an *isolated* sample of the magnesium enolate (**3**). However when Nesmeyanov et al.[3,4] hydrolyzed the *entire* reaction mixture, isolation of ketone (**4**) was complicated by the presence of the α-brominated ketone (**5**) from which separation was difficult. These reactions are outlined in Scheme 1. Since we were interested in using a high-yield conjugate addition reaction as a model for mechanistic studies, our original intent was to resolve the discrepancy between the above reports with respect to the α-bromoketone (**5**) making use of GC/MS and HPLC in a quantitative study.



SCHEME 1

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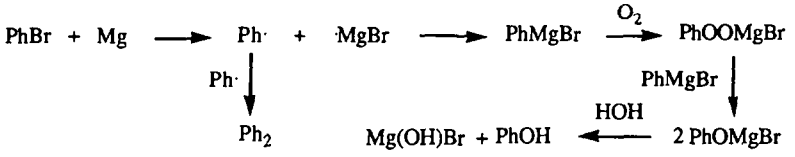
RESULTS AND DISCUSSION

GC/MS Study

The conjugate addition reaction of phenylmagnesium bromide to benzalacetomesitylene (**1**) was carried out as previously described[2-5] and the dried ether extract was subjected to GC/MS analysis. Besides the expected ketone (**4**), several other peaks appeared. These were all identified by their MS patterns and comparison with authentic samples as follows (relative retention times in scan numbers in parentheses): significant amounts of biphenyl (276) and diphenylethanal (390); trace amounts of bromobenzene starting material (93), phenol (106), 1-phenyl-1-ethanol (138), and mesitol (2,4,6-trimethylphenol) (198). In order to determine at which stage of the overall reaction the various products were formed, the ether extract from the formation of phenylmagnesium bromide was examined and the following peaks were formed and identified as above: bromobenzene, phenol, 1-phenylethanol, and biphenyl.

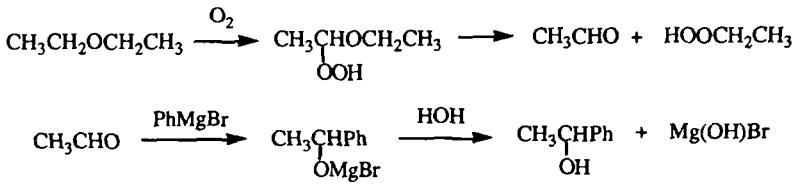


SCHEME 2

These latter byproducts can be rationalized as shown in Scheme 2. (The other byproducts will be discussed below.) Phenyl radical (Ph·) is known to be an intermediate during the formation of Grignard reagents from alkyl halides and magnesium. Coupling of two phenyl radicals forms biphenyl. Reaction of the phenyl radical (or phenylmagnesium bromide) with a trace of oxygen forms the hydroperoxide salt which on further reaction forms bromomagnesium phenoxide salt which forms phenol after hydrolysis. The two-carbon fragment needed for the formation of 1-phenylethanol must come from ether solvent. Oxidation of ether would form the hydroperoxide as shown. Decomposition of this would give ethanal which could react with phenylmagnesium bromide to form the bromomagnesium salt which would yield 1-phenylethanol on hydrolysis (Scheme 3).

HPLC Study

In order to check the results from the GC/MS study and to verify the absence of the bromoketone (**5**) among the products since it might not have passed through the GC column, or was decomposed at the high temperature of the column, an HPLC study was also carried out. Several peaks appeared in the HPLC chromatogram as was the case in the GC/MS study. The



SCHEME 3

largest peak appeared at a retention time of 4.1 which was at about the same position as that for an authentic sample of Kohler's ketone (**4**). The peak for an authentic sample of the bromoketone (**5**) appeared at a retention time of 4.4 whereas no trace of a peak appeared at this position in the chromatogram of the reaction mixture. This shows clearly that the bromoketone is not present among the products of the reaction under the conditions used. It should be noted that Nesmeyanov et al.[3,4] stated that the bromoketone was formed during oxidation in the presence of magnesium bromide or RMgBr.

