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Review Article

INDANE-1,3 DIONE AS ANTICOAGULANT AGENTS: A STATE OF REVIEW

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ABSTRACT

1,3-Indanedione is an organic compound is the molecular formula C9H6O2. Chemically, it is β-diketone 1,3-Indanedione, a powerful catalyst, with anticoagulant activity with aromatic core has become prominent in pharmacy during the year, 1,3-Indandione has become an important part of multifaceted reactions in the development of various compounds, , minerals. Anticoagulants, commonly known as anticoagulants, are chemical substances that prevent or reduce blood clotting and prolong the clotting time. Research on the literature revealed that derivatives of indan 1,3 dione, in particular 2-arylsulfonyl indan-1,3 dione, have been found to be potent blood anticoagulants. Previously, they were prepared by sealing Claisen containing diethyl phthalate and arylmethylsulfon by methods analogous to the production of indan-1,3-dione from diethyl phthalate and ethyl acetoacetate. In search of improved oral anticoagulants, 1, 3-dione in a different way involving Knoevenagel reaction between phthalin anhydride and arylsulfonyl acetate. The reaction is based on the observation that phthalin anhydride can act as a carbonyl compound in Perkin-type reactions. This article is a summary of indane 1,3 dione as anticoagulant agents.

Keywords: 1,3-Indanedione, Knoevenagel, Claisen

INTRODUCTION

1,3-Indanedione is an organic compound is an the molecular formula $C_9H_6O_2$.Chemically,it is a β-diketone 1,3-Indanedione, a potent pharmacophore, with an anticoagulant activity with an aromatic nucleus has gained prominence in medicinal chemistry during the years,1,3-Indandione has become a vital component in multi component chemical reactions in developing various drugs, bio conjugates, agrochemicals, etc. The β-dicarbonyl moiety of the Indanedione is established as an important starting material in various organic transformations because of its cost effective, eco-friendliness and operational simplicity, easy to handle, and low toxicity properties and affording higher yields of corresponding products [1]. The last two decades have witnessed profound changes in indane 1,3-diones chemistry in both quality and quantity. Synthesis of compound in a number up to now unexplored fields has been developed. Some old problems have been reconsidered.

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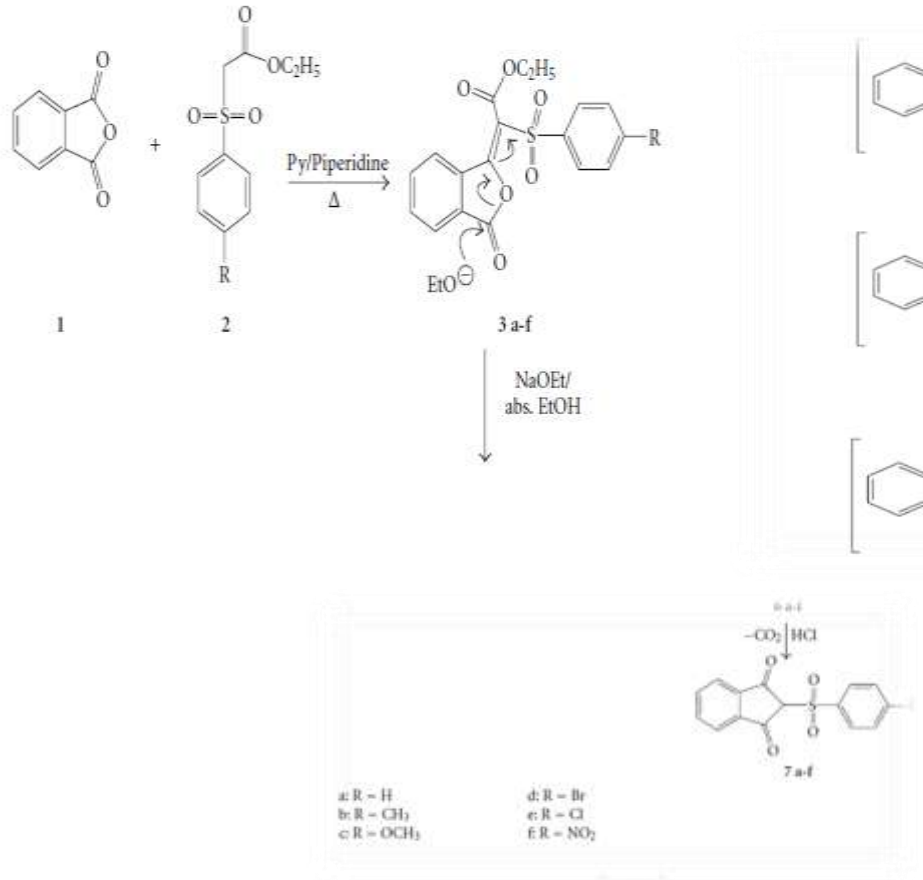
Anticoagulants, commonly known as blood thinners, are chemical substances that prevent or reduce coagulation of blood, prolonging the clotting time [2]. Anticoagulants are closely related to anti platelet drugs and thrombolytic drugs by manipulating the various pathways of blood coagulation [3]. Anticoagulants are medicines that help prevent blood clots. They're given to people at a high risk of getting clots, to reduce their chances of developing serious conditions such as strokes and heart attacks.

