

Antioxidant Evaluation and Synthesis of Novel Anhydrides from Stobbe Dicondensation: A Green Chemistry approach

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Abstract— In present communication, one pot synthesis of acid esters (1) by Stobbedicondensation of alkylidene/arylidene succinates with aldehydes or ketones and their subsequent hydrolysis to diacids (2), namely Fulgenic acids were reported. The Stobbedicondensation of various aromatic aldehydes or ketones with dimethyl succinate gives different types of cyclized products (3), namely (3E,4E)-3,4-dibenzylidenedihydrofuran-2,5-dione (3a), 3,4-bis (diphenyl methylene) dihydrofuran-2,5-dione(3b), (3Z, 4Z) 3, 4-bis ((4-chlorophenyl) (phenyl) (methylene) dihydrofuran-2, 5-dione (3c), (3E,4E)-3, 4-bis(1-phenylethylidene) dihydrofuran-2,5-dione (3d), (Z)-3-((4-chlorophenyl) (phenyl) methylene)-4-(diphenyl methylene)dihydrofuran-2,5-dione (3e), (3Z,4E)-3-((4-chlorophenyl) (phenyl) methylene) -4-(1-phenyl ethylidene) dihydrofuran-2, 5-dione (3f), (3Z, 4Z)-3, 4-bis (furan-2-ylmethylene) dihydrofuran-2, 5-dione (3g) and (3E, 4E)-3,4-di (butan-2-ylidene) dihydrofuran-2, 5-dione(3h) through green approach. The improved yields of Fulgenic acids and its anhydrides (Fulgides) were observed by the green approach as compared with other classical methods employed so far.

Key words: Green Synthesis, Hexamethylenetetramine, Stobbe Condensation, Aryl Aldehydes and Ketones, Antioxidant Activity

I. INTRODUCTION

The earlier classical methods for the formation of Fulgenic acid and their anhydride forms [1,2] are more time consuming and involves use of hazardous solvents like benzene, ether etc., and hence are not eco-friendly. Most of these solvents used for Fulgenic acid synthesis are inflammable, corrosive and have reported to be toxic and carcinogenic effect on exposed beings. Present work describes an eco-friendly one pot synthesis method for Stobbe condensation with minimal use of solvents. In contrast to extensive use of solvents and hazardous chemicals used in previous methods [3]; currently studied green method requires fewer amounts of dry solid reagents, for the formation of acid esters [4]. Moreover, solvent free condition improves the yield and heat energy consumption by the reaction is also averted.

Stobbe condensation under solvent free condition using hexamethylene tetramine was carried out with dimethyl succinate, aliphatic aldehyde forms acid-esters, ketone and aromatic, which on saponification yielded corresponding diacids (2) [5]. Organic photochromic compounds such as Fulgenic acids are potential candidates for application in erasable optical information media [6]. This green approach not only increases the product yield, but also maintains and raises its photochromic strength. The Fulgides i.e. anhydrides (cyclized forms) are the promising materials in optical memory devices, optical switches and sensors, especially dyes and inks. These are representative class of photochromic

organic [7, 8, 9] molecules which exhibits several interesting properties for diverse applications in fields such as data storage or high resolution spectroscopy. The anhydride products are prepared by cyclisation of dicondensation diacids by using silica and perchloric acid.

Hans Stobbe first investigated fulgides around the twenty first century. He reported their synthesis by the reaction now known as Stobbe condensation, which was extensively investigated by Johnson and his coworkers who reviewed the subject in 1951. Fulgides (3) were first and extensively synthesized by Stobbe 1904 early in the 20th century. Fulgenic acid is bioactive monomer against cancer so it is acting as anticancerous compound [10]. The antioxidant is a molecule that inhibits oxidation of biomolecule. Oxidation is a chemical reaction that can produce free radicals leading to chain reactions that may damage cells and initiates diseased condition [11]. Antioxidants are classified into two broad divisions, depending on whether they are soluble in water (hydrophilic) or in lipids (lipophilic). In general, water soluble antioxidants react with oxidants in the cells cytosol and the blood plasma, while lipid soluble antioxidants protect cell membrane from lipid peroxidation [12]. In presently study, we determined the solubility property of Fulgenic acid esters (1).

The photochromism of a fulgide (3) occurs between one of the colourless open forms (hereafter abbreviated as the "E-form" (E) as geometry of double bond connecting aromatic ring and succinic anhydride is usually E and photocyclized coloured form (abbreviated as C-form (C)). Nevertheless, there is an additional photochemical E-Z isomerization pathway. The "Z-form" (Z), geometrical isomer of E-form, is not considered as an important member of photochromic system. To date, there has been no report that Z-form cyclizes directly by absorbing one photon to give C-form.

Therefore, E-to-Z photo isomerization, competing with photochromic E-to-C isomerization, is an energy-wasting as well as system-complicating process in terms of "photochromism of fulgides" (Hadjoudis and Mavridis 2004).

