Synthesis of Substituted Chalcones by Aldol Condensation: A Preliminary Step in Antimalarial Drug Development

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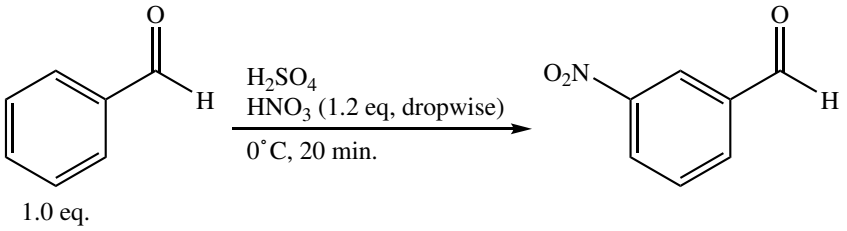
INTRODUCTION

Malaria remains a major public health issue with nearly 230 million cases estimated worldwide in 2019, the vast majority of which were reported in Africa owing to infection by protozoan parasites in the genus *Plasmodium*, most notably *Plasmodium falciparum*.[1] Historically, chloroquine and its derivatives have been used to treat malaria however, the emergence of chloroquine-resistant strains of *P. falciparum* has greatly decreased the efficacy of these treatments creating an urgent need for alternative antimalarial compounds.[1,2] Chalcones are a class of α,β-unsaturated ketones belonging to the flavonoid family which remain of significant interest due to their relatively simple synthetic chemistry and diverse application as scaffolds in medicinal chemistry.[3] Discovery of the antimalarial activity of the naturally occuring chalcone Licochalcone A, originally isolated from Chinese licorice roots, has prompted research into chalcones and chalcone hybrids as antimalarial candidates.[4,5] Hybridization has been explored as a method for overcoming drug resistance in *P. falciparum*, this is supported by the observation that many chloroquine derivatives and analogs retain activity against chloroquine-resistant strains of *P. falciparum*.[4,6] Chloroquine-chalcone based hybrids have been shown to have potent antimalarial activity against chloroquine-resistant *P. falciparum* in vitro when compared with chloroquine.[6] Likewise, triazole linked chalcones, ferrocenyl chalcones, and caffeine based chalcones among others have been evaluated as potential antimalarial, antitrypanosomal, antileishmanial, and antiplasmodial agents.[3,7,8] Structure-activity relationship studies of various chalcone derivatives have shown that different structural requirements exist for antimalarial and antileishmanial activity respectively, with the A ring being more significant in antileishmanial activity compared with antimalarial activity in which both A and B rings are important.[9] Stereoisomerism has also been shown to have an effect on the antimalarial activity of chalcone derivatives. Synthesis and evaluation of conformationally restricted derivatives of known antiplasmodial chalcones has demonstrated that Z-locked chalcone derivatives are effectively inactive while E-locked analogs show equivalent activity and potency to the parent chalcone.[10] Chalcone derivatives lacking the α,β-unsaturated ketone bridge exhibit significantly less antimalarial activity, with saturated analogs showing a 10-fold decrease in antimalarial activity.[11] In this paper, we report the synthesis of the chalcones, 3'-nitrochalcone and 4-methoxy-3'-nitrochalcone. This contributes to the current knowledge of chalcone synthesis and provides a simple and versatile method for the synthesis of potentially antimalarial substituted chalcones.

METHODS AND RESULTS

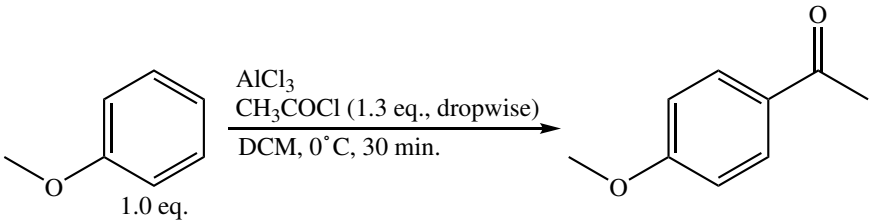
Instrumentation. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Ultrashield™ ($CDCl_3$, 400 MHz) calibrated using deuterated solvent ($CDCl_3$: ^{1}H NMR: 7.26 ppm). IR spectra were recorded on a Nicolet Summit™ FTIR spectrometer. UV-Vis spectra were recorded on a Vernier Fluorescence/UV-Vis spectrophotometer.



Scheme 1: Nitration of benzaldehyde

Procedure. Benzaldehyde (10.4 g, 98.0 mmol) was added to a 250 mL round bottom flask and cooled to 0°C, followed by addition of sulfuric acid (30 mL). To this solution, nitric acid (7 mL) was added dropwise over 10 minutes, and allowed to stir for 10 minutes. Reaction progress was monitored with TLC (9:1 hexanes:EtOAc). When the reaction was complete, the reaction mixture was quenched with ice (˜50 mL), the crude product was filtered by vacuum, and recrystallized from isopropanol.

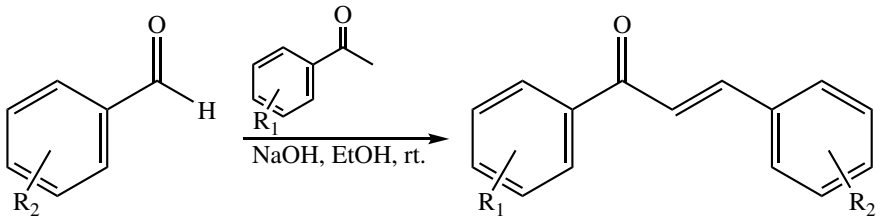
3-nitrobenzaldehyde: yellow crystals. Hexanes:EtOAc 9:1 $R_f = 0.43$. ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ 7.761 - 7.801 (t, 1H), 8.236 - 8.256 (d, 1H), 8.487 - 8.516 (dq, 1H), 8.728 (s, 1H), 10.134 (s, 1H). **IR** (neat): 3069, 2981, 2884, 1698, 1523, 1348, 1198 cm^{-1} **UV-Vis:** $\lambda_{max} = 220$ nm. **MP:** 47.6°C. **Yield:** (7.901 g, 53.35%).



