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Antioxidant evaluation and Synthesis of novel Anhydride from StobbeMonocondensation: A green chemistry approach

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Abstract:*In present communication, one pot synthesis of acid esters (1) by Stobbemonocondensation of alkylidene/arylidene succinates with aldehydes or ketones and their subsequent hydrolysis to diacids (2), namely Itaconic acids were reported. The Stobbemonocondensation of various aromatic aldehydes or ketones with dimethyl succinate gives different types of cyclized products (3), namely (E)-3-benzylidenedihydrofuran-2,5-dione (3a), (E)-3-(1-phenylethylidene)dihydrofuran-2,5-dione (3b), 3-(propan-2-ylidene) dihydrofuran-2,5-dione (3c), (E)-3-(1-phenylethylidene)dihydrofuran-2,5-dione (3d), (E)-3-(1-(furan-2-yl)ethylidene)dihydrofuran-2,5-dione (3e) and (Z)-3-ethylidenedihydrofuran-2,5-dione (3f) through green approach. The improved yields of Itaconic acid and its anhydride (Itaconate) 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.*

1. Introduction:

Itaconic acid is a white colorless crystalline carboxylic acid obtainedbyfermentationofcarbohydratesand used in the manuf acturing of synthetic resins. The earlier classical methods for the formation of Itaconic 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 Itaconic 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 hexamethylenetetramine 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 Itaconic 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 Itaconates 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 monocondensationdiacids by using silica and perchloric acid.

Biologically, Itaconic acid is produced by human and mouse primary macrophage cells. It has *in vitro* antimicrobial activity by arresting glyoxylate shunt at isocitratelyase, where bacteria like *Salmonella enterica* and *Mycobacterium tuberculosis*, utilizes fatty acids or acetate as the limiting carbon source. Itaconic acid is bioactive monomer against cancer so it is acting as anticancer 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 Itaconic acid esters (**1**).

Itaconic acid has been applied in a numerous range of industries. Throughout the 1950s, itaconic acid was used in industrial adhesives. Overall, in this period, itaconic acid was used at an industrial scale and plenty amounts of it were required. The sulfonated form or alkali salt of poly itaconic acid is employed as a detergent and in shampoos. The polymerized ethyl, methyl, or vinyl esters of itaconic acid are used as plastics, elastomers, coatings and adhesives, [13] (Mitsuyasu et al., 2009). Characteristics of the coating and plastic, which is compounded by using 1-5% itaconic acid and styrene, include light color, easy separation, easy to paint, water-fast and antisepsis; it can be used in the manufacture of high-strength enhanced plastic fiberglass and in the coating of carpets and book covers [14] (Jin et al., 2010). Itaconic acid may also be used as artificial gems and synthetic glasses with special nonlinear characteristics [15] (Kin et al., 1998).In 1990s, the applications of itaconic acid have been developed to biomedical fields, like the ophthalmic, dental and drug delivery fields. Another application of itaconic acid is in the preparation of Glass Ionomer Cement (GIC). GICs demonstrated to be useful adjuncts in restorative dentistry [16] (Nagaraja and Kishore, 2005). Crisp and Wilson (1980) synthesized a copolymer of acrylic and itaconic acid that turned out to be indefinitely stable in aqueous solution. This copolymer was the initial commercial marketable cement. An N-vinylcaprolactam-containing copolymer of acrylic itaconic acid [17] (Moshaverinia et al., 2009) and poly (acrylic acid-co-itaconic acid) [18] (Culbertson, 2006) was developed to be used in functional and mechanical GICs. These materials have found increasing applications in clinical dentistry [19] (Okabe et al., 2009).

2. Materials and Methods:

2.1 Reagents:

The following reagents were used for experiments were obtained from Merck. Dimethyl succinate, hexamethylenetetramine, benzophenone, anhydrous methanol, ethylene dichloride, sulphuric acid, alcoholic potassium hydroxide, acetophenone, benzaldehyde, acetone, 1-(furan-2-yl)ethanone ,benzene, petroleum ether, n-hexane, etc. All the above solvents were purified by the reported procedures [20] .2, 2-Diphenyl-1-picrylhydrazyl (DPPH) was purchased from Sigma-Aldrich, USA. All other chemicals used were of high analytical grade.

