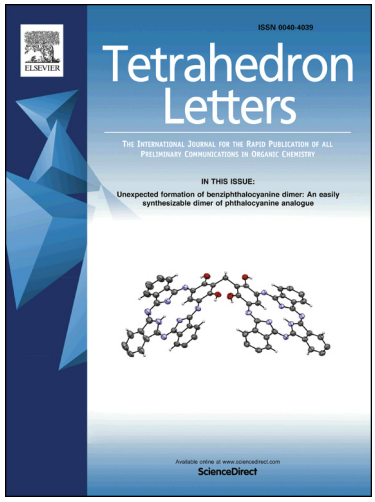

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Graphical Abstract

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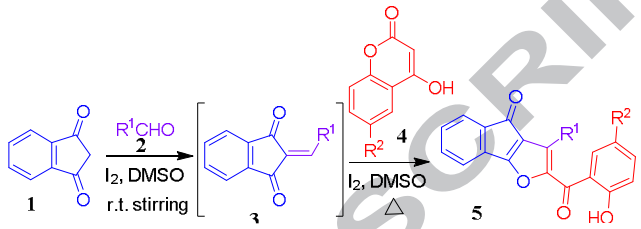

Synthesis of highly functionalized indeno[1,2-*b*]furans

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Abstract- Some novel functionalized indeno[1,2-*b*]furans were synthesized from the reaction of indandione/indanone and aldehydes at room temperature followed by the reaction of the Knoevenagel condendensed intermediate with 4-hydroxycoumarins in the presence of iodine as catalyst in dimethyl sulfoxide (DMSO) under thermal conditions. The reaction involved in a condensation and Michael addition followed by lactone ring opening and intramolecular cyclization process to afford the product in high yield in easy work-up procedure.

Key words: Indandione; Indeno[1,2-*b*]furan; 4-Hydroxycoumarin; Aldehyde; Iodine; Dimethyl sulfoxide.

Indenofurans which exist both as indeno[1,2-*b*]-furans and indeno[1,2-*c*]furans constitute the structural motifs of a large number of biologically relevant compounds of natural as well as synthetic origin. Indeno[1,2-*b*]furans moiety is the basic structure of strigolactones **1** (Fig 1), the family of plant hormones responsible for diverse biological activity such as growth regulation, nodule formation, root architecture and inhibition of shoot branching etc.[1,2] Again, solanacol **2**, which is also a natural strigolactones isolated from the root exudates of tobacco and tomato possess the indeno[1,2-*b*]furan-2-one skeleton.[3] A synthetic analog of this compound GR24 **3** is used as the reference compound in seed germination bioassay of parasitic weeds.[4] In spite of the importance of the indeno[1,2-*b*]furans, only a few methods have been developed for the synthesis of these compound. The

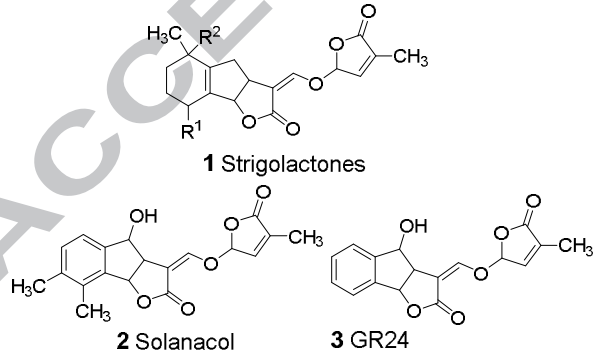

Fig. 1: Natural and synthetic indeno[1,2-b]furan-2-ones

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existing methods include ring-closing metathesis/ atom-transfer ring closure strategy,[5] lactonization of 2-substituted indanone,[6] [2 + 2] cycloaddition-oxidation sequence,[7] cobalt-catalyzed domino reaction between 2-bromoaryl aldehyde and dimethyl itaconate,[8] acid catalyzed double cyclization,[9] intramolecular carboxypalladation of alkynoic acids followed by intramolecular olefin insertion[10] etc. Recently, Gong *et.al.* reported few compounds containing indeno[1,2-*b*]furan moiety along with other furochromenes by using addition-cycloisomerization process.[11] Similarly, Majumder *et.al*. synthesized some dihydroindeno[1,2-*b*]furans utilizing microwave reaction strategy.[12]