Scheme 2: Acetylation of anisole

Procedure. Aluminum chloride (14 g) in DCM (15.0 mL) was added to a 250 mL two-necked round bottom flask and cooled to 0°C, followed by dropwise addition of acetyl chloride (9.27 g, 118 mmol) in DCM (10.0 mL) over 10 minutes with magnetic stirring. To the resulting mixture was added anisole (10.0 g, 93.9 mmol) dropwise over 30 minutes. Reaction progress was monitored using TLC (9:1 hexanes:EtOAc). When the reaction was completed, the reaction mixture was quenched in a beaker containing ice (˜30 mL) and hydrochloric acid (10 mL), then neutralized with saturated sodium bicarbonate. The resulting mixture was extracted with saturated sodium bicarbonate (2x1 vol.), washed with brine (1 vol.), dried with anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure.

4-methoxyacetophenone: Colorless solid/pale yellow liquid. Hexanes:EtOAC 9:1 $R_f = 0.53$. ^{1}**H-NMR** (400 MHz): δ 2.539 (s, 3H), 3.849 (s, 3H), 6.907 - 6.929 (d, 2H) 7.912 - 7.934 (d, 2H). **IR** (neat): 2970, 2842, 1671, 1597, 1509, 1417, 1357, 1247, 1169, 1025, 956, 832 cm^{-1}. **UV-Vis:** $\lambda_{max} = 270$ nm. **Yield:** (9.247 g, 66.24%).



Scheme 3: Formation of chalcone

Prodedure. To a 150 mL Erlenmeyer flask was added 3-nitrobenzaldehyde (0.76 g, 5.0 mmol) followed by the acetophenone (5.0 mmol) and 95% EtOH (4 mL). Once all the solid was dissolved, NaOH solution (0.5 mL) was added with constant stirring until the mixture solidified. After 5 minutes of additional stirring, the resulting solid was quenched with ice water (˜10 mL), filtered by vacuum, and recrystallized from hot 95% EtOH.

3-(3-nitrophenyl)-1-phenylprop-2-en-1-one: light green powder. ^{1}**H-NMR** (400 MHz): δ 7.527 - 7.564 (t, 2H), 7.608 - 7.644 (t, 2H), 7.648 - 7.684 (d, 1H), 7.823 - 7.863 (d, 1H), 7.922 - 7.941 (d, 1H), 8.043 - 8.067 (d, 2H), 8.259 - 8.282 (dq, 1H), 8.519 - 8.528 (t, 1H). **IR** (neat): 3071, 1659, 1606, 1526, 1446, 1349, 1217 cm^{-1}. **UV-Vis:** $\lambda_{max} = 237$ nm. **Yield:** (1.989 g, 158.3%)

1-(4-methoxyphenyl)-3-(3-nitrophenyl)prop-2-en-1-one: blue-green powder. ^{1}**H-NMR** (400 MHz): δ 3.914 (s, 3H), 7.005 - 7.027 (d, 2H), 7.596 - 7.636 (t, 1H), 7.648 - 7.687 (d, 1H), 7.806 - 7.846 (d, 1H), 7.906 - 7.925 (d, 1H), 8.061 - 8.083 (d, 2H), 8.239 - 8.268 (dq, 1H), 8.515 - 8.524 (t, 1H). **IR** (neat): 3357, 2981, 2888, 1662, 1595, 1521, 1339, 1258, 1167 cm^{-1}. **UV-Vis:** $\lambda_{max} = 322$ nm. **Yield:** (847 mg, 59.92%).

DISCUSSION

3-nitrobenzaldehyde. The final yield was 7.901 g, corresponding to a 53.35% yield. The experimental NMR spectra showed two doublets at 8.25 and 8.50 ppm, as well as a triplet at 7.78 ppm and a singlet at 8.73 ppm, indicating *meta* substitution. The experimental IR spectrum showed two strong N-O stretching peaks at 1523 and 1346 cm^{-1}.

1-(4-methoxyphenyl)ethan-1-one. The final yield was 9.247 g, corresponding to a percent yield of 66.24%. The experimental NMR spectrum showed two singlet peaks at 2.54 and 3.85 ppm corresponding to the terminal CH_3 groups of the acetyl and methoxy groups respectively as well as two doublet peaks at 6.92 and 7.92 confirming *para* disubstitution. The experimental IR spectrum also confirmed the transformation of the starting material with a strong C=O stretching peak at 1671 cm^{-1}.

3-(3-nitrophenyl)-1-phenylprop-2-en-1-one. The final yield was 1.989 g, corresponding to a percent yield of 158.3%. The inflated yield of $> 100\%$ indicated that the final product was not dried sufficiently after recrystallization. This was reinforced by the appearance of solvent peaks corresponding to ethanol in the NMR spectrum (quartet at 3.72 ppm, singlet at 2.62 ppm, and triplet at 1.24 ppm), and broad O-H stretching peak centered at 3357 cm^{-1} in the IR spectrum. Conversion of the starting materials was supported by the lack of the singlet aldehyde C-H peak at 10.13 ppm in the NMR spectrum and lack of the aldehyde H-C=O: C-H stretch at 2981 cm^{-1} in the recorded IR spectrum.

1-(4-methoxyphenyl)-3-(3-nitrophenyl)prop-2-en-1-one. The final yield was 847 g, corresponding to a percent yield of 59.92%. After the initial recrystallization of the final product, a brown impurity was observed which did not clear after washing on the filter with chilled ethanol. The product was then recrystallized a second time from ethanol; product loss from which could potentially account for the lower than expected yield. The experimental NMR spectrum

obtained indicated the conversion of the starting materials, evident by the lack of the singlet peaks at 10.13 and 2.54 ppm corresponding to the aldehyde C-H and terminal CH_3 of the acetyl group in 3-nitrobenzaldehyde and 4-methoxyacetophenone respectively. The formation of the final product was also indicated by the fact that the measured λ_{max} value was higher than those of either starting material (322 nm vs. 270 & 220 nm) indicating a greater degree of conjugation in the product than either of the starting materials.

CONCLUSION

In this paper, the synthesis of 3'-nitrochalcone and 4-methoxy-3'-nitrochalcone has been shown. This synthesis demonstrates a simple and effective method for the production of novel chalcone derivatives with substituents on both A and B rings. These results contribute to the existing body of knowledge on chalcone synthesis and provide a starting point for the synthesis of more structurally complex hybrid chalcones for evaluation as antimalarial candidates.