2.2 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 ^{1}H-NMR spectra was recorded on a BrukerAvance II 400 MHz spectrometer in D_2O 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 [21, 22].

2.3 Material synthesis

A mixture of dimethyl succinate (9.0 g, 0.09 moles) and aldehydes or ketones were added dropwise to a suspension of hexamethylenetetramine (12.6 g, 0.09 moles). 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% Na_2CO_3. On further acidification, finally it gives acid ester which was again recrystallized with n-hexane/benzene -petroleum ether. Finally, the obtained acid ester was saponified with alcoholic KOH at room temperature for 1 hour followed by acidification and recrystallization which would give a solid crystalline natured diacids (Z)-2-benzylidenesuccinic acid (**2a**), 2-(diphenylmethylene)succinic

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acid (**2b**), 2-(propan-2-ylidene)succinic acid (**2c**),(Z)-2-(1-phenylethylidene)succinic acid (**2d**), (Z)-2-(furan-2-ylmethylene)succinic acid (**2e**) and (Z)-2-ethylidenesuccinic acid (**2f**) . Further these diacids undergo cyclisation in presence of silica and perchloric acid (1:1) to give anhydrides (E)-3-benzylidenedihydrofuran-2,5-dione **(3a)**, (E)-3-(1-phenylethylidene)dihydrofuran-2,5-dione **(3b)** and 3-(propan-2-ylidene) dihydrofuran-2,5-dione **(3c)** , (E)-3-(1-phenylethylidene)dihydrofuran-2,5-dione **(3d)**,(E)-3-(1-(furan-2-yl)ethylidene)dihydrofuran-2,5-dione **(3e)** and(Z)-3-ethylidenedihydrofuran-2,5-dione **(3f).**

2.4 Spectroscopic Analysis of Anhydrides

2.4.1 (E)-3-benzylidenedihydrofuran-2, 5-dione (3a)

R1, R2 = Ph, H (9.54g, 0.09 mole) in Scheme 2 and Table 1, Entry 1.

IR (KBr): 3220, 3165, 1649, 1575, 1524, 1481, 1450, 1396, 1301, 1240, 880, 817, 665, 641, 581 cm^{-1};

1H NMR ***δ***; 7.49 (1H, s, br), 7.58 (1H, J=7.5Hz), 7.510 (1H, d, J=8.6 Hz), 7.290 (1H, s, br), 7.24 (1H, s, J=2.5 Hz) ***δ***;7.55, (1H, s, J= 5Hz) ***δ***; 3.40 (s, 2H, $-CH_2$, J= 6Hz); melting point 285°C **(Table 1)**.

2.4.2 (E)-3-(1-phenylethylidene) dihydrofuran-2,5-dione (3b)

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

IR (KBr): 3240, 3180, 3104, 2093, 2951, 1670, 3020, 2895, 1560,890, 648 cm^{-1}1H NMR, ***δ***; 7.44(1H, s, br, J=7.5Hz), 7.41(1H, s, br J=8.5Hz), 7.410(1H, s, J=6.5Hz), 7.40(1H, s, J=7.2Hz), 7.33(1H, s, J=6.5Hz), 7.654(1H, s, J=8.5Hz), 7.69(1H, s, J=8.1Hz), 7.45(1H, s, J=7.10Hz), 7.36(1H, s, J=9.5Hz), 7.89 (s, 1H, -CH, J=7.4Hz); ***δ***; 2.84 (s, 2H, d, $-CH_2$, J=8.6 Hz); melting point 206°C**(Table 1)**.

2.4.3 3-(propan-2-ylidene) dihydrofuran-2, 5-dione (3c)

R1, R2 = Me, Me (5.22 g, 0.09mol) in Scheme 2 and Table 1, Entry 3.

IR (KBr): 3202, 2980, 3060, 3190, 1708, 1568, 1023, 985, 934, 824, 728cm^{-1}1H NMR, ***δ***; 2.16 (3H, s, $-CH_3$, J=2.5Hz), 2.37 (3H, s, $-CH_3$, J=8.2Hz), 2.56 (2H, s, $-CH_2$, J=6.4Hz); melting point 214°C(**Table 1**).