Quantitation of Yield of Kohler's Ketone; Enol Identification

Based on the use of an authentic sample of Kohler's ketone (**4**) for integration of the peak at 4.1 retention time, the surprising result was an unusually high yield for the product. However, it was observed that the intensity of this peak decreased with time (followed for a period of over 100 hours) whereas a sample of authentic Kohler's ketone (**4**) under the same conditions did not change in intensity (Fig 1).

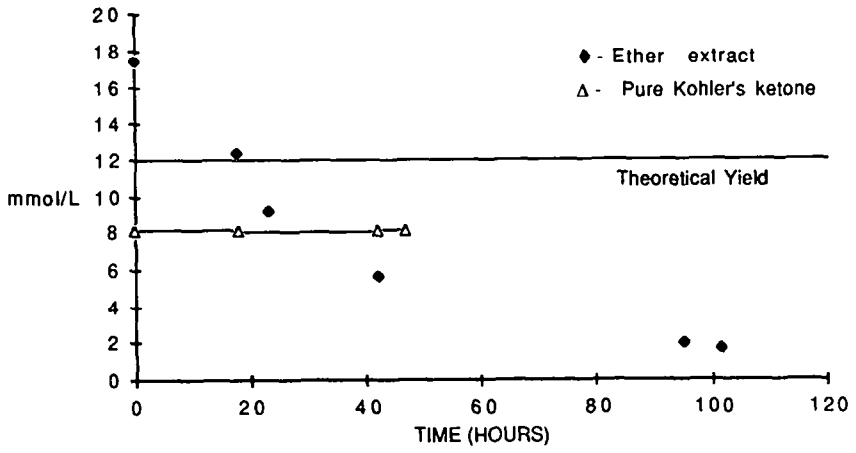
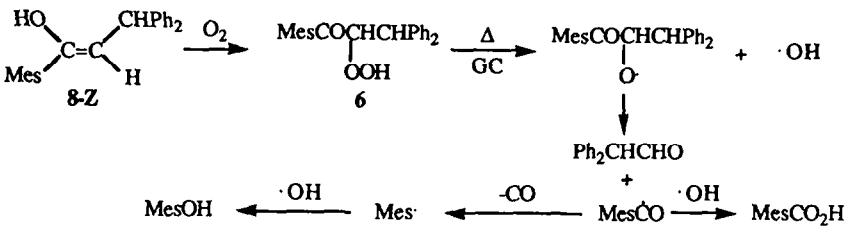


Fig. 1. Comparison of rate of change in intensity of HPLC peaks at 4.1 min retention time of Kohler's ketone (4) with that of ether extract of reaction product from conjugate addition of phenylmagnesium bromide to benzalacetomesitylene (1) at 254 nm at 25 ± 1° C in ether/acetonitrile (1:3 by volume). Concentrations in mmol/L based on Kohler's ketone.

Because of these results the product of the conjugate addition reaction (Kohler's ketone, **4**) was isolated from the reaction mixture semiquantitatively in 74% yield. The mother liquor from the crystallization was analyzed by GC to give an additional 9% of product for a total yield of 83%. In a second run, the entire reaction mixture was analyzed using HPLC. In this case the yield of Kohler's ketone was 85%. Thus it appeared that the cause of the anomalous size of the peak at 4.1 retention time was the presence of an intermediate enol which was eluted at the same time as Kohler's ketone. During the workup procedure the enol is converted into the ketone (**4**) by a combination of acid catalysis and heating. An ir spectrum of the ether solution before workup showed a broad peak in the OH stretching region at 3500 cm^{-1} and no absorption in the C=O stretching region. In addition when the ether solution from the reaction was chromatographed on a different HPLC column, only one peak appeared at a retention time of 7.3 whereas when a sample of Kohler's ketone was added, two peaks appeared-the ketone at 7.6 and the enol at 7.3. Also the uv spectrum of the ether solution from the reaction showed a gradual decrease in absorption from about 235 to 285 nm whereas that from the solution with Kohler's ketone added showed a broad peak centered at about 250-255 nm.