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APPENDIX A: SPECTRA

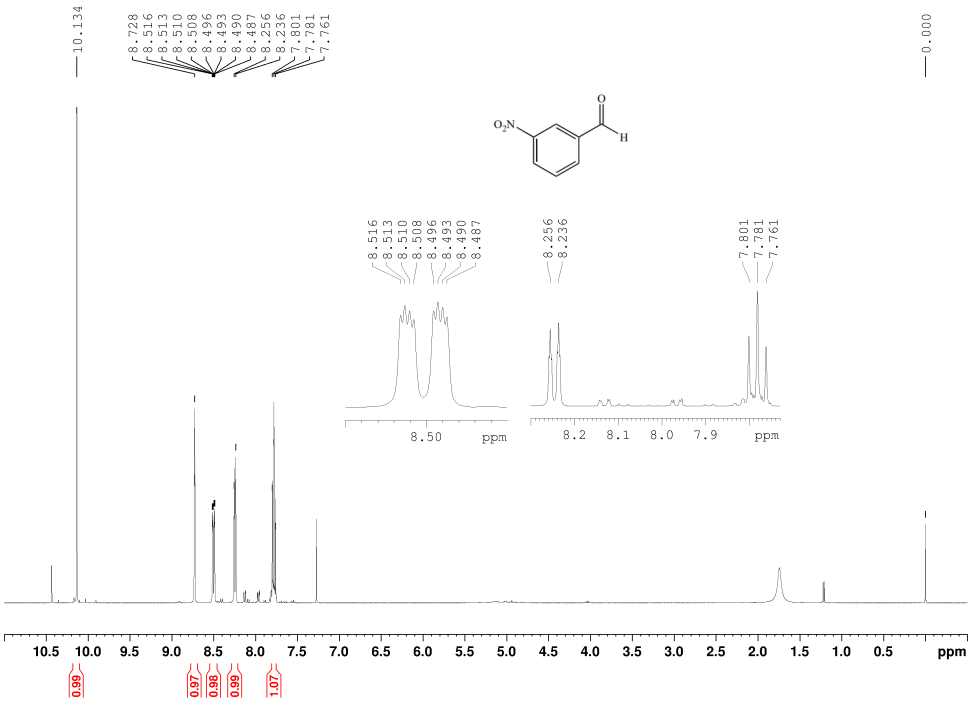

Figure 1: 3-nitrobenzaldehyde NMR

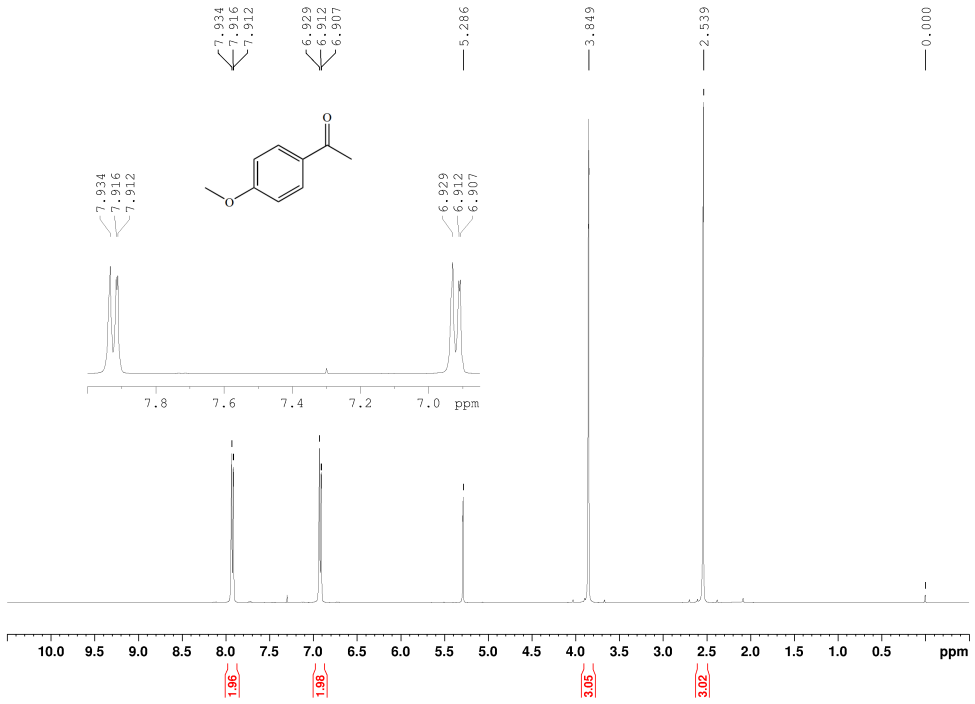

Figure 2: 1-(4-methoxyphenyl)ethan-1-one NMR