A survey of literature revealed that derivatives of indane 1,3 diones particularly 2-aryl sulfonyl indane-1,3-diones have been found to be potent blood

anticoagulants [4]. Earlier,these were prepared by the Claisen condensation involving diethyl phthalate and aryl methyl sulphones [5-6] by a procedure analogous to the preparation of indane-1,3-dione from diethyl phthalate and ethyl acetoacetate [7]. In search of improved oral anticoagulants, synthesized 2(arylsulfonyl) indane-1, 3-diones by a different route involving Knoevenagel reaction between phthalic anhydride and aryl sulfonylacetates. The reaction is based on the observation that phthalic anhydride can function as a carbonyl compound in Perkin-type reactions [8].

Malaichamy Jeyachandran and Penugonda Ramesh find that in an attempt to produce improved analogues of 2- (arylsulfonyl) indan-1,3-diones, the condensation of arylsulfonic acid with phthalic anhydride was attempted under various conditions. Although the reaction with arylsulfonic acid failed, the corresponding arylsulfonylacetates reacted slightly with phthalic anhydride in the presence of pyridine-piperidine medium to give phthalylarylsulfonylacetates 3, which resulted in further reaction with sodium ethoxide in dry ethanol and subsequent heating with 1: 1 HCl 2 - (arylsulfonyl) indan-1,3-dione 7a-f (Scheme 1). The structures of the synthesized compounds 7a-f were determined by IR and NMR spectroscopic data and elemental analysis. Compounds 7a-f was homogeneous by TLC and contained sulfur. The presence of a sulfone group in 7 af was confirmed by IR bands [15] in the regions 1300–1360 cm - 1 (asymmetrical S = O str.) And 1120–1140 cm - 1 (symmetrical S = O str.) As well as by the presence by Detected The intact indan-1,3-dione unit was also confirmed by the IR bands in the 1640–1670cm - 1 region. The 1H NMR spectra of 7 af are very similar and, in addition to complex multiplets, also show aromatic protons in the δ 7.0–7.5 region and a one-proton singlet in the δ 4.0–5.5 region, which corresponds to the lonely methine (H2) can be assigned to the indan-1,3-dione unit; The exact chemical shift of H-2 is influenced by the nature of the substituents on the arylsulfonyl group and the degree of enolization of the indan-1,3-dione unit [9].



Examination of the results of the antibacterial activity of 7 af revealed that bulky nuclear substituents at the 4-position of the benzenesulfonyl unit decrease the antibacterial activity, especially against gram-positive bacteria (S. aureus), an empirically inverse relationship between the activity and the size of the nuclear substituents. The observed decreasing order of antibacterial activity of 7a-f against gram positive bacteria, 7c (R = OMe, Es = - 0.55)> 7e (R = Cl, Es = - 0.97) = 7d (R = Br, Es = - 1.16)> 7b (R = Me, Es = -

1.24) ≈7f (R = NO2, Es = - 2.52) reflected an empirically inverse correlation between Taft's acidity and steric factor (Es), which is a measure for [20] the steric mass of the substituents and the bulky substituents have larger negative values for Es. An analysis of the results of the anticoagulant activity of 7 a-f (Table 3) showed that an opposite trend was observed in this case, ie there is a direct correlation is exist between the anticoagulant activity and the size of the core substituents. Thus the observed increasing order of anticoagulant activity is 7f (R = NO 2, Es = - 2.52) = 7d (R = Br, Es = - 1.16)> 7b (R = Me, Es = - 1.24) > 7e (R = Cl, Es = - 0.97) ≈7c (R = OMe, Es = - 0.55) reflected a direct correlation between the anticoagulant activity and the steric taffeta factor (Es). These conflicting results underline that bulky groups reduce the activity of the compound by preventing it from fitting properly into the receptor binding site. On the other hand, bulky substituents can also increase activity by forcing a compound to adopt the required active conformation at the binding site [9].