Dimethyl sulfxide (DMSO) is not only a nontoxic solvent but also a mild oxidizing agent which is used in various organic transformation reactions *e.g*. Pfitzner-Moffat oxidation, Swern oxidation etc.[13] DMSO in combination with iodine is an efficient system of reagent which is successfully utilized in many important organic reactions.[14]

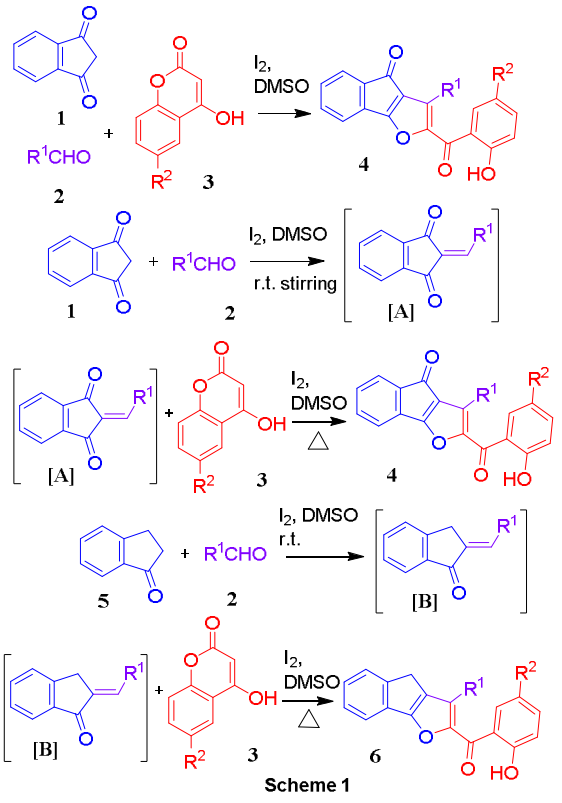
In continuation of our work on the preparation of varied heterocyclic compounds of biological significance,[15] recently we synthesized some furo[3,2-*c*]coumarins from the reaction of 4-hydroxycoumarins and aldehydes.[16] Taking the advantage from the mechanism of that reaction, we have developed an efficient method for the synthesis of some novel and highly functionalized indeno[1,2-*b*]furans **4/6** from the reaction of indandione/indanone **1/5**, aldehydes **2** and 4-hydroxycoumarins **3** in the presence of iodine as catalyst and using DMSO as solvent as well as

oxidizing agent, which is reported in this paper (Scheme 1). The products were isolated through a very simple work-up procedure and filtration process.

At the beginning of the study, we utilized three components *viz* 1,3-indandione **1**, benzaldehyde **2** ($R^1 = C_6H_5$) and 4-hydroxycoumarin **3** ($R^2 = H$) in one-pot reaction protocol in the presence of iodine as catalyst and DMSO as solvent at different temperature (Scheme 1). It was observed that, a new product was formed without the involvement of 4-hydroxycoumarin **3** ($R^2 = H$) when the reaction was performed at room temperature, and the compound was confirmed as the Knoevenagel condensation product **[A]** of 1,3-indandione **1** and benzaldehyde **2** ($R^1 = C_6H_5$). Then the temperature of the reaction was slowly raised, and within 60-90 ^oC a few other compounds formed in addition to the desired product **4** ($R^1 = C_6H_5$, $R^2 = H$). Interestingly, when the three-component reaction was carried out initially at room temperature and then at 90^oC, it produced the desired product **4** ($R^1 = C_6H_5$, $R^2 = H$) in good yield. It could be justified from the study that benzaldehyde **2** ($R^1 = C_6H_5$) reacts with 1,3-indandione **1** at room temperature to give their Knoevenagel condensed products, and in contrary 4-hydroxycoumarin **3** ($R^2 = H$) needs high temperature for the identical condensation process. Therefore, at high temperature, benzaldehyde **2** ($R^1 = C_6H_5$) produced two distinct Knoevenagel condensed products by reacting with 1,3-indandione **1** as well as 4-hydroxycoumarin **3** ($R^2 = H$) respectively. The two compounds so formed reacted further with 4-hydroxycoumarin **3** ($R^2 = H$) leading to the formation of a number of compounds in addition to the desired product **4**. On the other hand, when the reaction was performed initially at room temperature, only the Knoevenagel condensed compound of 1,3-indandione **1** and benzaldehyde **2** ($R^1 = C_6H_5$) was formed which reacted with 4-hydroxycoumarin **3** ($R^2 = H$) at 90 ^oC leading to the formation of the desired indeno[1,2-*b*]furans **4** in good yield. However, the best result was obtained when 1,3-indandione **1** was reacted with benzaldehyde **2** ($R^1 = C_6H_5$) in DMSO in the presence of iodine first to produce the knovenagel condensed product **[A]**, and then added the 4-hydroxycoumarin **3** ($R^2 = H$) to the same pot without isolating the compound **[A]** and refluxed the reaction mixture. It was further confirmed by performing the reaction in two steps. Then, we optimized the load of the catalyst and observed that 10 mol% of iodine is sufficient to afford maximum yield of the product, and further increase or decrease in the load of the catalyst did not improve the yield of the product.