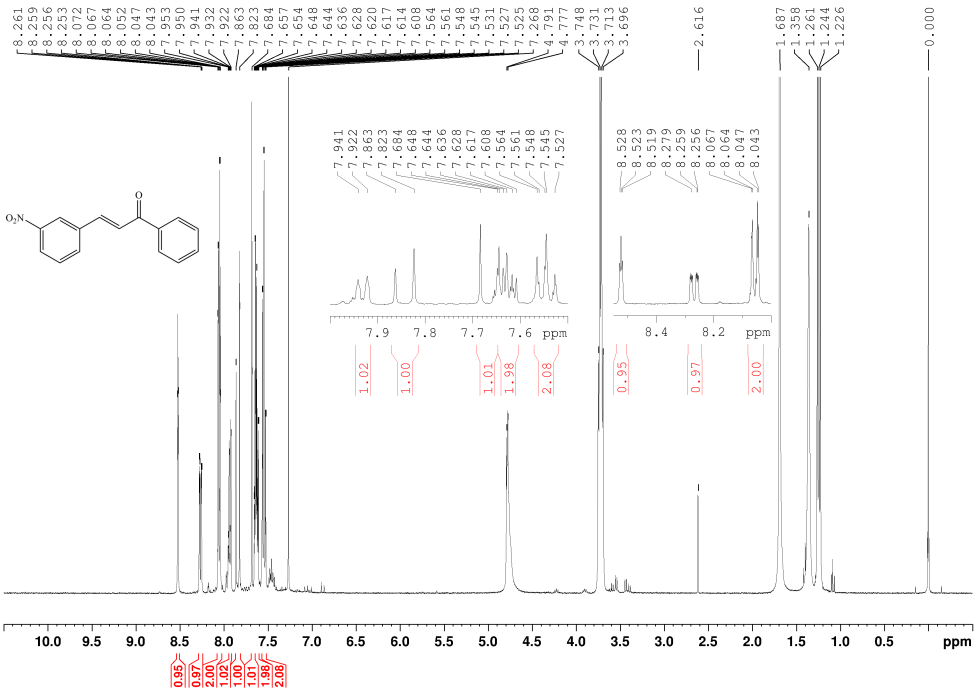

Figure 3: 3-(3-nitrophenyl)-1-phenylprop-2-en-1-one NMR

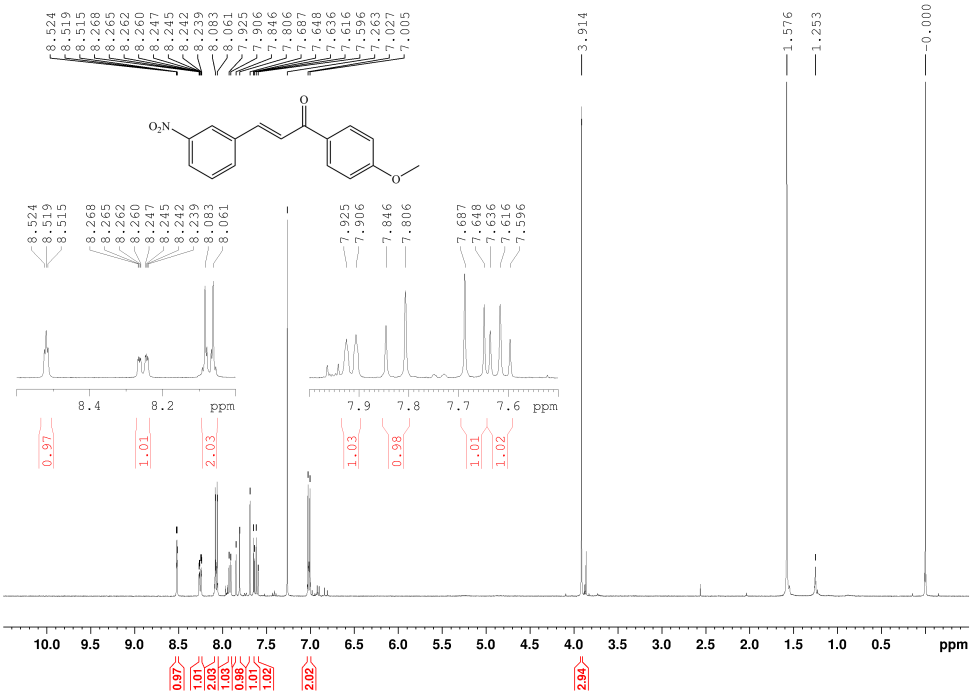

Figure 4: 1-(4-methoxyphenyl)-3-(3-nitrophenyl)prop-2-en-1-one NMR

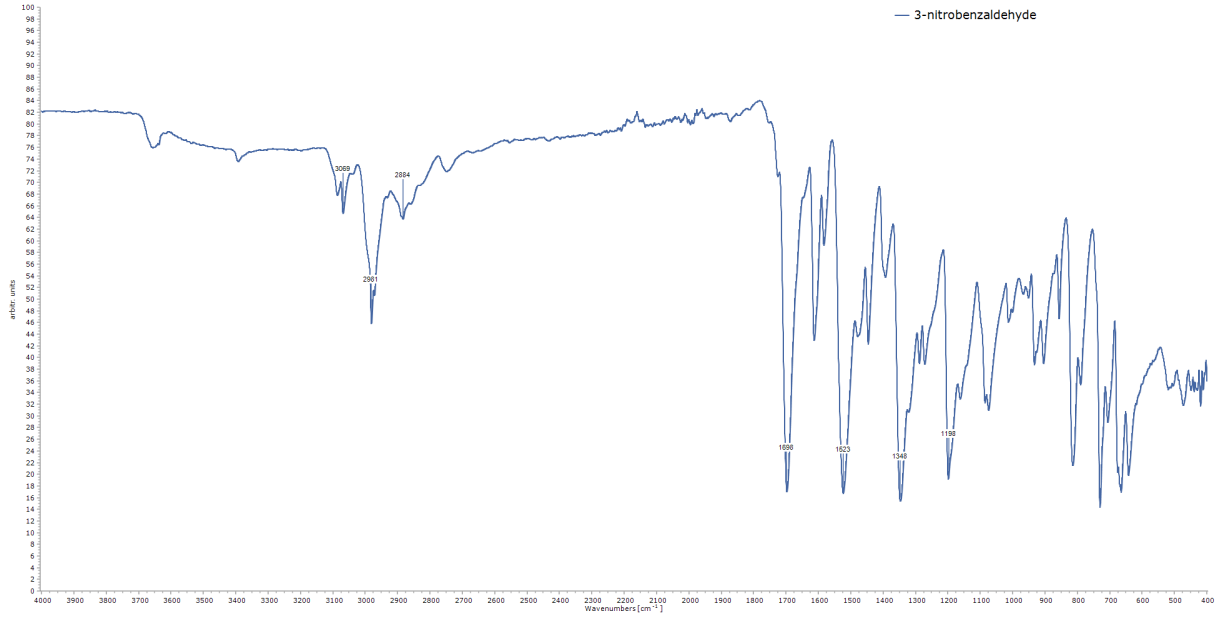