Enol Oxidation

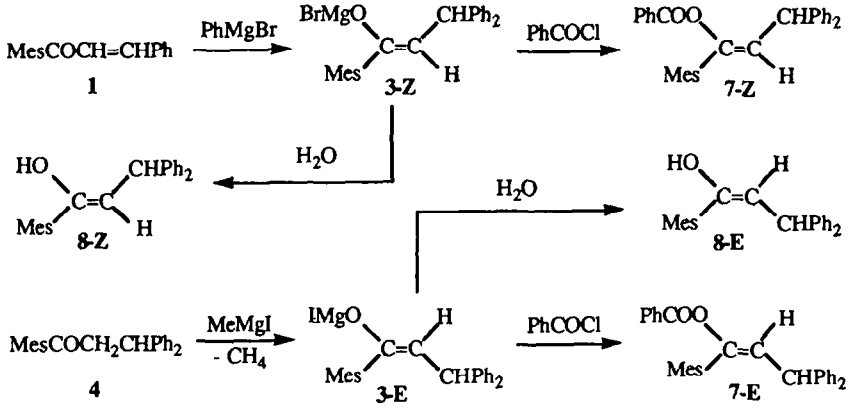
In previous studies[6] of oxidative behavior of alkyl mesityl ketones a stable α-ketohydroperoxide (from benzyl mesityl ketone)was isolated and characterized. In the present study it was noted that as the enol HPLC peak decreased, a peak which appeared at 2.8 retention time increased with time. This peak was identified as the α-ketohydroperoxide (**6**) (Scheme 4) by comparison with an authentic sample prepared according to the previously published procedure[7] of bubbling oxygen into a petroleum ether solution of the enol obtained from hydrolysis of the product of the conjugate addition reaction. In addition another strong peak which appeared in the HPLC at 2.4 retention time was identified by comparison with an authentic sample as diphenylethanal (Scheme 4). This is an expected fragmentation product from the hydroperoxide on the basis of the previous study[6] and was identified as one of the products in the GC/MS study above. The hydroperoxide would be expected to decompose under the high temperature conditions of the GC/MS study. Mesitoic acid is also an expected product[6] but would not be expected to pass through the GC column. Mesitol could be formed by elimination of carbon monoxide from mesitoyl radical followed by combination of mesityl and hydroxyl radicals (Scheme 4).



SCHEME 4

E/Z Enol Isomers

Since the structure of the enol benzoate (7) (Scheme 5) prepared by reacting benzoyl chloride with the magnesium enolate of the conjugate addition reaction was determined to be Z on the basis of ^1H nmr vinyl shielding constants[5] as later confirmed by an X-ray crystal structure study[8], it was of interest whether or not the enol at the 4.1 retention time in the HPLC had retained its configuration or was an equilibrating mixture of enols and/or the keto form. Since the E enol benzoate (7E) had also been previously[5] prepared and identified by ^1H nmr vinyl shielding constants[5], it seemed that the E-enol (8E) could be prepared and studied by HPLC analogous to the preparation of the Z enol (8Z). The preparation of the magnesium enolate (3E) was carried out by reacting Kohler's ketone (4) with methylmagnesium iodide followed by hydrolysis. HPLC analysis of the dry ether extract showed a peak at a retention time of 3.6 as compared with that of 4.1 of the enol from the conjugate addition reaction showing that both enols had maintained their configurations. To our knowledge[9,10] this is the first report of separate preparations of E and Z enols. Furthermore it was observed that the E-enol peak in the HPLC did not decrease as rapidly as the Z-enol from the conjugate addition reaction. The uv spectrum of the E-enol was about the same as that of the Z-enol with respect to shape and intensity in the HPLC solvent at about the same concentration. The decrease in the intensities



SCHEME 5

of the Z and E enol peaks at 4.1 and 3.6 retention times respectively was followed. Both rates followed first order plots and the relative rates were in a ratio of about 7:1 of Z:E enols. This is in accord with the qualitative observation made by Nesmeyanov et al.[3,4] that the magnesium enolate from the conjugate addition oxidized much more readily than the one formed from reaction of Kohler's ketone with a Grignard reagent.