II. MATERIALS AND METHODS

A. Reagents

The following reagents were used for experiments were obtained from Merck. Dimethyl succinate, hexamethylene tetramine, benzophenone, p- Cl-benzophenone, anhydrous methanol, ethylene dichloride, sulphuric acid, alcoholic potassium hydroxide, acetophenone, benzaldehyde, acetone, benzene, petroleum ether, n-hexane, etc. All the above solvents were purified by the reported procedures [13]. 2, 2-Diphenyl-1-picrylhydrazyl (DPPH) was purchased from

Sigma-Aldrich, USA. All other chemicals used were of high analytical grade.

B. Instrumentation

The infrared spectra were obtained on a Bruker AVANCE 520 Fourier transform Infrared spectrometer using KBr pellets from SAIF Punjab University Chandigarh, India. High resolution ¹H-NMR spectra was recorded on a Bruker Avance II 400 MHz spectrometer in D₂O with TMS as an internal standard. Melting points were measured on a digital Electrothermal 9100 Melting Point Apparatus and reported without correction. Ultra violet and visible spectra were measured for 10⁻⁴ M in toluene solution. The pH-metric titrations were conducted in aqueous ethanol (50:50, v/v) on an automatic recording Electronic Corporation of India limited (ECIL) pH-meter (Model pH 821) having a glass-calomel electrode assembly. Molecular weights of acidic products were determined by titrimetric method as their equivalent weights. The general procedures for Stobbe condensation were modified by using green method [14, 15].

C. Material Synthesis

A mixture of dimethyl succinate (9.0 g, 0.09 mole) and aldehydes or ketones were added dropwise to a suspension of Hexamethylene tetramine (12.6 g, 0.09 mole). The reaction mixture was ground in mortar and pestle for 10 minutes and allowed to stand for another 20 minutes. Then 3N HCl was added in small amounts. Alcohol was distilled off under reduced pressure and reaction mixture was extracted with ether at room temperature. Acidic substances were separated by using 10% Na₂CO₃. On further acidification, finally it gives acid ester which was again recrystallized with n-Hexane /Benzene petroleum ether. Further on esterification, with anhydrous CH₃OH, ethylene dichloride and conc. H₂SO₄ at room temperature it gives diester. Once again the diesters was mixed with aldehydes or ketones and Hexamethylene tetramine, the same procedure was repeated and recrystallization was done with n-Hexane /Benzene, petroleum ether which gives 2nd acid ester. Finally the obtained 2nd acid ester was saponified with alcoholic KOH at room temperature for 2 hours and followed by acidification and recrystallization which would give a solid crystalline natured diacids (2Z,3E)-2,3-dibenzylidenesuccinic acid (2a), 2,3-bis(diphenylmethylene)succinic acid(2b), (2Z,3Z)-2,3-bis((4-chlorophenyl)(phenyl)methylene)succinic acid(2c), (2Z,3Z)-2,3-bis(1-phenylethylidene)succinic acid(2d), (Z)-2-((4-chlorophenyl)(phenyl)methylene) - 3-(diphenylmethylene)succinic acid(2e), (2Z,3Z)-2-((4-chlorophenyl)(phenyl)methylene) - 3-(1-phenylethylidene)succinic acid (2f), (2Z,3E)-2,3-bis(furan-2-ylmethylene)succinic acid(2g), (2Z,3Z)-2,3-di(butan-2-ylidene)succinic acid(2h).

Further these diacids undergo cyclisation in presence of silica and perchloric acid (1:1) to give anhydrides (3E,4E)-3,4-dibenzylidenedihydrofuran-2,5-dione (3a), 3,4-bis(diphenylmethylene)dihydrofuran-2,5-dione (3b), (3Z, 4Z) 3, 4-bis ((4-chlorophenyl)(phenyl)methylene) dihydrofuran-2, 5-dione (3c), (3E,4E)-3,4-bis(1-phenylethylidene) dihydrofuran-2,5-dione (3d), (Z)-3-((4-chlorophenyl)(phenyl)methylene)-4-(diphenylmethylene)dihydrofuran-2,5-dione (3e), (3Z,4E)-3-((4-chlorophenyl)(phenyl)methylene)-4-(1-phenylethylidene)dihydrofuran-2,5-dione (3f), (3Z,4Z)-3,4-bis(furan-2-ylmethylene)dihydrofuran-2,5-

dione (3g) and (3E,4E)-3,4-di(butan-2-ylidene)dihydrofuran-2,5-dione (3h).