Figure 5: 3-nitrobenzaldehyde IR

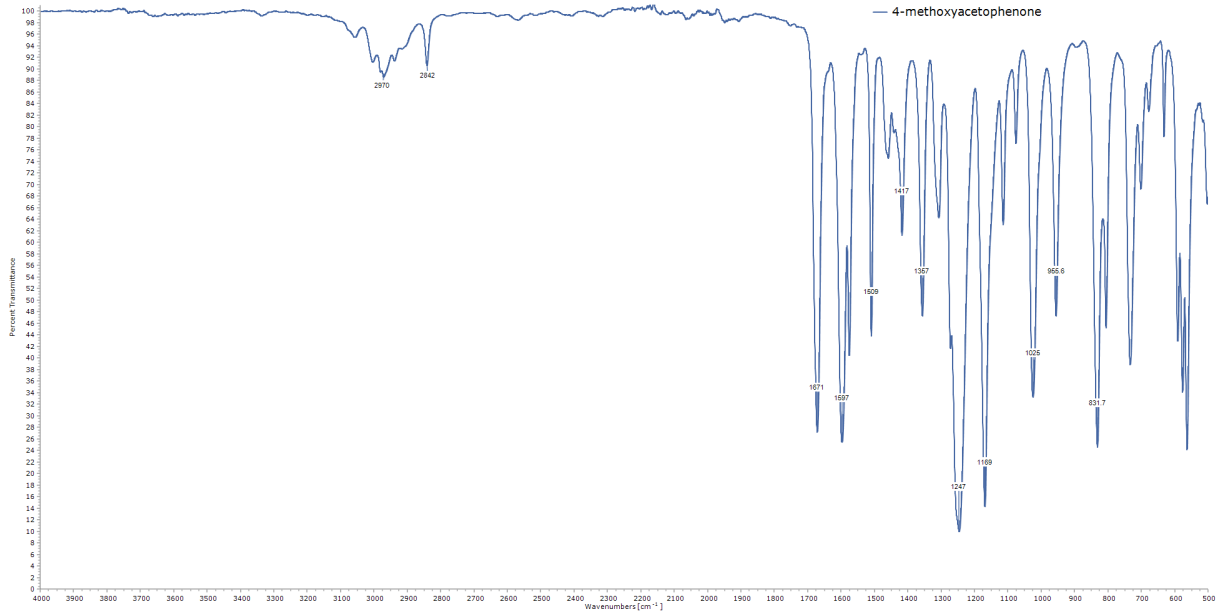

Figure 6: 1-(4-methoxyphenyl)ethan-1-one IR

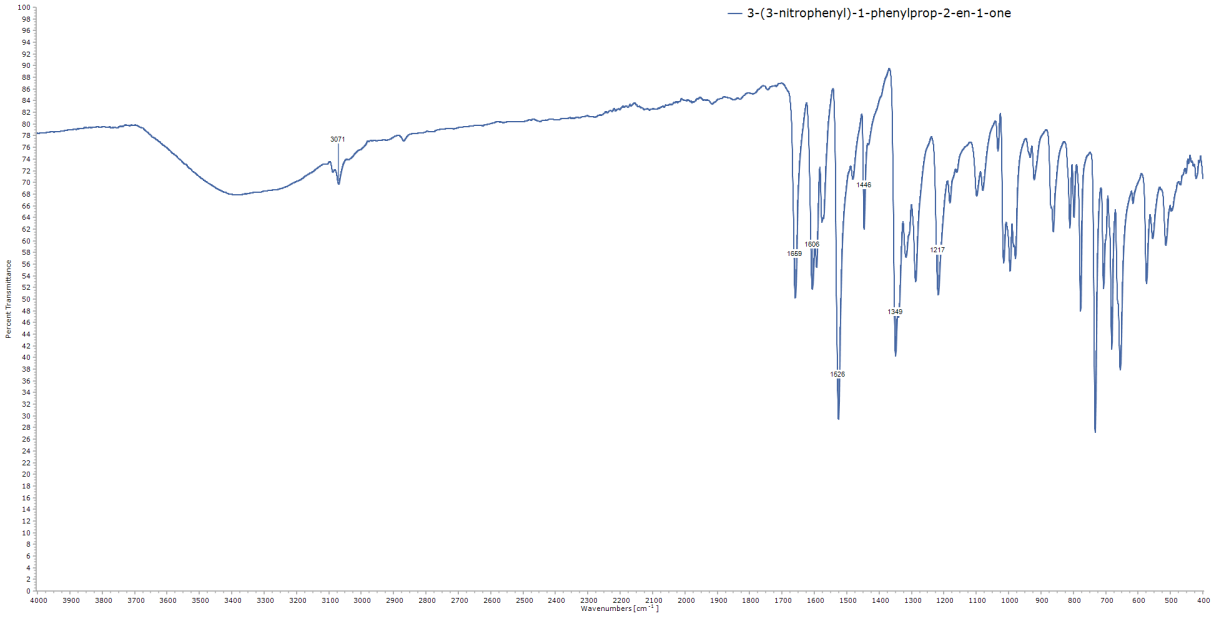

Figure 7: 3-(3-nitrophenyl)-1-phenylprop-2-en-1-one IR

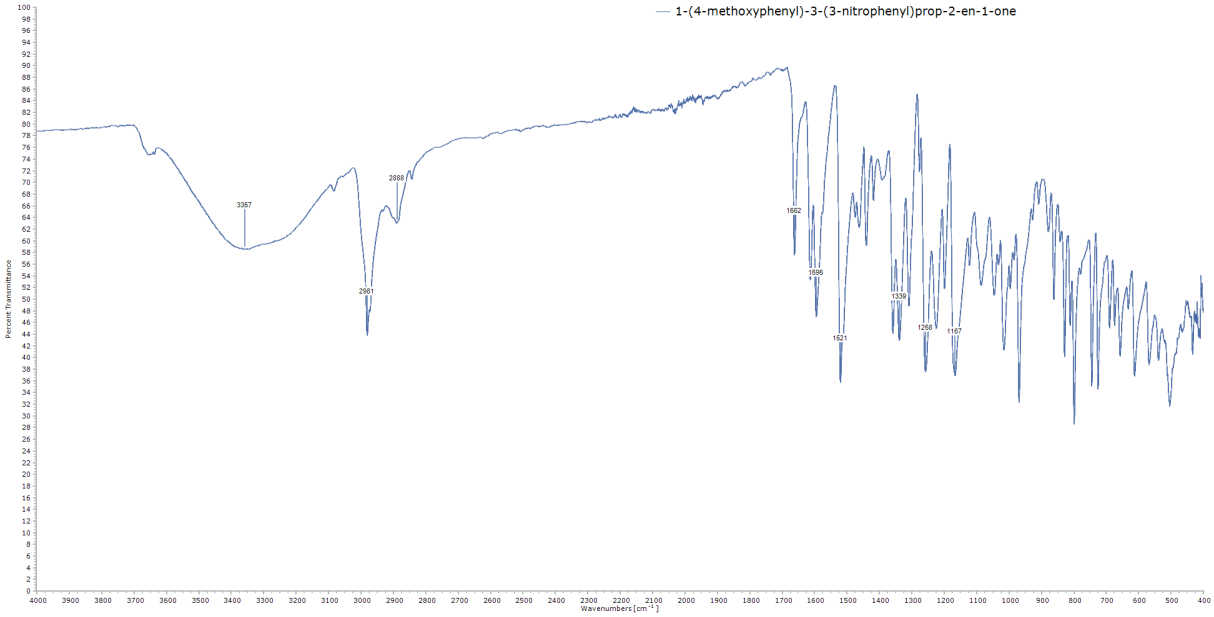