In trying to rationalize the difference in reaction rates between the E and Z enols, a mechanism is postulated based on that formulated[11] for oxidation of alkenes. The transition state postulated for alkene oxidation is shown in Fig. 2 and the analogous one for the E enol oxidation in Fig. 3. Because of the constraints of the cyclic transition state, a large increase in transition state energy would be expected for the E enol over that for the Z enol resulting in a slower rate for the E enol oxidation. This increase in the energy of the transition state for the E enol results from steric interference between the mesityl and diphenylmethyl groups on the same side of the double bond as indicated from molecular models.

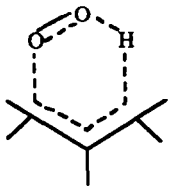


Fig. 2

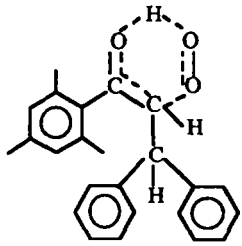


Fig. 3

EXPERIMENTAL

Materials

Benzalacetomesitylene (1)

(1) was synthesized by a previously described procedure[5] in 94% yield from a mixed aldol condensation of acetomesitylene and freshly distilled benzaldehyde. It was recrystallized from petroleum ether (bp 30-60° C): mp 60-61° C; IR (Nujol) 1648 (C=O str), 1628,1612, 1578 cm-^{1}; ^{1}H NMR (CCl_4) 2.12(6H, s), 2.26(3H, s), 6.70(2H, s), 7.21(5H, m), 6.65(1H, d), 7.03(1H, d).

3,3-Diphenyl-1-(2,4,6-trimethylphenyl)propan-1-one (Kohler's ketone) (4)

A solution of benzalacetomesitylene (1) (5.00 g, 0.02 mole) in anhydrous diethyl ether (30 mL) was gradually added with stirring to a filtered solution of phenylmagnesium bromide. Phenylmagnesium bromide was prepared from 0.729 g (0.030 mole) of magnesium and 3.870 g (0.025 mole) of bromobenzene in 60 mL of diethyl ether.

After completion of addition the reaction mixture was refluxed for about 40 min. A saturated solution of ammonium chloride (50 mL) was added to the reaction mixture and stirred vigorously. The aqueous layer was extracted three times with 50 mL portions of diethyl ether. The combined ethereal layer was washed three times with 50 mL portions of distilled water and dried over anhydrous sodium sulfate. Ether was removed in a rotary evaporator leaving the ketone (4) which was obtained as a yellow solid. It was recrystallized from absolute ethanol as a white crystalline solid in 84% yield. The entire isolation procedure was completed in less than an hour with minimum exposure to atmospheric oxygen: mp 80.5-81.5° C; IR (Nujol) 1692 (C=O str.), 1609, 1597 cm-^{1}; ^{1}H NMR ($CDCl_3$) 7.20(10H, m), 6.72(2H, s), 4.80(1H, t), 3.46(2H, d), 2.19(3H, s), 1.88(6H, s).

2-Bromo-3,3-diphenyl-1-(2,4,6-trimethylphenyl)propan-1-one (5)

The α-bromoketone (5) was prepared by reacting equimolar quantities of Kohler's ketone (4) and bromine according to Kohler's procedure[12] and recrystallizing from 95% ethanol: mp 171-172° C; IR (Nujol) 1696 (C=O str.), 1611 cm-^{1}; ^{1}H NMR ($CDCl_3$) 7.24(10H, m), 6.76(2H, s) 5.54(1H, d), 4.99(1H, d), 2.24(3H, s), 2.01(6H, s).

3,3-Diphenyl-2-hydroperoxy-1-(2,4,6-trimethylphenyl)propane-1-one (6)

The ketohydroperoxide (6) was prepared in 85% yield by bubbling oxygen into a solution of the hydrolysis product from the conjugate addition of phenylmagnesium bromide to benzalacetomesitylene according to the procedure of Kohler and Thompson[7]: mp 115.5-116.5° C; IR (Nujol) 3473 (OH str.), 1710 (C=O str.), 1696 cm-^{1}; ^{1}H NMR ($CDCl_3$) 9.25(1H,s), 7.25(10H, s), 6.78(2H, s), 5.64(1H, d), 4.62(1H, d), 2.27(3H, s), 1.94(6H, s).