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

R1, R2 = Ph, Me (10.813 g, 0.09 mol) in Scheme 2 and Table 1, Entry 4.

IR (KBr): 3172, 2984, 3190, 1778, 1598, 1724 , 552 cm^{-1}

1H NMR, ***δ***; 2.985 (3H, s, $-CH_3$, J=6.7Hz), 3.418 (2H, s, $-CH_2$, J=7.4Hz), 6.480(1H, J=7.5Hz), 6.702(1H, J=7.1Hz), 7.00(1H, J=8.5Hz), 7.20(1H, J=7.0Hz), 7.42(1H, J=8.6Hz), melting point 302°C (**Table 1**).

2.4.5 (E)-3-(1-(furan-2-yl)ethylidene)dihydrofuran-2,5-dione (3e)

R1, R2 = C4H4O, Me (9.90 g, 0.09mol)in Scheme 2 and Table 1, Entry 5.

IR (KBr): 3052, 2970, 2715, 1708, 1524, 1420, 1385 cm^{-1}

1H NMR, ***δ***; 2.635 (3H, s, $-CH_3$, J=6.2Hz), 2.914 (2H, s, $-CH_2$, J=8.4Hz); 7.789(1H, s, br, J=7.5Hz), 7.254(1H, s, br, J=9.5Hz), 6.451 (1H, s, br, J=4.4Hz), melting point 324°C (**Table 1**).

2.4.6 (Z)-3-ethylidenedihydrofuran-2, 5-dione (3f)

R1, R2 = Me, H (3.96 g, 0.09mol) in Scheme 2 and Table 1, Entry 6.

IR (KBr): 2864, 2801, 2795, 2064, 2648, 2358, 1589, 1426, 1380, 1458 cm^{-1}1H NMR, ***δ***; 2.684(3H, s, $-CH_3$, J=6.8Hz), 2.421 (2H, s, $-CH_2$, J=9.4Hz); 6.454 (1H, s, J=6.5Hz) melting point 294°C (**Table 1**).

2.5 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 µL of DPPH (150 μM prepared in 80% methanol) was mixed with 1µg (22 µL) of synthesized compound.Blank test and, vehicle control were prepared with equal amount of carrier solvent. Different concentrations (0.2µg, 0.4 µg, 0.6 µg, 0.8 µg, 1.0 µg, 1.25 µg and 2.5 µg) 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).

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Percent antioxidant activity were calculated by using following formula,