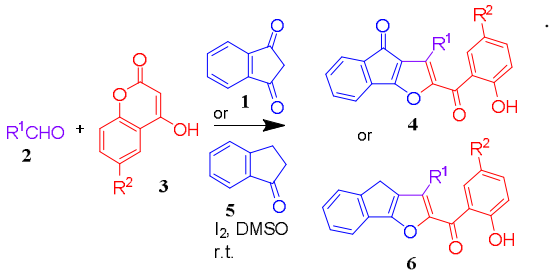
After optimizing the reaction conditions, the standard reaction was carried out[17] by taking equimolar amounts of 1,3-indandione **1** and benzaldehyde **2** ($R^1 = C_6H_5$) using iodine (10 mol%) as catalyst and DMSO as solvent at room temperature under stirring conditions. A solid compound appeared in the reaction mixture. After completion of the reaction (monitored by TLC) equimolar amount of 4-hydroxycoumarin **3** ($R^2 = H$) was added to the same pot and heated at 90^{o}C till the completion of the reaction (monitored by TLC). The mixture was cooled to room temperature and poured into a beaker containing water. The iodine was neutralized with sodium thiosulphate solution. The solid product appeared was isolated by filtration and purified by recrystallization from ethanol which afforded the pure indeno[1,2-*b*]furan derivative **4a** ($R^1 = C_6H_5$, $R^2 = H$) in 82% yield. The structure of the compound was ascertained from the spectroscopic data. The ^1H NMR spectra

Synthesis of indeno[1,2-*b*]furans 4 and 6



Scheme 1

Table 1: Synthesis of indeno[1,2-*b*]furans **4** & **6**



Ent.	R^1	R^2	R.T. (r.t.+ h)	Pd.	Yd.
1	C_6H_5	H	2 + 4	**4a**	82%
2	C_6H_5	Cl	2 + 4	**4b**	84%
3	C_6H_5	Me	2 + 4.5	**4c**	78%
4	*p*-OMe-C_6H_4	H	2 + 6	**4d**	75%
5	*p*-OMe-C_6H_4	Cl	2 + 6	**4e**	76%
6	*p*-OMe-C_6H_4	Me	2 + 6.5	**4f**	72%
7	*p*-NO_2- C_6H_4	H	2 + 3	**4g**	86%
8	*p*-NO_2- C_6H_4	Cl	2 + 3	**4h**	88%
9	*p*-NO_2- C_6H_4	Me	2 + 3	**4i**	83%
10	*p*- Me -C_6H_4	H	2 + 5.5	**4j**	80%
11	*p*- Me -C_6H_4	Cl	2 + 5	**4k**	82%
12	*p*- Me -C_6H_4	Me	2 + 6	**4l**	76%
13	*p*-Cl-C_6H_4	H	2 + 4	**4m**	84%
14	*p*-Cl-C_6H_4	Cl	2 + 3	**4n**	85%
15	*p*-Cl-C_6H_4	Me	2 + 4	**4o**	80%
16	*p*-Br-C_6H_4	H	2 + 4	**4p**	84%
17	*p*-Br-C_6H_4	Cl	2 + 3	**4q**	86%
18	C_6H_5	Cl	2 + 7	**6a**	66%
19	*p*-Cl-C_6H_4	H	2 + 7	**6b**	65%
20	*p*-Me-C_6H_4	H	2 + 8	**6c**	62%

Ent. = Entry, R.T. = Reaction time (r.t. = room temperature, h = heating), Pd. = Product, Yd. = Yield

of the compound showed the presence of the typical hydroxyl proton at δ 5.06 ppm as singlet and the presence of other thirteen aromatic protons at the range of δ 6.89-8.16 ppm. The mass spectrum showed sharp distinguishable peak of compound **4a** at 367.1 $(M + H)^+$. Generality of the reaction was established by synthesizing a series of indeno[1,2-*b*]furan derivatives **4b-q** by utilizing 1,3-indandione **1** with various substituted aryl aldehydes **2** and 4-hydroxycoumarins **3**, and characterizing them (Table 1). The reaction was also studied by utilizing aliphatic aldehyde in the reaction process, but no satisfactory results were obtained under our reaction conditions.