D. Spectroscopic Analysis of Anhydrides

- 1) (3E, 4E)-3,4-dibenzylidenedihydrofuran-2,5-dione(3a)
 - R1, R2 = Ph, H (9.54g, 0.09 mole) in Scheme 2 and Table 1, Entry 1.
 - R3, R4 = Ph, H (9.54g, 0.09 mole) in Scheme 2 and Table 1, Entry 1.
 - 2) 3, 4-bis (diphenylmethylene) dihydrofuran-2, 5-dione(3b)
 - R1, R2 = Ph, Ph (16.38g, 0.09mol) in Scheme 2 and Table 1, Entry 2.
 - R3, R4 = Ph, Ph(16.38g, 0.09mol) in Scheme 2 and Table 1, Entry 2.
- IR (KBr): 3480, 3360, 1810, 1725, 1530, 802, cm⁻¹
¹H NMR, δ; 7.42(1H, s, J=7.5Hz), 7.48(1H, s, J=7.8Hz), 7.50(1H, br, J=7.3Hz), 7.29(1H, J=7.1Hz), 7.24(1H, br, J=7.5Hz), δ; 7.55(1H, s, J=6.5Hz), 7.38(1H, s, J=7.5Hz), 7.21(1H, s, J=8.5Hz), 7.24(1H, s, J=7.2Hz), 7.35 (1H, br, J=7.3Hz), δ; 7.40, 7.21(2H, d, J=8.6 Hz); melting point 234°C (table 1).
- IR (KBr): 3010, 2912, 1720, 3020, 2895, 1760-1650 cm⁻¹
¹H NMR, δ; 7.41(1H, s, J=6.5Hz), 7.41(1H, s, J=7.5Hz) 7.44(1H, s, J=7.8Hz), 7.40(1H, s, J=7.3Hz), 7.38(1H, s, J=7.0Hz), 7.60(1H, s, J=7.7Hz), 7.39(1H, s, J=7.5Hz), 7.45(1H, s, J=7.8Hz), 7.36(1H, s, J=7.65Hz), 7.42(1H, s, J=7.8Hz); melting point 256°C (table 1).

Entry	R				Products	Yields (%)		Melting Point (°C)	Molecular Weight	Time [min]
	R ₁	R ₂	R ₃	R ₄		Classical	Green ^a			
1	Ph, H	Ph, H			(3a)	62.65	82.89	285	188	120
2	Ph, Ph	Ph, Ph			(3b)	69.15	86.14	206	264	120
3	p-Cl-Ph, Ph	p-Cl-Ph, Ph			(3c)	85.01	94.88	214	140	125
4	Ph, Me	Ph, Me			(3d)	70.05	88.69	302	202.2	120
5	Ph, Ph	p-Cl-Ph, Ph			(3e)	68.47	86.94	324	192.1	120
6	Ph, Me	p-Cl-Ph, Ph			(3f)	72.65	90.11	294	126.1	120
7	C ₂ H ₅ O, H	C ₂ H ₅ O, H			(3g)	68.59	87.62	284	256.21	120
8	Et, Me	Et, Me			(3h)	70.05	90.08	198	208.25	120

Table 1: Synthesis of various anhydrides (3a – 3b) in the presence of HClO₄- SiO₂ by reaction of various aldehydes and ketones at room temperature

Entry	Reagent or catalyst (g)	Solvent	Time (min)	Yield (%)	Temp.	Product
1	HClO ₄ -SiO ₂ (0.14)	dimethyl succinate	120	82.89	rt	(3a)
2	HClO ₄ -SiO ₂ (0.14)	dimethyl succinate	120	86.14	rt	(3b)
3	HClO ₄ -SiO ₂ (0.14)	dimethyl succinate	125	94.88	rt	(3c)
4	HClO ₄ -SiO ₂ (0.14)	dimethyl succinate	120	88.69	rt	(3d)
5	HClO ₄ -SiO ₂ (0.14)	dimethyl succinate	120	86.94	rt	(3e)
6	HClO ₄ -SiO ₂ (0.14)	dimethyl succinate	120	90.11	rt	(3f)
7	HClO ₄ -SiO ₂ (0.14)	dimethyl succinate	120	87.62	rt	(3g)
8	HClO ₄ -SiO ₂ (0.14)	dimethyl succinate	120	90.08	rt	(3h)

Table 2: Optimization of reaction condition in the synthesis of anhydrides (3n-3h)

- 3) (3Z, 4Z) 3, 4-bis ((4-chlorophenyl)(phenyl)(methylene) dihydrofuran-2, 5-dione(3c)
 - R1, R2 = p- Cl-Ph, Ph (19.44g, 0.09mol) in Scheme 2 and Table 1, Entry 3.
 - R3, R4 = p- Cl-Ph, Ph(19.44g, 0.09mol) in Scheme 2 and Table 1, Entry 3.
- IR (KBr): 1772, 2908, 2102, 1760, 1650, 885, 815 cm⁻¹
¹H NMR, δ; 7.21(1H, s, J=6.5Hz), 7.42(1H, s, J=6.2Hz), 7.44(1H, s, J=6.5Hz), 7.48(1H, s, J=6.3Hz), 7.48 (1H, s, J=7.5Hz), 7.64(1H, s, J=7.3Hz), 7.31(1H, s, J=6.8Hz), 7.75(1H, s,