[(Vehicle control – Test)/Vehicle control] X 100

3. Results and Discussions:

In this research article, Itaconic acids were prepared via Stobbe condensation using hexamethylenetetramine through green context. Further these diacids undergo cyclisation in presence of silica and perchloric acid (1:1) to give anhydrides.Stobbe condensation generally involves use of metal alkoxideas a catalyst in refluxing alcohol, particularly, butanol[23]. Alkoxides are oncogenes and can cause cancer if exposed to body parts. On the other hand, use of butanol is discarded and instead of that, in this research paper hexamethylenetetramine was taken for the reaction. The advantages are short reaction time, good yield, less by-products. Itaconates (**3a**, **3b**, **3c, 3d, 3e, 3f**) synthesized using current method is of high purity compared with classical synthesis. The synthesized Itaconates have specific melting and boiling temperature with precise NMR peak values. In previous synthetic methods, tremendous heat was used, which leads impure diacids with less percentage yield [24]. The bluish colored crystalline solid natured diacids prepared by using benzaldehyde which on cyclisation gives anhydride **(3a)** exhibited a molecular formula $C_{11}H_8O_3$ showed characteristic stretching frequencies of C=O (1700 cm^{-1}), aromatic -CH (3030 cm^{-1}), C=C (1500 cm^{-1}), aromatic -CH (3000 cm^{-1}) (**Figure 1**). Similarly, ^{1}H NMR spectrum also showed five –CH groups on δ; 7.49, 7.58, 7.51, 7.29, 7.24 (s, 5H, -CH), and one –H on ***δ***; 7.55, (s, 1H, -H). Also it shows two -CH_2 groups on; 3.40 (s, 2H, -CH_2) (**Figure 2**).The bluish green colored crystalline solid natured diacids prepared by using benzophenone which on cyclisation gives anhydride (**3b**) having molecular formula $C_{17}H_{12}O_3$ also showed characteristic stretching frequencies of C=O (1670 cm^{-1}), aromatic C-H (3240-3180 cm^{-1}), C=C (1560 cm^{-1}), aromatic -CH (3020-2895 cm^{-1}) (**Figure 1**). Similarly, ^{1}H NMR spectrum also showed one –CH_2 group on ***δ***; 2.84 (s, 2H, -CH_2) and other aromatic hydrogen's on the corresponding peak values ***δ***; 7.44, 7.41, 7.41, 7.40, 7.33, 7.654, 7.69, 7.45, 7.36, 7.89 (s, 10H, -CH) (**Figure 2**). The obtained peak values were sharp and accurate for their corresponding groups which proved the dominancy of green approach on classical method. Likewise pale yellow colored crystalline solid natured diacids prepared by using acetone which on cyclisation gives anhydride (**3c**) having molecular formula $C_7H_8C_3$ also showed characteristic stretching frequencies, anhydride C=O (1708 cm^{-1}), -CH_3 (3202-2980 cm^{-1}), -CH_3 (3060-3190 cm^{-1}) -CH (3202 cm^{-1}), C=C (1568 cm^{-1}) (**Figure 1**). ^{1}H NMR spectrum also showed required peak values for two-CH_3 groups ***δ***; 2.16 (s, 3H, -CH_3); ***δ*** 2.37 (s, 3H, -CH_3) and it shows one peak for -CH_2 group 2.56 (s, 2H, -CH_2) (**Figure 2**).The pale yellow colored crystalline solid natured diacids prepared by using acetophenonewhich on cyclisation gives anhydride (**3d**) having molecular formula $C_{12}H_{10}O_3$ also showed characteristic stretching frequencies of anhydride C=O (1708 cm^{-1}), -CH_3 (3202-2980 cm^{-1}), aromatic -CH (3060-3190 cm^{-1}), aromatic C=C (1598-1724 cm^{-1}) (**Figure 1**). Similarly, ^{1}H NMR spectrum also showed ***δ***; 2.985 (s, 3H, -CH_3); ***δ*** 3.418 (s, 2H, -CH_2); 6.480, 6.702, 7.00, 7.20, 7.42(s, -CH) (**Figure 2**). The pale yellow-orange colored crystalline solid natured diacids prepared by using 1-(furan-2-yl)ethanonewhich on cyclisation gives anhydride (**3e**) having molecular formula $C_{10}H_8O_4$ also showed characteristic stretching frequencies of anhydride C=O (1728-1720 cm^{-1}), -CH_3 (3052-2970 cm^{-1}), aromatic C=C (1385-1524 cm^{-1}) (**Figure 1**). Similarly, ^{1}H NMR spectrum also showed***δ***; 2.635 (s, 3H, -CH_3); ***δ*** 2.914 (s, 2H, -CH_2); 7.789, 7.254, 6.451 (s, 3H,-CH) (**Figure 2**). The pale yellow colored crystalline solid natured diacids prepared by using acetaldehyde which on cyclisation gives anhydride (**3f**) having molecular formula $C_6H_6O_3$ also showed characteristic stretching frequencies of anhydride C=O (1589 cm^{-1}), aliphatic alkane C-H (1426-1380 cm^{-1}), -CH_3 (2864-2795 cm^{-1}), C=C (1458cm^{-1}) (**Figure 1**). Similarly, ^{1}H NMR spectrum also showed ***δ***; 2.684(s, 3H, -CH_3); ***δ*** 2.421 (s, 2H, -CH_2); 6.454 (s, H) (**Figure 2**).Antioxidant potential of a chemical entity having biological importance, as origin of most chronic disease is oxidative stress [25]. 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