Again, when ketones, *viz* acetophenone was utilized in the reaction process, no reaction occured at room temperature, and at elevated temperature a number of compounds were formed from which we could not isolate any desired product. It is because arylglyoxal formed from acetophenone at high temperature under the reaction conditions[18] might have reacted with 1,3-indandione **1** as well as 4-hydroxycoumarins **3** and prevented the formation of the desired furo[2,3-*d*]pyrimidines. As a result, we restricted our studies to aldehydes only.

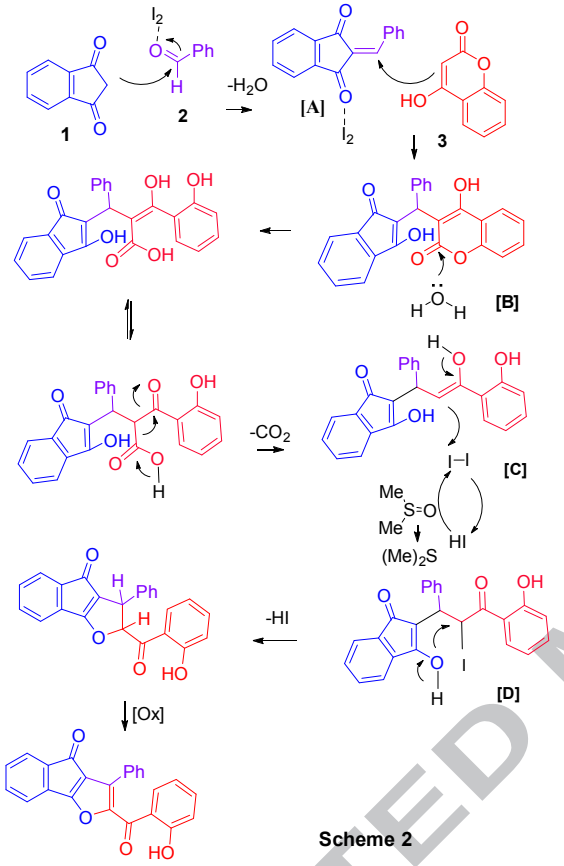
The reaction was also studied by utilizing indan-1-one **5** with aldehydes **2** and 4-hydroxycoumarins **3** in the reaction process (Scheme 1) and found to be comparatively less reactive and took more time to provide lower yield of the product indeno[1,2-*b*]-furans **6** (Table 1).

The effect of substituent on the substrates was also studied carefully, and observed that aldehydes and coumarins with electron withdrawing substituent in the aromatic ring were more reactive than the electron donating substituent and provided better yield of the products.

A plausible mechanism of the reaction is outlined in the scheme 2 taking the formation of product **4a** as example. First, 1,3-indandione **1** reacted with benzaldehyde **2** (R^1 = Ph) in the presence of iodine as catalyst to produce the intermediate **[A]**. The intermediate **[A]** was then attacked by the 4-hydroxycoumarin **3** (R^2 = H) to afford the intermediate **[B]** which undergoes a lactone ring opening[19] and decarboxylation process in the presence of iodine to produce the intermediate **[C]**. Subsequently, the intermediate **[C]** produced the iodinated compound **[D]** which after intramolecular cyclization with the elimination of hydrogen iodide followed by oxidation produced the aromatized indeno[1,2-*b*]furans **4a**, and there are precedence of such transformations.[20] But in the present reaction protocol, DMSO oxidized iodide to iodine and recycles it in the reaction process. So, besides being

solvent DMSO also acts as oxidizing agent in the reaction process to produce the desired indeno[1,2-*b*]furans compound.