J=8.5Hz), 7.45(1H, s, J=5.5Hz), 7.40(1H, s, J=6.6Hz); δ :7.44(1H, s, J=8.6Hz), 7.47(1H, s, J=6.8Hz), 7.44(1H, s, J=9.5Hz), 7.57(1H, s, J=9.6Hz), 7.68(1H, s, J=8.6Hz), 7.60(1H, s, J=6.6Hz), 7.39(1H, s, J=8.5Hz), 7.55(1H, s, J=5.8Hz), 7.46(1H, s, J=4.3Hz), 7.44(1H, s, J=4.8Hz); melting point 210°C (table 1).

4) (3E, 4E)-3, 4-bis (1-phenylethylidene) dihydrofuran-2, 5-dione (3d)

– R1, R2 = Ph, Me (10.08, 0.09mol) in Scheme 2 and Table 1, Entry 4.

– R3, R4= Ph, Me (10.08, 0.09mol) in Scheme 2 and Table 1, Entry 4.

IR (KBr): 1872, 3020, 3180, 2891, 2915cm⁻¹

¹H NMR; 7.41(1H, s, J=4.3Hz), 7.42(1H, s, J=8.4Hz), 7.47(1H, s, J=7.3Hz), 7.48(1H, s, J=6.4Hz), 7.58(1H, s, J=7.7Hz), 7.64(1H, s, J=7.4Hz), 7.71(1H, s, J=5.6Hz), 7.85(1H, s, J=6.3Hz), 7.45(1H, s, J=7.2Hz), 7.48(1H, s, J=7.8Hz); δ 2.95, 2.98(2 CH₃, d, J=8.6 Hz); melting point 223°C (table 1).

5) (Z)-3-((4-chlorophenyl)(phenyl)methylene)-4-(diphenylmethylene)dihydrofuran-2,5-dione(3e)

– R1, R2= Ph, Ph(16.38g, 0.09mol) in Scheme 2 and Table 1, Entry 5.

– R3, R4= p- Cl-Ph, Ph(19.44g, 0.09mol) in Scheme 2 and Table 1, Entry 5.

IR (KBr): 1872, 1623, 3120, 3052, 685, 795, 1760, 1650cm⁻¹.

¹H NMR; δ 7.25(1H, s, J=8.4Hz), 7.31(1H, s, J=5.01Hz), 7.25(1H, s, J=6.4Hz), 7.36(1H, s, J=8.1Hz), 7.52(1H, s, J=7.4Hz), 7.42(1H, s, J=7.10Hz), 7.41(1H, s, J=4.4Hz), 7.53(1H, s, J=5.4Hz), 7.54(1H, s, J=8.0Hz), 7.61(1H, s, J=4.4Hz), 7.35(1H, s, J=6.4Hz), 7.36(1H, s, J=8.3Hz); δ 7.42(1H, s, J=6.4Hz), 7.52(1H, s, J=3.9Hz), 7.36(1H, s, J=7.4Hz), 7.54(1H, s, J=4.7Hz), 7.53(1H, s, J=8.8Hz), 7.63(1H, s, J=8.10Hz), 7.58(1H, s, J=8.4Hz); melting point 269°C (table 1).

6) (3Z, 4E)-3-((4-chlorophenyl)(phenyl)methylene)-4-(1-phenylethylidene)dihydrofuran-2,5-dione(3f)

– R1, R2 = Ph, Me (10.08, 0.09mol) in Scheme 2 and Table 1, Entry 6.

– R3, R4= p- Cl-Ph, Ph(19.44g, 0.09mol) in Scheme 2 and Table 1, Entry 6.

IR (KBr): 1572, 1623, 2704, 920-795, 1680, 1550cm⁻¹

¹H NMR; δ 7.332(1H, s, J=8.4Hz), 7.25(1H, s, J=6.4Hz), 7.52(1H, s, J=7.2Hz), 7.51(1H, s, J=8.0Hz), 7.56(1H, s, J=6.4Hz), 7.65(1H, s, J=6.7Hz), 7.35(1H, s, J=5.4Hz); δ 7.52(1H, s, J=8.4Hz), 7.65(1H, s, J=8.0Hz), 7.45(1H, s, J=5.4Hz), 7.54(1H, s, J=4.34Hz), 7.65(1H, s, J=3.4Hz), 7.45(1H, s, J=6.5Hz), 7.52(1H, s, J=8.4Hz); δ 6.25(s, CH₃); melting point 254°C (table 1).

7) (3Z, 4Z)-3, 4-bis (furan-2-ylmethylene) dihydrofuran-2, 5-dione(3g)

– R1, R2 = C₅H₆O, H(8.64, 0.09mol) in Scheme 2 and Table 1, Entry 7.

