Synthesis, characterization, and photoisomerization studies of chalcone derivatives

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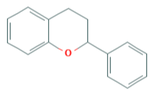
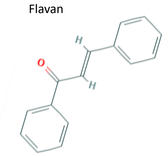
Abstract

In the present study, preparation of *Z*-2(3,5-Dimethoxybenzylidene)-1-Indanone (*Z*-DMBI) was conducted using a UV-light irradiation study of *E*-2(3,5-Dimethoxybenzylidene)-1-Indanone (*E*-DMBI). *E*-DMBI was prepared through a solvent free Claisen-Schmidt reaction between 1-indanone and 3,5-dimethoxybenzaldehyde. All synthesized compounds were characterized using melting point and spectroscopy studies (IR and NMR). Yellow needle-like crystals of *Z*-DMBI were also characterized using X-ray crystallography. Photoisomerization, kinetics studies, and rate constant of *E*-DMBI → *Z*-DMBI were studied using UV spectroscopy in acetonitrile, ethanol, ethyl acetate, and dichloromethane. As the first step in the preparation of flavans, 2-hydroxy chalcone was prepared by an aldol reaction between salicylaldehyde and acetophenone.

Introduction



Flavan



Chalcones

- Chalcones are commonly used in pharmaceuticals for anti-fungal, anti-malarial, and anti-inflammatory.
- Flavans are used to treat diabetes inflammation, cancer, viruses, and osteoporosis.
- Photoisomerization does not need the use of harsh conditions with low yields.
- There may be different pharmaceutical activities for the *Z* isomer.

Present work and designing strategy

- The object of the study to successfully produce and characterized *Z*-2(3,5-Dimethoxybenzylidene)-1-Indanone, and to synthesize flavan and flavanone from salicylaldehyde and acetophenone.

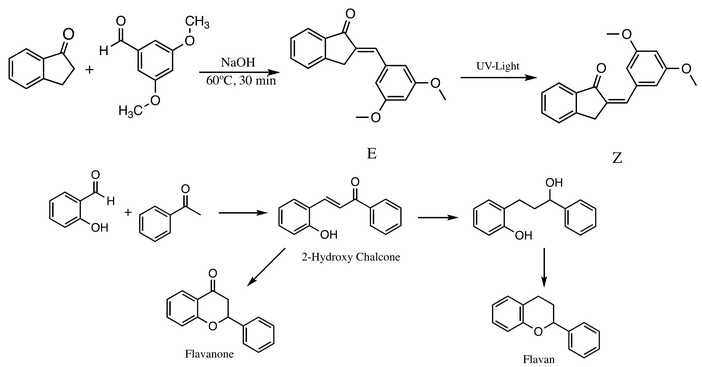


Figure 1. Reaction scheme for the preparation Z-DMBI, flavone and flavan

Methods

Preparation of flavan intermediate.

- Acetophenone (1 mL) was mixed with NaOH (aq, 40 %, 4 mL) and ethanol (20mL).
- The reaction mixture was refluxed for 2.5 h at 60 ºC, and allowed to cool the room temperature, and added into cold H2O (20 mL).
- The mixture was neutralized with HCl until acidic giving 2-Hydroxychalcone. •2-Hydroxychalcone (200 mg) was mixed with ethanol (10 mL) and NaBH4 (0.170 g) was slowly added and stirred for 30 min at 25 ºC
- Mixture was cooled to room temperature and neutralized with HCl (2M).
- The solution was separated using ethyl acetate and was dried with Na2SO4 to produce flavan intermediate.

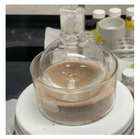
Figure 2: Separation of 2-Hydroxy Chalcone (L) and Figure 4: Column chromatography of Z-DMBI

- Isomerization of E-2(3,5-Dimethoxybenzylidene)-1-Indanone (E-DMBI)
- 1-Indanone (400 mg) was added to a beaker and heated at 60 ºC for 5 min and 3,5-Dimethoxybenzaldehyde (500 mg) was added and mixed.
- NaOH (82 mg) was grounded and slowly added to the reaction mixture while stirring.
- The reaction mixture was removed from heat, quenched with HCl, and washed with H_2O, and was recrystallized using ethanol (100 mL, heated at 70 oC for 1 min).
- A 20µM solution of E- DMBI was prepared and placed on a Dual UV Transilluminator, VWR® at 365nm.
- The UV-spectrum was taken throughout the isomerization using a Lambda 265 UV/Vis Spectrometer, PerkinElmer®.
- A 11.6µM solution was prepared and irradiated for 4 hours and column chromatography was performed to purify the Z DMBI
- UV spectra were also taken with different solvents of ethanol, ethyl acetate, acetonitrile, and dichloromethane.

Results and discussion

- Yellow Powder
- 49.19% Yield
- Melting Point: 144.1-144.9ºC
- TLC → pure
- All characteristics showed pure 2-Hydroxy Chalcone

Figure 3: 2-Hydroxy Chalcone

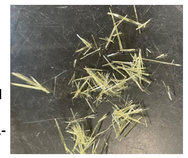


- Clear Liquid
- TLC showed 3 compounds
- Column chromatography is needed before continuing synthesis

Figure 4: Flavan Intermediate

- White, fluffy, needle like structure
- Melting Point: 174-175ºC
- 87 % Yield
- All characteristics showed pure E-2(3,5-Dimethoxybenzylidene)-1-Indanone