Figure 8: 1-(4-methoxyphenyl)-3-(3-nitrophenyl)prop-2-en-1-one IR

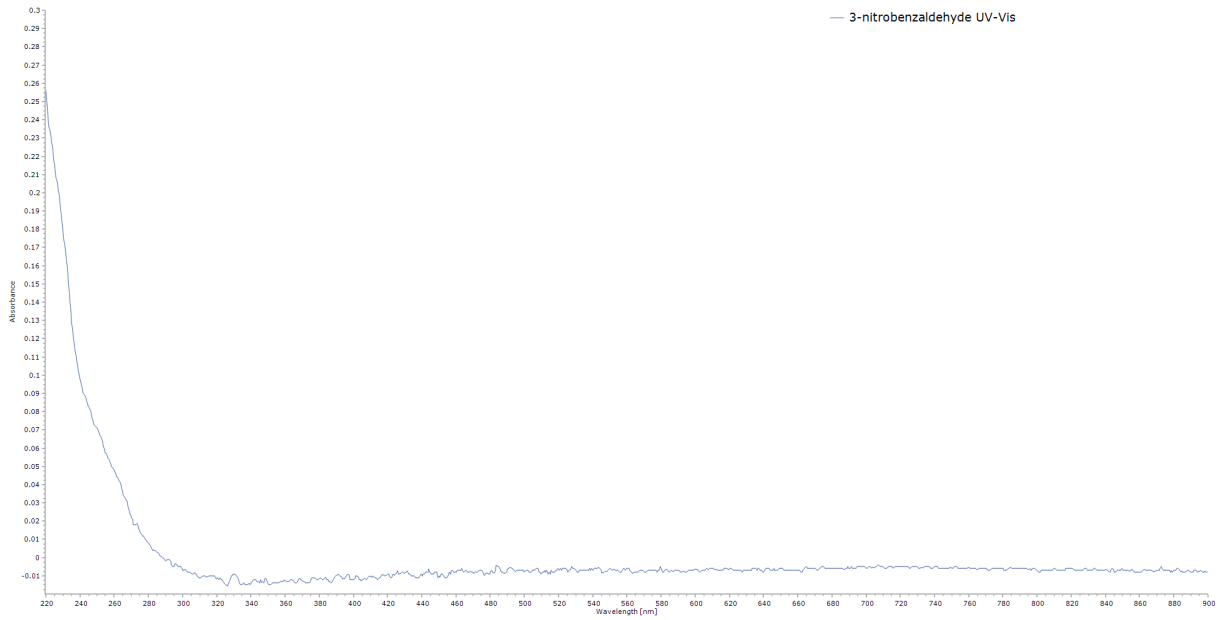

Figure 9: 3-nitrobenzaldehyde UV-Vis

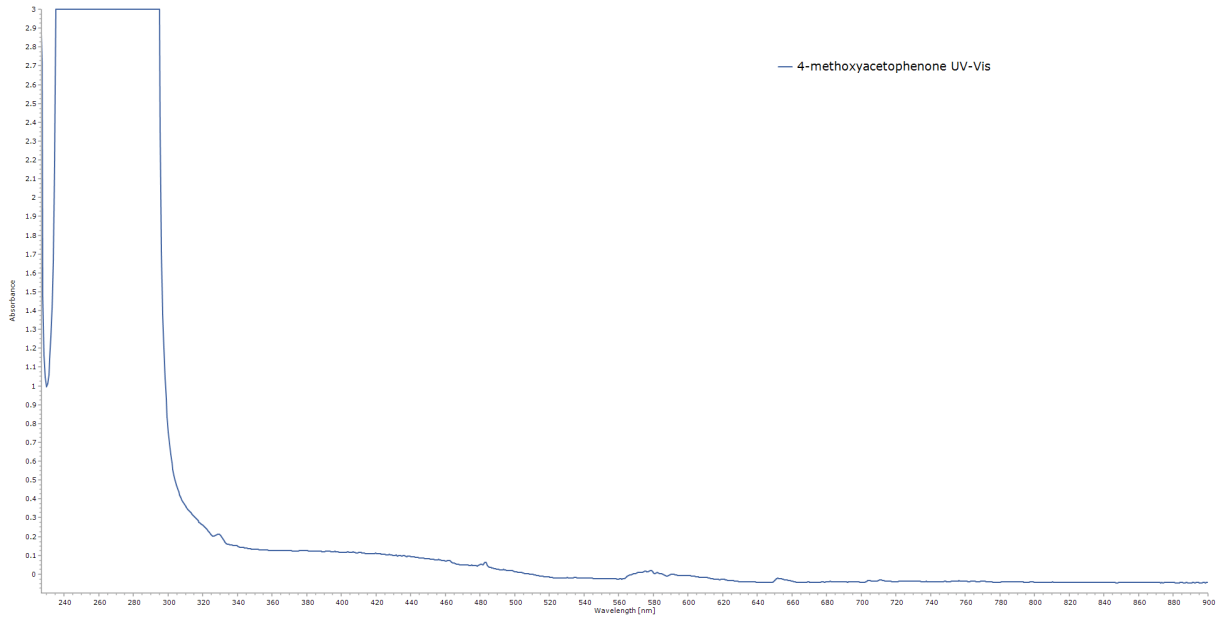

Figure 10: 1-(4-methoxyphenyl)ethan-1-one UV-Vis

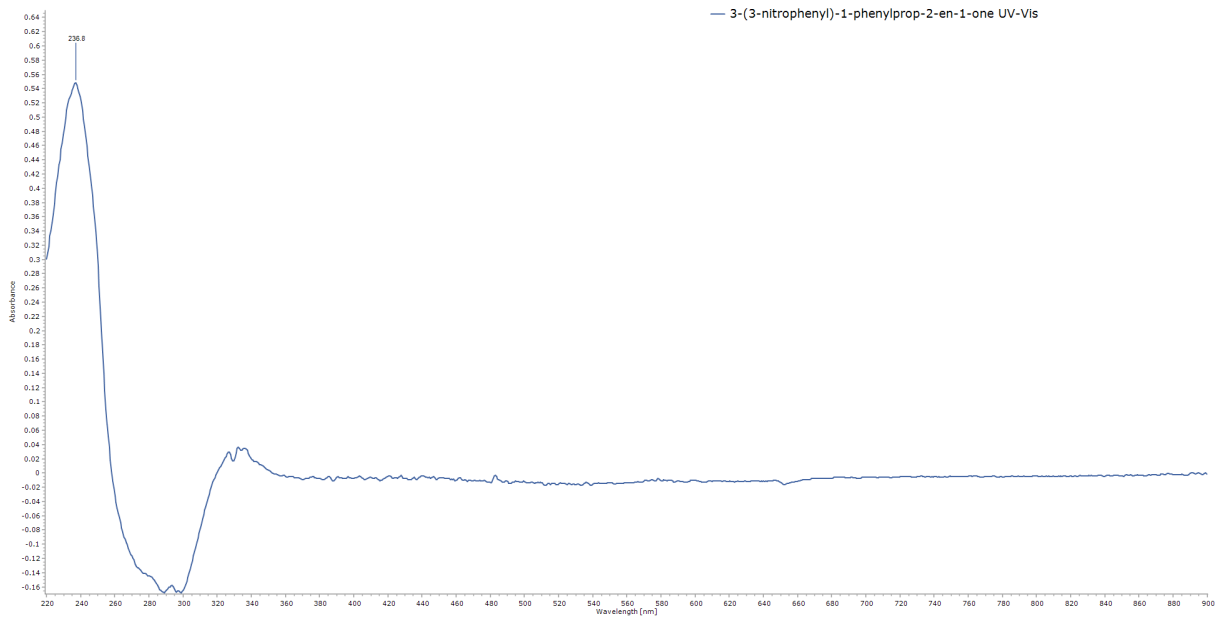