– R3, R4= C₅H₆O, H(8.64, 0.09mol) in Scheme 2 and Table 1, Entry 7.

IR (KBr): 1882, 1584, 3380, 3192, 1682, 1555cm⁻¹

¹H NMR; δ 8.34(1H, s, J=6.5Hz), 8.56(1H, s, J=6.8Hz), 8.45(1H, s, J=7.5Hz), 8.42(1H, s, J=7.2Hz), 6.35(1H, s, J=4.5Hz), 6.65(1H, s, J=5.2Hz), 6.61(1H, s, J=6.6Hz), 6.45(1H, s, J=6.1Hz); melting point 284°C (table 1).

8) (3E,4E)-3,4-di(butan-2-ylidene)dihydrofuran-2,5-dione(3h)

– R1, R2 = Et, Me (6.48g, 0.09mol) in Scheme 2 and Table 1, Entry 8.

– R3, R4= Et, Me (6.48g, 0.09mol) in Scheme 2 and Table 1, Entry 8.

IR (KBr): 1872, 3180, 3075, 2975, 2765cm⁻¹

¹H NMR; 2.045, 2.057(2H, -CH₂, d, J=6.5Hz); δ 1.524(1H, s, J=6.1Hz), 1.502(1H, s, J=8.5Hz), 1.238, (1H, s, J=4.5Hz), 1.235(1H, s, J=5.020Hz); for melting point 198°C (table 1).

E. Antioxidant Assay

Diphenylpicrylhydrazyl (DPPH) was used to assay antioxidant activity of presently synthesized compounds in a 96-well plate, by modified method of Fukumoto and Mazza (2000) and briefly described here as follows. In each well, 200 μ L of DPPH (150 μ M prepared in 80% methanol) was mixed with 1 μ g (25 μ L) of synthesized compound. Blank test and, vehicle control were prepared with equal amount of carrier solvent namely ethanol. Different concentrations (0.2 μ g, 0.4 μ g, 0.6 μ g, 0.8 μ g, 1.0 μ g, 1.25 μ g and 2.5 μ g) of ascorbic acid (vitamin C) were used to prepare standard plot. All samples were assayed in triplicates and the plate was incubated for 6 h at room temperature. After incubation, the absorbances were measured at 517 nm in a multimode reader (Tecan Infinite M200). Percent antioxidant activity were calculated by using following formula, and the values generated were further used to compare antioxidant potential between ascorbic acid and test compounds.

$$[(\text{Vehicle control} - \text{Test}) / \text{Vehicle control}] \times 100$$

III. RESULTS AND DISCUSSIONS

In this research article, Fulgenic acids were prepared via Stobbedicondensation using hexamethylene tetramine through green context. Further these diacids undergo cyclisation in presence of silica and perchloric acid (1:1) to give anhydrides.

Stobbe condensation generally involves the use of metal alkoxides as a catalyst in refluxing alcohol, particularly, butanol [16]. On the other hand, use of butanol is discarded and instead of that, in this research paper Hexamethylene tetramine was taken for the reaction. The advantages are short reaction time, good yield, less by-products.

The Fulgides (3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h) synthesized using current method is of high purity compared with classical synthesis. The synthesized Fulgides have specific melting and boiling point, NMR peak values. In previous synthetic methods tremendous heat was used, which leads to impure diacids with less percentage yield [17].

The bluish colored crystalline solid natured diacid prepared by using aldehyde i.e. benzaldehyde which on cyclisation gives anhydride (3a) exhibited a molecular formula C₁₈H₁₂O₃ showed characteristic stretching frequencies of aromatic C-H (3480-3360cm⁻¹), anhydride C=O (1810-1725cm⁻¹), aromatic -CH (802cm⁻¹), C=C (1530cm⁻¹) (Figure 1). Similarly, ¹H NMR spectrum also showed ten -CH groups on δ ; 7.42, 7.48, 7.50, 7.29, 7.24, 7.55, 7.38, 7.21, 7.24, 7.35 (m, 10H, -CH), (Figure 2). Also, it shows two Hydrogen atoms on δ ; 7.40, 7.21 (d, 2H).

The bluish red colored crystalline solid natured diacid prepared by using ketone i.e. Benzophenone which on cyclisation gives anhydride (3b) having molecular

formula $C_{30}H_{20}O_3$ also showed characteristic stretching frequencies of aromatic C-H ($3010-2912\text{cm}^{-1}$), anhydride C=O (1720cm^{-1}), aromatic -CH ($3020-2895\text{cm}^{-1}$), aromatic C=C ($1760-1650\text{cm}^{-1}$) (Figure 1). Similarly, ^1H NMR spectrum shows aromatic hydrogen's on the corresponding peak values δ ; 7.41, 7.41, 7.44, 7.40, 7.38, 7.60, 7.39, 7.45, 7.36, 7.42 (m, 10H, -CH); (Figure 2). The obtained peak values were sharp & accurate for their corresponding groups which proved the dominance of green approach on classical method.