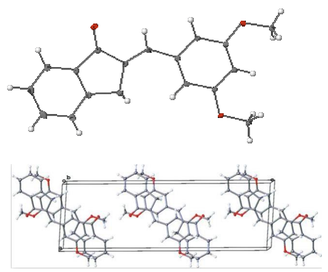
Figure 5: Crystals of E-DMBI



- Yellow, needle like crystals
- Melting point: 103.0-104.0ºC
- 25 % Yield

Figure 6: Crystals of Z-DMBI

X-ray Crystal Studies



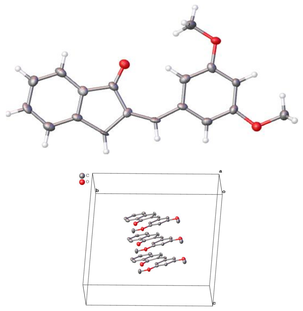
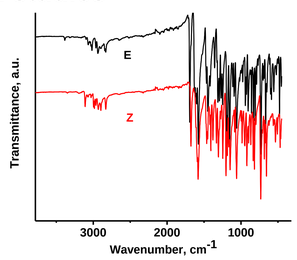


Figure 7: *E*-DMBI X-ray crystal structure

Figure 8: *Z*-DMBI crystal structure

IR studies



Analysis	E Isomer (cm^{-1})	Z Isomer (cm^{-1})
C-H stretch O-CH_3	2827.2	2835.5
C-H stretch	2962	2931.7
C=O stretch	1694.58	1677.55
C=C	1577.73	1580.93

Figure 9: IR spectra of E and Z DMBI

UV Studies

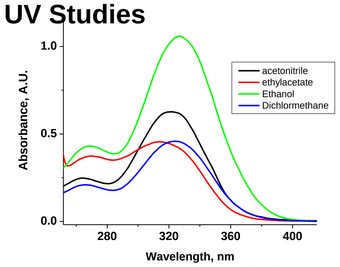


Figure 10: UV spectra, *E*-DMBI in various liquids (22.7µM)

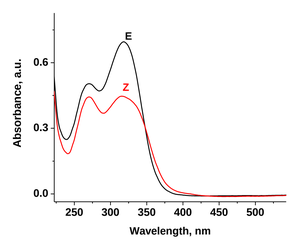


Figure 10: UV spectra of E and Z-DMBI in acetonitrile (22.7µM)

Solvent	Concentration µM	Molar Absorptivity Coefficient at 320 nm (L mol^{-1} cm^{-1})	Molar Absorptivity Coefficient at 264 nm (L mol^{-1} cm^{-1})
Acetonitrile (*Z*-DMBI)	22.7	19093	18035
Acetonitrile (*E*-DMBI)	22.7	27582	10920
Ethanol (*E*-DMBI)	20.6	4925	20291
Dichloromethane (*E*-DMBI)	22.7	19969	9176
Ethyl Acetate (*E*-DMBI)	22.7	19634	15978

Results and discussion

NMR Studies

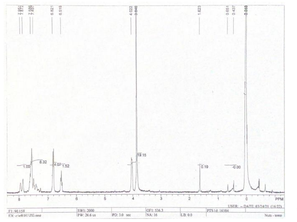


Figure 11: NMR spectrum of *E*-DMBI

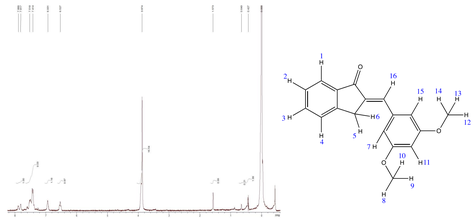


Figure 12: NMR spectrum of *Z*-DMBI

Hydrogen	*E* Isomer Peak (ppm)	*Z* Isomer Peak (ppm)
11	6.5	6.5
7	6.8	7.5
15	7.4	7.4
5, 6	4.0	3.9
2, 3	7.6	7.5
1, 4	7.9 and 7.8	7.9 and 7.8
16	7.6	6.9
8, 9, 10, 12, 13, & 14	3.9	3.9
Impurity (H_2O)	1.6	1.6

E-Z photoisomerization kinetic studies of DMBI

- ~20µM solutions of E-DMBI were irradiated at 365 nm in four liquids using a UV transilluminator.
- The rate constants were determined using first order rate equation

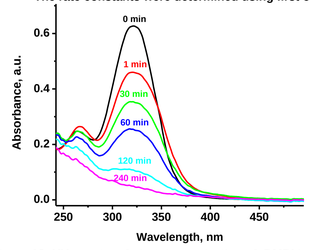


Figure 13: UV spectra of photoisomerization of DMBI in acetonitrile

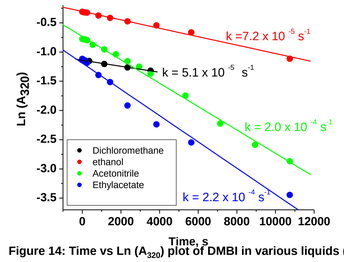


Figure 14: Time vs Ln (A_{320}) plot of DMBI in various liquids (slope = -k)

Conclusions and future directions

The synthesis of and photoisomerization of E-2(3,5-dimethoxybenzylidene)-1-Indanone (Melting Point: 174-175ºC, 87 % Yield) was successfully conducted and the compound was characterized using melting point and spectral analysis. The *Z* isomer of DMBI was prepared (25 % obtained yield, 103.0-104.0 ºC) and characterized using spectral and X-ray crystal analysis. Kinetics of *E-Z* photoisomerization of DMBI was conducted and the rate constants were determined in ethyl acetate (2.2 x 10^{-4} s^{-1}), acetonitrile (2.0 x 10^{-4} s^{-1}), dichloromethane (5.1 x 10^{-5} s^{-1}), and ethanol (7.2 x 10^{-5} s^{-1}). Flavan intermediate compound was also prepared, and the reaction to prepare flavan and flavanone will be conducted in the future.

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