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synthesized Itaconates 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 5**, showed the antioxidant potentials of 1 µg/mL of Itaconate in terms of ascorbic acid (µg) equivalent. Highest ascorbic acid equivalent (9.31 µg) were recorded by (E)-3-(1-(furan-2-yl)ethylidene)dihydrofuran-2,5-dione **(3e)** may be due to presence of 1-(furan-2-yl)ethanone group. Itaconate**(3a)**, **(3b)**, (**3d)** had ascorbic acid equivalent 9.29 µg, 8.18 µg and 9. 05 µg respectively for each µg of compound. All these compounds are having a bulkier aromatic ring which increases the antioxidant nature. Similarly Itaconate**(3c)** and **(3f)** have antioxidant potentials 3.67 µg and 7.09 µg respectively. 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 [26].The therapeutic efficiency of presently synthesized Itaconates in different *in vitro*models is our future strategy to evaluate their potency as lead compounds.

4. Conclusion:

The greener chemical reaction strategy managed to synthesize Itaconic acids (diacids) (**2a**, **2b**, **2c, 2d, 2e, 2f**)successfully by simple and efficient means with improved yield. Solvent free Stobbe condensation of aromatic aldehydes and aliphatic, aromatic ketones with dimethyl succinate at room temperature occurred smoothly to give substituted acid ester which on further saponification gives diacid [27]. These diacids undergo cyclisation in presence of silica and perchloric acid to give anhydrides (**3**).This methodology brought down not only the reaction time but also the uses of hazardous organic solvents (as possible) [28]. The prepared anhydrides (**3a, 3b, 3c, 3d, 3e, 3f)** 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 Itaconates may lead to identification of novel compounds to study in the area of pharmaceuticals.

Figure Legends:

Structural determination of Itaconates(3a, 3b, 3c, 3d, 3e, 3f) 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.

Figure 1:IR graphical representation of anhydrides

Figure 2: NMR graphical representation of anhydrides

Figure 3: MASS graphical representation of anhydrides

Figure 4: Antioxidentacvtivity of cyclized products (Itaconates)

Figure 5:Reaction Schemes of Experimental Work

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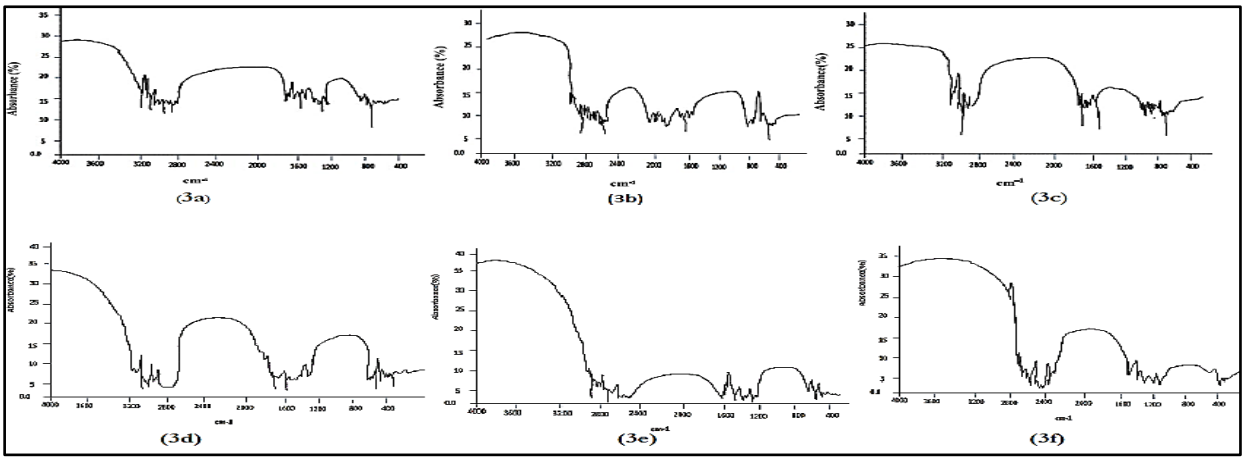