Biphenyl, 1-phenyl-1-ethanol and diphenylethanal were commercial samples used in confirmation of products.

Apparatus

GC/MS determinations were carried out using a Finnigan-1020 instrument with a GE SE-54 capillary column. HPLC analyses were done with a HP-1090 instrument with a uv diode array detector. Reverse phase HP C-8 (100 x 4.6 mm) and VYDAC C-18-300 (150 x 4.6) columns were used.

^{1}H nmr spectra were recorded on a JEOL FX90Q, 89.55 MHz instrument using tms as an internal standard. Infrared spectra were recorded using either Perkin Elmer model 1320 or Mattson Cygnus 100 FT IR instruments.

Melting points were taken using a Thiele apparatus and are uncorrected.

Procedures

GC/MS determinations

GC/MS analyses were carried out on the dry ether extract obtained during the course of preparation of Kohler's ketone. The GC was temperature programmed from 100°to 250° C at a rate of 10° C/min. The mass spectrometer was scanned from 60 to 450 amu in 2.0 sec.

The presence of bromobenzene, phenol, mesitol, biphenyl, 1-phenylethanol, diphenylethanal and Kohler's ketone (4) was confirmed by carrying out GC/MS determinations of authentic samples of these compounds under identical conditions. The identities were established by comparing the retention times and mass spectra.

A sample of phenylmagnesium bromide was hydrolyzed with saturated ammonium chloride. The hydrosylate was extracted with ether. The ether layer was washed several times with distilled water and dried over anhydrous sodium sulfate. A GC/MS run of this ether extract was carried out under similar conditions. The presence of bromobenzene, phenol, biphenyl and 1-phenylethanol was confirmed by carrying GC/MS runs of authentic samples.

Quantitation of Kohler's ketone (4) was carried out by performing a calibration with known amounts of pure Kohler's ketone and using benzalacetomesitylene (1) as internal standard. GC/MS runs were carried out before the addition of internal standard to confirm that there was no unreacted benzalacetomesitylene since it is one of the starting compounds.

HPLC determinations:

The ether extract was diluted with acetonitrile (HPLC grade). HPLC runs were carried out on the filtered solutions with a solvent composition of 72% acetonitrile and 28% water at a flow rate of 0.8 ml./min. The column temperature was maintained constant at 36° C. Retention times are in min.

In the chromatogram the presence of peaks due to biphenyl, diphenylethanal, ketohydroperoxide and Kohler's ketone was confirmed by running authentic samples of each and comparing the retention times and uv spectra of the various peaks. The amount of Kohler's ketone was estimated using a multilevel calibration with known amounts of pure Kohler's ketone and using benzalacetomesitylene as internal standard. As before the absence of benzalacetomesitylene in the ether extract was confirmed before adding as the internal standard.

E-Enol preparation:

E-magnesium enolate was obtained by reacting methylmagnesium iodide with Kohler's ketone according to the procedure of Nesmeyanov et al.[3]. The magnesium enolate was hydrolyzed, extracted with ether and dried over anhydrous sodium sulfate. The same hydrolysis and extraction procedure employed for the preparation of Kohler's ketone was followed. HPLC runs were carried out with this ether extract.

Rates of oxidation of E and Z Enols:

The rates were determined by following the decrease in the HPLC peaks of the enols at 4.1 and 3.6 retention times of Z and E enols respectively at a wavelength of 254 nm (band width = 20 nm) in ether/acetonitrile solution (1:3 by volume) at 25 ±1° C. Ether extracts of the enols prepared as described above were dissolved in the solvent. The concentrations of the Z and E enols in ether before dilution were 15.8 and 6.87 mmol/L respectively. The rate constants were derived from the first order plots. The kinetics was followed for about 100 hours for the Z enol and about 170 hours for the E enol. The rate constants obtained for Z and E enols were $3.7 \pm 0.5 \times 10^{-2}$ hr^{-1} and $0.53 \pm 0.02 \times 10^{-2}$ hr^{-1} respectively.

ACKNOWLEDGEMENT

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