Figure 11: 3-(3-nitrophenyl)-1-phenylprop-2-en-1-one UV-Vis

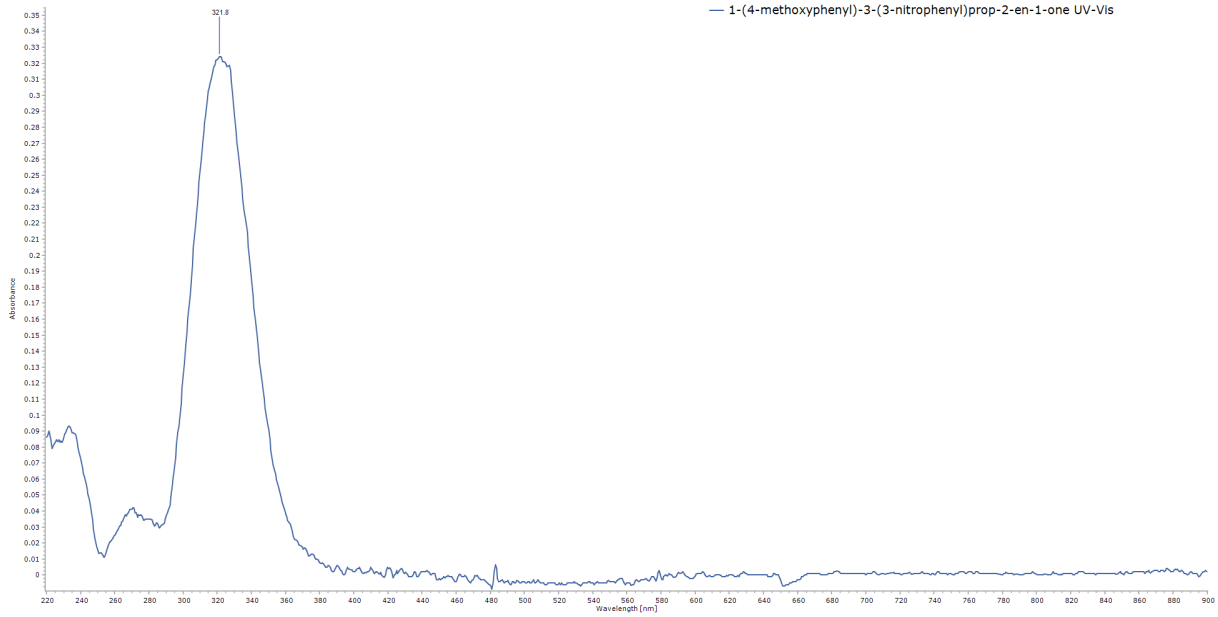

Figure 12: 1-(4-methoxyphenyl)-3-(3-nitrophenyl)prop-2-en-1-one UV-Vis

APPENDIX B: MECHANISMS

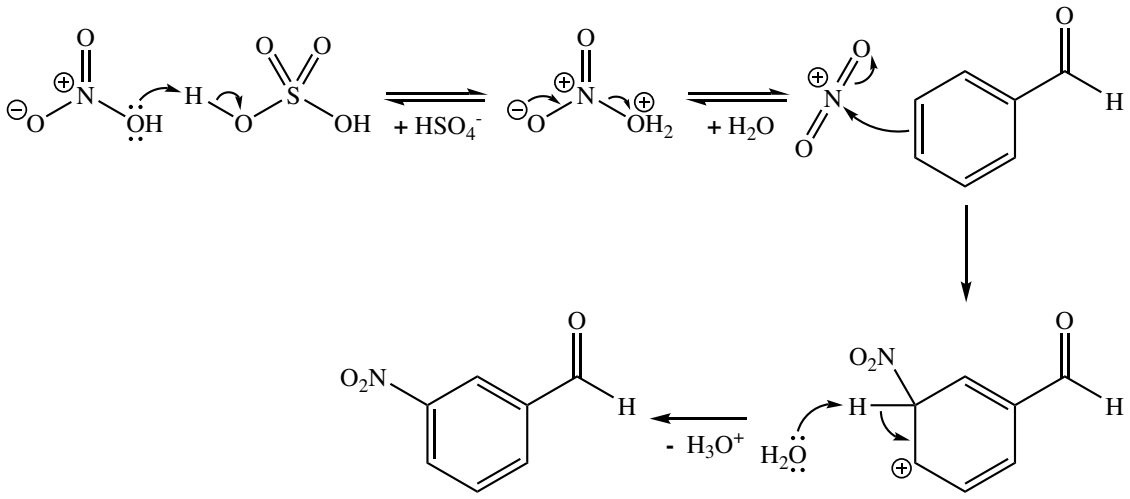