Figure 1: IR graphical representation of anhydrides

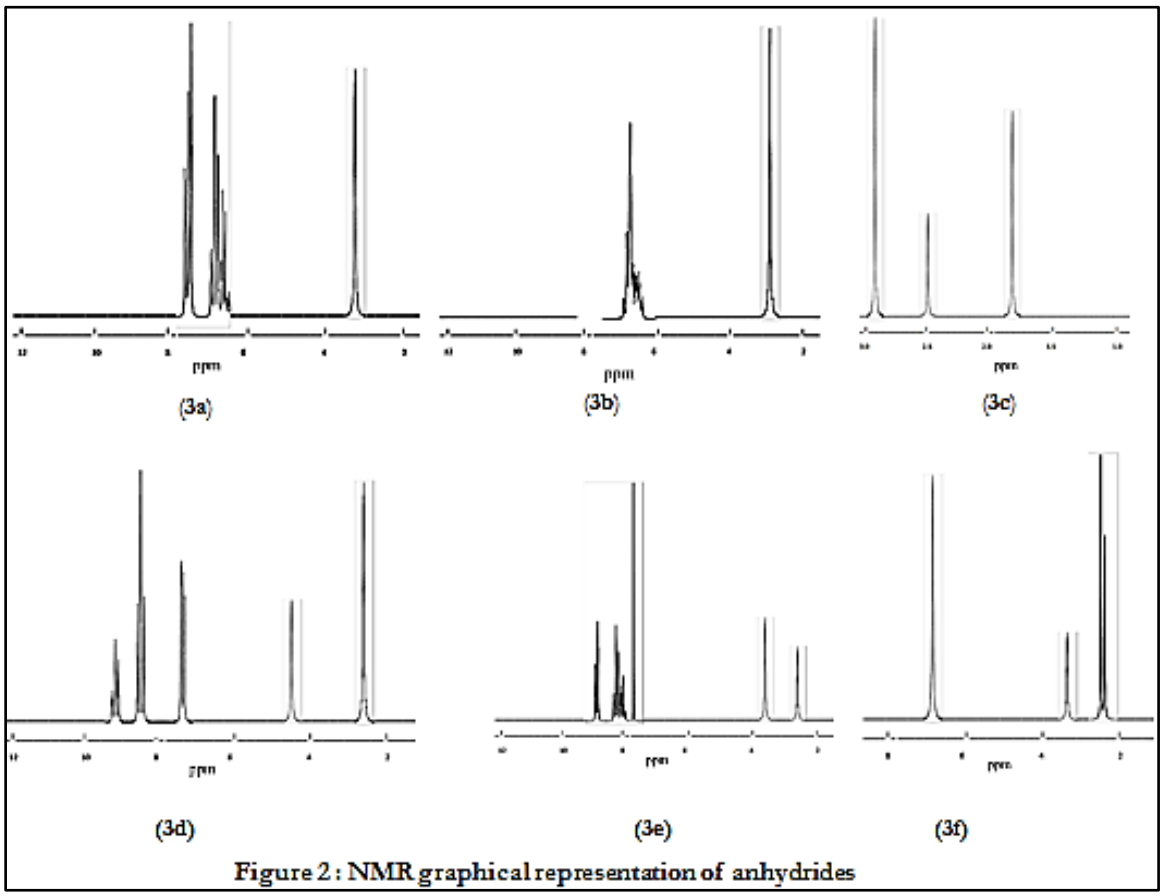

Figure 2: NMR graphical representation of anhydrides

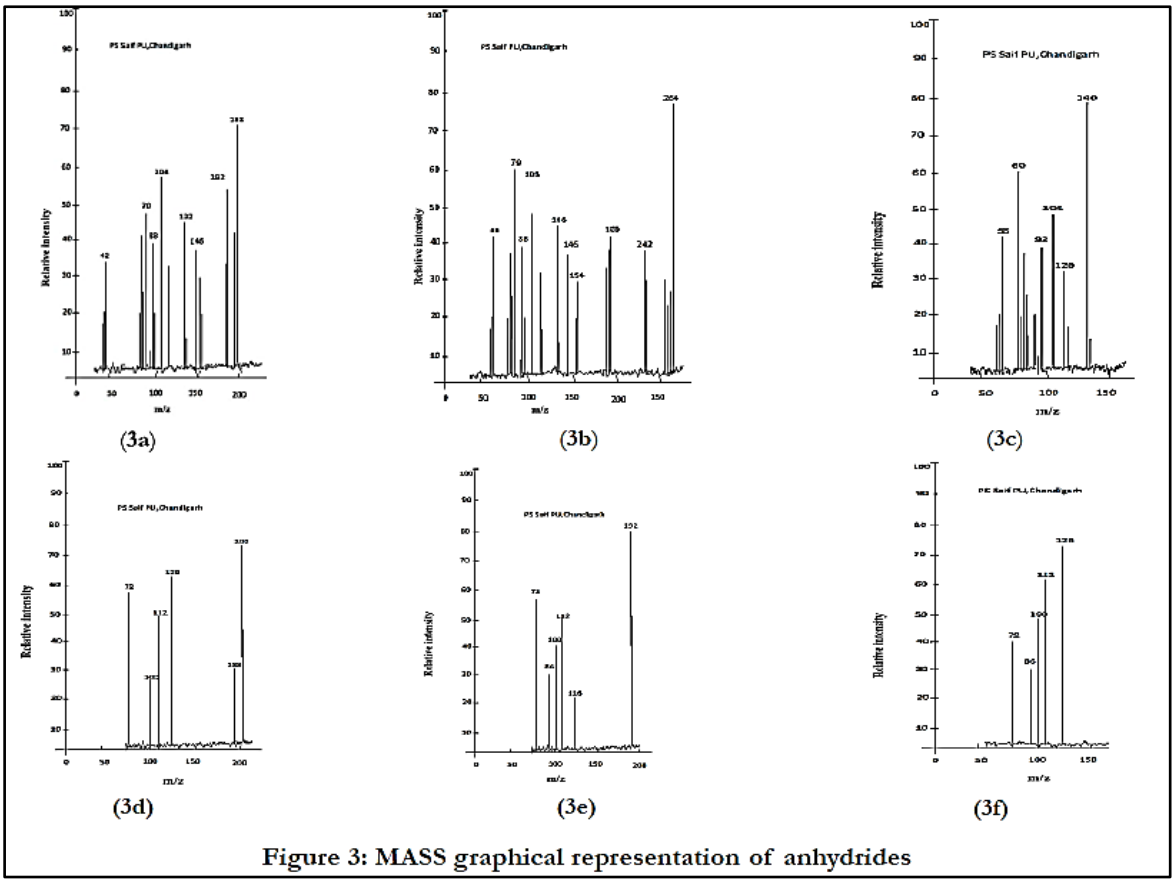