The pale green colored crystalline solid natured diacid prepared by using ketone i.e. p-chlorobenzophenone which on cyclisation gives anhydride (3c) having molecular formula $C_{30}H_{18}Cl_2O_3$ also showed characteristic stretching frequencies, anhydride C=O (1772cm^{-1}), aromatic C-H ($2908-2102\text{cm}^{-1}$), aromatic (C-Cl stretch) ($885-815\text{cm}^{-1}$) and ($812-780$), aromatic C=C ($1760-1650\text{cm}^{-1}$) (Figure 1). ^1H NMR spectrum also showed the required peak values 7.21, 7.42, 7.44, 7.48, 7.48, 7.64, 7.31, 7.75, 7.45, 7.40 (m, 10H, -CH); 7.44, 7.47, 7.44, 7.57, 7.68, 7.60, 7.39, 7.55, 7.46, 7.44 (m, 10H, -CH); (Figure 2).

The pale green colored crystalline solid natured diacid prepared by using ketone i.e. Acetophenone which on cyclisation gives anhydride (3d) having molecular formula $C_{20}H_{16}O_3$ also showed characteristic stretching frequencies, anhydride C=O (1872cm^{-1}), aromatic -CH ($3020-3180\text{cm}^{-1}$), CH_3 ($2891-2915\text{cm}^{-1}$) (Figure 1). ^1H NMR spectrum also showed the required peak values for five aromatic -CH₅, 5.2, 5.64, 5.72, 6.15, 5.86 (m, 5H, -CH); along with one, -CH₂ group δ 2.45 (s, 2H, -CH₂). Also it shows one, -CH₃ group on δ 2.91 (s, 3H CH₃). (Figure 2).

The pale yellow colored crystalline solid natured diacid prepared by using ketones i.e. Benzophenone and p-chlorobenzophenone which on cyclisation gives anhydride (3e) having molecular formula $C_{30}H_{19}ClO_3$ also showed characteristic stretching frequencies Of anhydride C=O ($1872-1623\text{cm}^{-1}$), aromatic C-H ($3120-3052\text{cm}^{-1}$), aromatic (C-Cl stretch) ($685-795\text{cm}^{-1}$), aromatic C=C ($1760-1650\text{cm}^{-1}$) (Figure 1). Similarly, ^1H NMR spectrum shows aromatic hydrogen's on the corresponding peak values δ 7.25, 7.31, 7.25, 7.36, 7.52, 7.42, 7.41, 7.53, 7.54, 7.61, 7.35, 7.36 (m, 12H, -CH); δ 7.42, 7.52, 7.36, 7.54, 7.53, 7.63, 7.58 (m, 7H, -CH) (Figure 2).

The pale green colored crystalline solid natured diacid prepared by using ketones i.e. Acetophenone and p-chlorobenzophenone which on cyclisation gives anhydride (3f) having molecular formula $C_{25}H_{17}ClO_3$ also showed characteristic stretching frequencies Of aromatic anhydride C=O ($1572-1623\text{cm}^{-1}$), aromatic C-H ($2936-2704\text{cm}^{-1}$), aromatic (C-Cl stretch) ($920-795\text{cm}^{-1}$), aromatic C=C ($1680-1550\text{cm}^{-1}$) (Figure 1). Similarly, ^1H NMR spectrum shows aromatic hydrogen's on the corresponding peak values δ 7.332, 7.25, 7.52, 7.51, 7.56, 7.65, 7.35 (m, 7H, -CH); δ 7.52, 7.65, 7.45, 7.54, 7.65, 7.45, 7.52 (m, 7H, -CH). Also it shows one, -CH₃ group on δ 6.25 (s, CH₃); (Figure 2).

The pale yellowish green colored crystalline solid natured diacid prepared by using aldehyde i.e. Furfural which on cyclisation gives anhydride (3g) having molecular formula $C_{14}H_8O_5$ also showed characteristic stretching frequencies Of anhydride C=O ($1882-1584\text{cm}^{-1}$), aromatic -CH ($3380-3192\text{cm}^{-1}$), aromatic C=C ($1682-1555\text{cm}^{-1}$) (Figure 1). Similarly, ^1H NMR spectrum shows aromatic hydrogen's on

the corresponding peak values δ 8.34, 8.56, 8.45, 8.42, 6.35, 6.65, 6.61 (m, 7H, -CH); δ 6.45 (s, H); (Figure 2).