Figure 13: Mechanism of the nitration of benzaldehyde

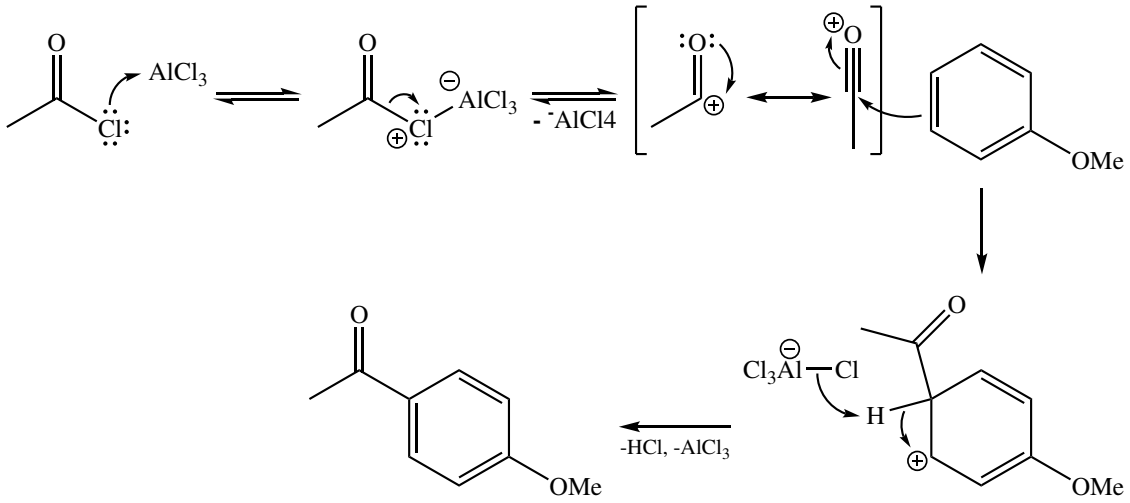

Figure 14: Mechanism of the acetylation of acetophenone

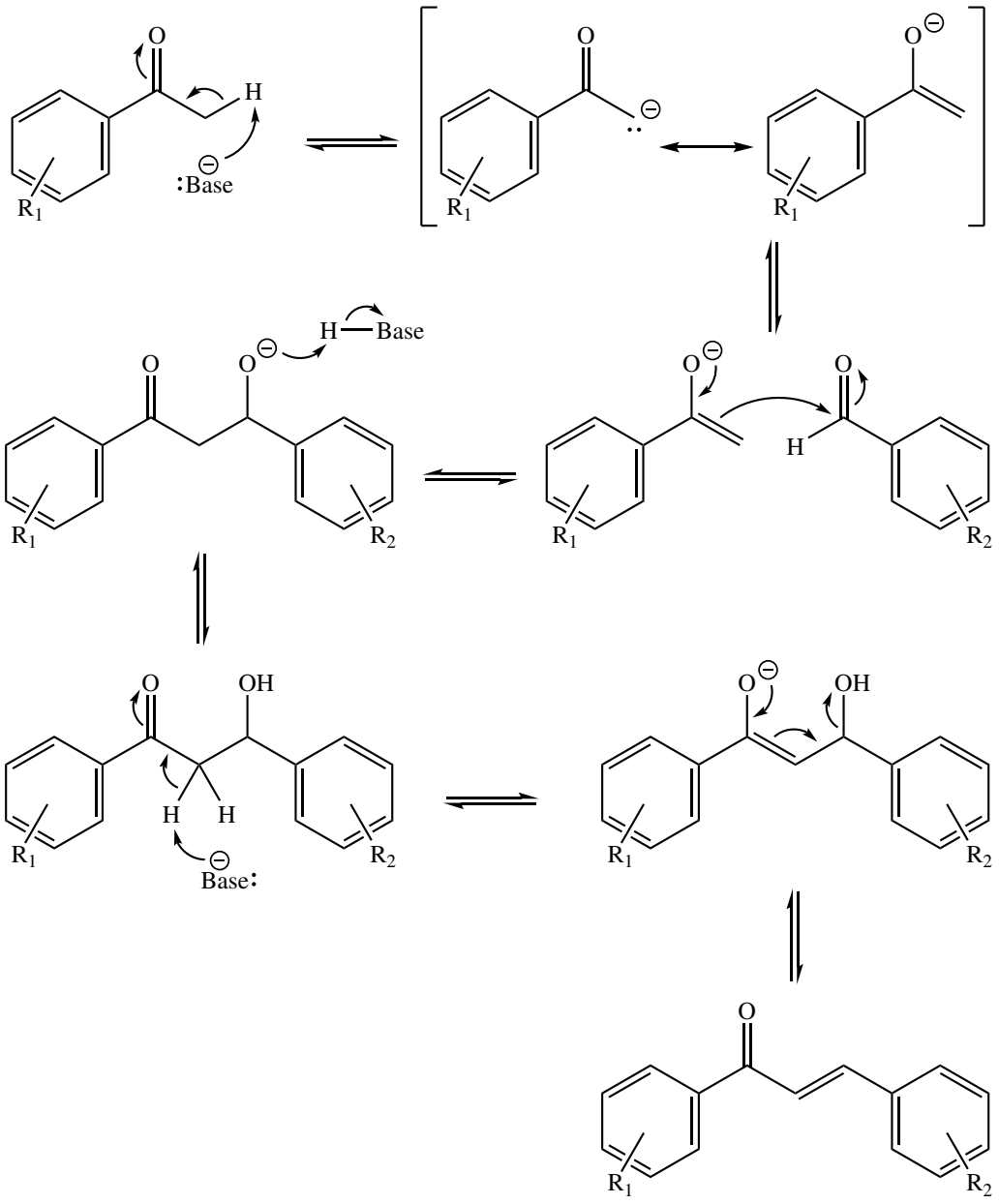

Figure 15: Mechanism of the formation of chalcone