Figure 3: MASS graphical representation of anhydrides

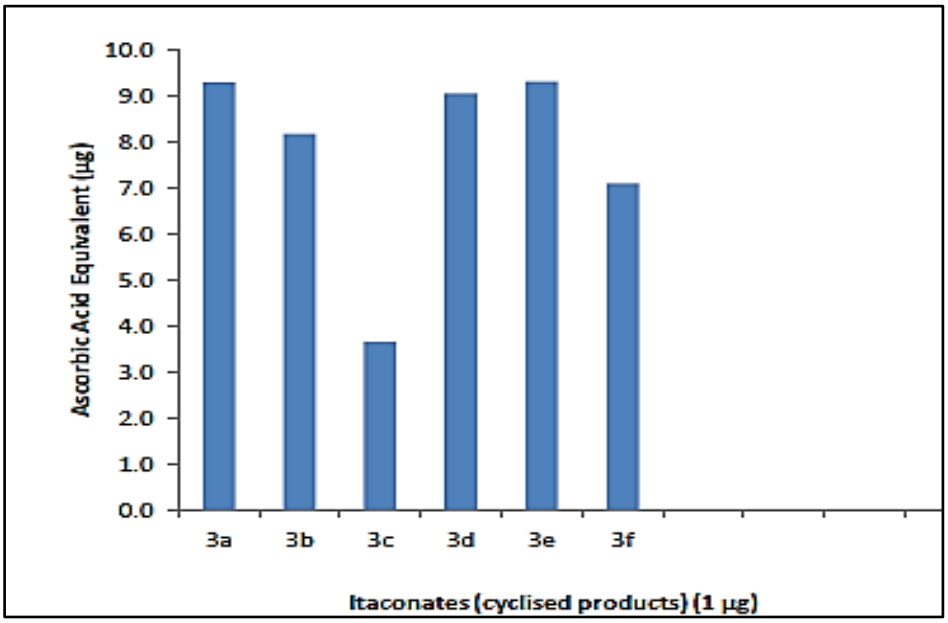

Figure 4: Antioxidentacvtivity of cyclized products (Fulgides)