The pale green colored crystalline solid natured diacid prepared by using ketone i.e. Butanone which on cyclisation gives anhydride (3h) having molecular formula $C_{12}H_{16}O_3$ also showed characteristic stretching frequencies Of anhydride C=O (1872cm^{-1}), aromatic -CH ($3180-3075\text{cm}^{-1}$), CH_3 ($2975-2765\text{cm}^{-1}$) (Figure 1). Similarly, ^1H NMR spectrum shows aromatic hydrogen's on the corresponding peak values δ ; 2.045, 2.057 (d, 2-CH₂); δ 1.524, 1.502, 1.238, 1.235 (m, 4-CH₃); (Figure 2). The obtained peak values were sharp & accurate for their corresponding groups which proved the dominance of green approach on classical method.

Antioxidant potential of a chemical entity having biological importance, as origin of most chronic disease is oxidative stress [18]. Cells under the influence of oxidative stress, inevitably produces reactive radicals, which surpasses over antioxidant machinery and construct damages to biomolecules. In present study, antioxidant potentials of synthesized Fulgides were estimated by using a violet colored free radical DPPH, which upon reduction becomes colorless or pale yellow. DPPH color intensity was inversely proportional to antioxidant potentials of chemical compounds. The Figure 6, showed the antioxidant potentials of 1 $\mu\text{g/mL}$ of Fulgides in terms of ascorbic acid (μg) equivalent. Highest ascorbic acid equivalent (13.37 μg) were recorded by (3E, 4E)-3, 4-dibenzylidenedihydrofuran-2,5-dione (3a) may be due to presence of two extra phenyl groups. Fulgide 3, 4-bis (diphenylmethylene) dihydrofuran-2, 5-dione (3b), (3Z, 4Z) 3, 4-bis ((4-chlorophenyl) (phenyl) (methylene) dihydrofuran-2, 5-dione (3d) had ascorbic acid equivalent 11.77 μg and 9.10 μg respectively for each μg of compound. While approximately 6 μg to 3 μg of ascorbic acid equivalent antioxidant potential confirmed due to the compounds (3c), (3e), (3f), (3g) and (3h). Fulgide (3Z, 4Z) 3, 4-bis ((4-chlorophenyl) (phenyl) (methylene) dihydrofuran-2, 5-dione (3c) had ascorbic acid equivalent 5.41 μg due to the presence of two p-Cl-benzophenone groups. Chlorine atoms are responsible for the decrease value of antioxidant potentials. Fulgides (Z)-3-((4-chlorophenyl) (phenyl) (methylene)-4- (diphenyl methylene) dihydrofuran-2, 5-dione (3e), (3Z, 4E)-3-((4-chlorophenyl) (phenyl) (methylene)-4-(1-phenylethylidene) dihydrofuran-2, 5-dione (3f), (3Z, 4Z)-3, 4-bis (furan-2-ylmethylene) dihydrofuran-2, 5-dione (3g) had ascorbic acid equivalent 6.31 μg , 3.83 μg , 5.31 μg respectively. Due to presence of methyl and electronegative atom, values of antioxidant potentials decreases. Similarly (3E, 4E)-3, 4-di(butan-2-ylidene) dihydrofuran-2, 5-dione (3h) has only ethyl and methyl groups, due to unavailability of aromatic groups its antioxidant activity is less. Exploration of diverse chemical compound for antioxidative activity is mandatory, as to work on variety of pathogenic circumstances, for example in neurodegenerative diseases an antioxidant must have to cross blood-brain barrier but most of the antioxidant cannot, as like carotenoids [19]. The therapeutic efficiency of presently synthesized Fulgides in different in vitro models is our future strategy to evaluate their potency as lead compounds

IV. CONCLUSION

The greener chemical reaction strategy managed to synthesize Fulgenic acid (2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h)

successfully by simple and efficient means with improved yield. The solvent free Stobbe condensation of aromatic aldehydes and aliphatic, aromatic ketones with dimethyl succinate at room temperature occurred smoothly to give substituted acid esters which on further saponification give diacids. These diacids undergo cyclisation in presence of silica and perchloric acid (1:1) to give anhydrides. This methodology brought down not only the reaction time but also the uses of hazardous organic solvents (as possible) [20, 21]. The prepared anhydrides (3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h) can also be used in the preparation of photosensitive glasses, photosensitive toys and other instruments, Optical data recording like Compact Disc, preparation of photosensitive inks for security purpose, and variable density filters. Further, antioxidative nature of these anhydrides may lead to identification of novel compounds to study in the area of pharmaceuticals.

A. Figure Legends

Structural determination of Fulgides(3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h)synthesized by green method. The Anhydrides which were prepared through green method were obtained in better yields as compared to the classical methods. Their structural determination was done by using NMR-IR –Mass Spectral values.