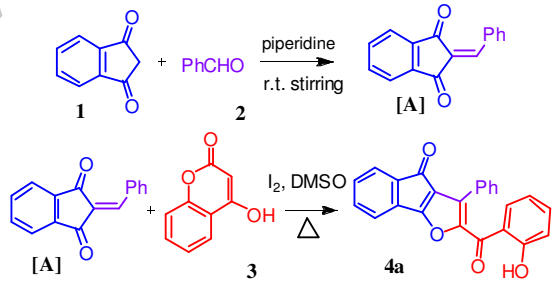
Mechanism of the formation of indeno[1,2-*b*]furans 4a



Scheme 2

The mechanism was further established by performing the reaction in two steps. Accordingly, first, the intermediate **[A]** was synthesized from the reaction of 1,3-indandione **1** and benzaldehyde **2** (R^1 = Ph) in the presence of iodine as catalyst using DMSO as solvent at room temperature under stirring conditions. The product, which appeared in solid form was isolated by filtration and found to be comparable in all respect with the authentic sample.[21] The intermediate **[A]** so obtained was then reacted with equimolar amounts of 4-hydroxycoumarin **3** (R^2 = H) in the presence of iodine as catalyst using DMSO as solvent under refluxing conditions which afforded the desired product **4a**. The intermediate **[A]** could also be prepared in a short time using piperidine as catalyst in ethanol which on treatment with 4-hydroxycoumarin **3** (R^2 = H) in the presence of iodine in DMSO produced the product **4a**.

Stepwise synthesis of indeno[1,2-*b*]furans 4a



In conclusion, we have synthesized some new functionalized indeno[1,2-*b*]furans in an one-pot reaction protocol using indandione/indanone, aldehydes and 4-hydroxycoumarins in the presence of iodine as catalyst in dimethyl sulfoxide (DMSO). A suitable mechanism is given for the formation of the product which was further established by performing the reaction in two different steps. This methodology which can be further explored towards the synthesis of diverse furan fused compounds is a valuable addition to chemistry of indeno[1,2-*b*]furans in particular and heterocyclic compounds as a whole.

Acknowledgement:

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17. **General Procedure for preparation of indeno[1,2-*b*]furans**: A mixture of 1,3-Indandione **1** (146 mg, 1 mmol), benzaldehyde **2** ($R^1 = C_6H_5$, 106 mg, 1 mmol) and I_2 (10 mol%) were taken in round bottomed flask containing 5 mL of DMSO and it was stirred at room temperature for 2 h. Then, added equimolar amount of 4-hydroxycoumarin **3** (R^2 = H, 162 mg, 1 mmol) into the reaction mixture and heated at 90 ˚C for 4 h (till completion of the reaction monitored by Thin Layer Chromatography). After completion of the reaction, the mixture was cooled to room temperature and poured into a beaker containing 25 mL water. Then, aqueous solution of sodium thiosulphate (5 ml of 5% solution) was added to the reaction mixture to neutralise the iodine. The crude product **4a** was obtained by filtration and purified by recrystallization from ethanol that afforded the pure indeno [1,2-*b*] furan in 82% yield. The structure of the compound was ascertained from the spectroscopic data and elemental analysis.
Yield: 300 mg (82%); Light yellow solid; Rf (Pet. Ether.60-80/EtOAc, 7:3) 0.65; mp. 274.2-276.2˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.7 Hz, 1H), 7.96 (td, *J* = 7.6, 1.0 Hz, 1H), 7.87 (td, *J* = 7.6, 1.0 Hz, 1H), 7.81 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.49 – 7.45 (m, 1H), 7.40 – 7.35 (m, 1H), 7.23 – 7.14 (m, 3H), 6.89 (d, *J* = 7.0 Hz, 2H), 5.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 92.1, 102.7, 111.7, 116.9, 123.2, 123.8, 124.2 (2C), 124.5, 128.4 (2C), 128.5 (2C), 132.7, 133.2 (2C), 136.7, 137.2, 140.0, 141.6, 155.3, 158.6, 167.9, 193.2; IR (KBr, cm^{-1}) ν_{max}:1176.8 ,1578.5, 1681.7, 1719.9, 3608.6; MS (ESI): 367.1 $[M+H]^+$; Anal. Cald. for $C_{24}H_{14}O_4$: C, 78.68; H, 3.85; Found: C, 78.66; H, 3.87.
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High Light:

- Demonstrated the utility of iodine with dimethyl sulphoxide as an efficient system of reagent in organic synthesis.
- Some novel functionalized indeno[1,2-*b*]furans were synthesized
- The mechanism was established by isolating the one intermediate and performing the reaction in two steps.
- The methodology has the potentiality to explore in the synthesis of diverse furan annelated heterocyclic compounds.