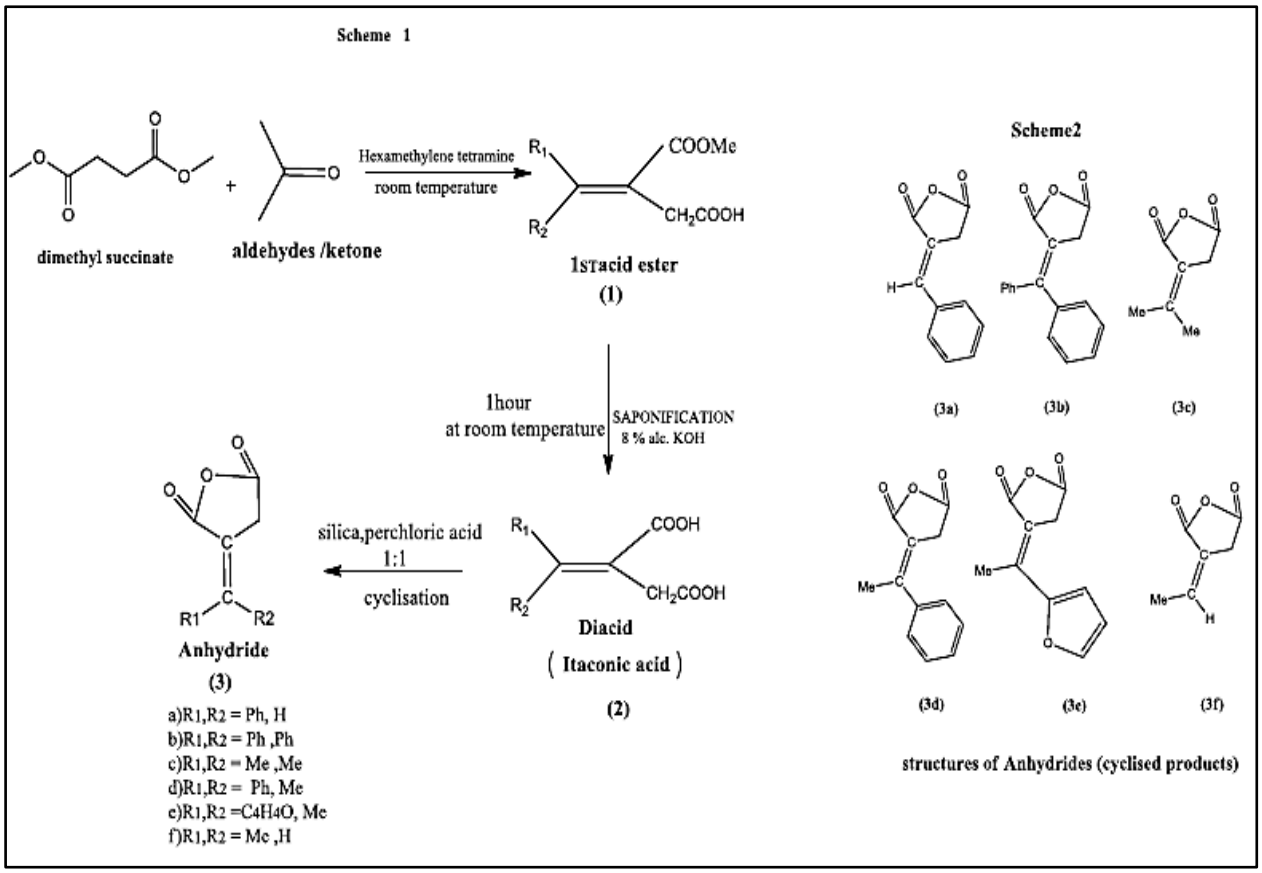

Figure 5: Reaction Schemes of Experimental Work

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