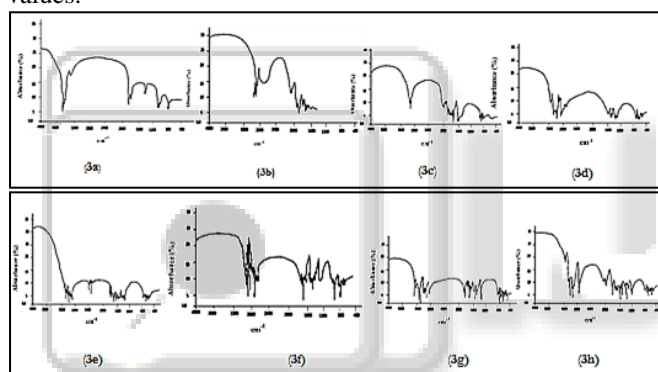


Fig. 1: IR graphical representation of anhydrides

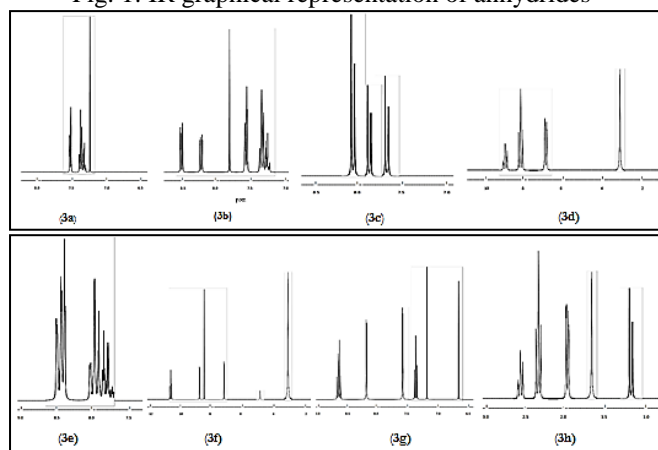


Fig. 2: NMR graphical representation of anhydrides

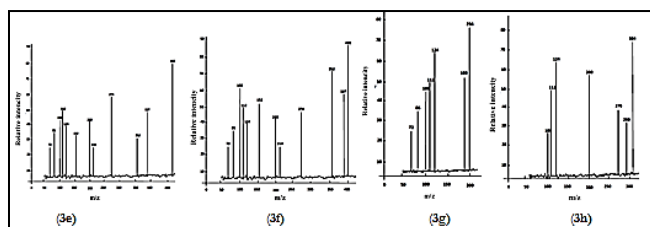
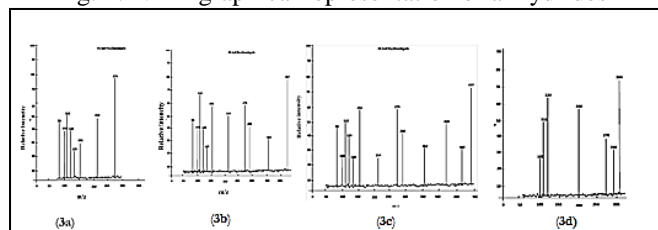


Fig. 3: MASS graphical representation of anhydrides

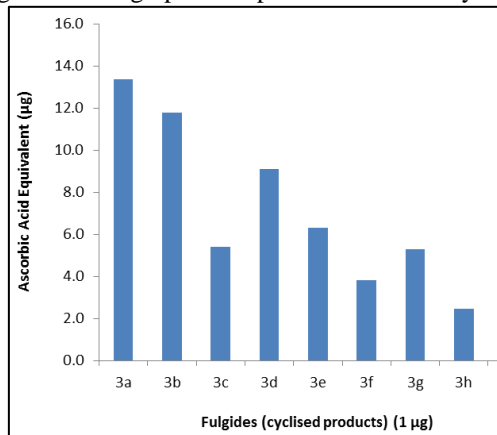


Fig. 4: Antioxidant activity of cyclized products (Fulgides)

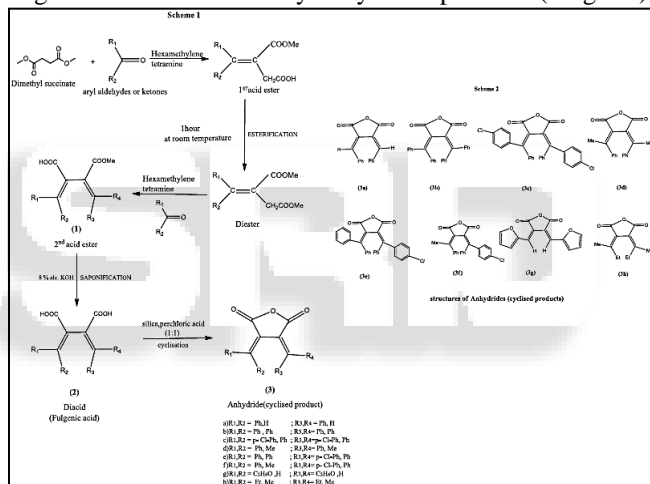


Fig. 5: Reaction Schemes of Experimental Work

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