Jubie .s et al. Performed a study using the substitutions indan-1,3-dione-bis-hydrazone, 2a-indan-1,3-dione-bis-phenylhydrazone, 2b-indan-1,3-dione-bis-4-nitrophenylhydrazone and 2c -Indane-1,3-dione-bis-2 by 4-dinitrophenylhydrazone, 2d-indane-1,3-dione-bis-semicarbazone, 2e-indane-1,3-dione-bis-thiosemi-carbazone, 2f-indane -1,3-dion-to-isonicotinic acid hydrazine

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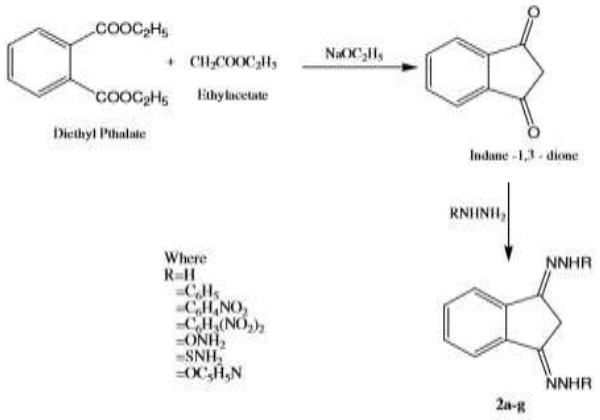


Scheme I

Table I — Physical properties of compounds **2a-g**

Compd	R	m.p. (°C)	Yield (%)	R_f value
2a	-H	185	68.59	0.69
2b	$-C_6H_5$	165	73.52	0.76
2c	$-C_6H_4NO_2$	195	76.81	0.86
2d	$-C_6H_4(NO_2)_2$	200	75.1	0.92
2e	$-CONH_2$	275	76.8	0.65
2f	$-CSNH_2$	220	68.4	0.44
2g	$-COC_5H_5N$	260	72.22	0.46

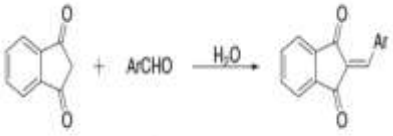
Solvent system for TLC – Benzene:Chloroform:Methanol (50:30:20)

From this it is concluded that the method used is essentially that described by Miller. Blood samples were collected ,from albino rats. The synthesized compounds 2a-g and sodium citrate added to the blood. The clotting time is measured. The anticoagulant activity increased [10].

Peng hui yang et al. Upon examining the chemistry of 2-arylidene-indane-1,3-diones, it was found that in the absence of a catalyst, 4-hydroxylbenzaldehyde readily condensed with indane-1,3-dione in water to give 2- (4-). Hydroxybenzylidene) indan-1,3-dione occasionally in high yield. We thought it might be a new general method for the synthesis of 2-arylidenindane-1,3-diones. As far as is known, there are no reports of the synthesis of 2-arylidenindane-1,3-diones in water at ambient temperature under catalyst-free conditions. First, we compared the method with traditional methods in organic solvents. Thus, the same reaction was carried out using 4-hydroxybenzaldehyde and indan1,3-dione as starting materials in different solvents in the presence or absence of a catalyst. The results are shown in Table 1. From Table 1 it can be seen that the clean synthesis of 2- (4-hydroxybenzylidene) indan-1,3-dione in water is more efficient than the conventional processes and products with high yield. The efficiency of the process could be attributed to the forced hydrophobic interaction between the substrates. In order to investigate the generality of this process, the reactions of various aromatic aldehydes

with indan1,3-dione were carried out in water. The results are shown in Table 2. Table 2 shows that simple aromatic aldehydes easily condense with indan-1,3-dione in water to give 2-arylidene-indan-1,3-diones. However, the substitution pattern had a major impact on the response. The reaction with aromatic aldehydes bearing electron-withdrawing groups usually went well and gave almost quantitative yields; those carrying electron-donating groups such as methoxy groups gave relatively poorer yields. Note that the reaction with hydroxyl aromatic aldehydes usually gave products in high yield. The given reaction mechanism is shown in Scheme 2. Water facilitated the deprotonation of indan-1,3-dione to form indan-1,3-dione carbanion. The latter attacked the carbonyl group of the aromatic aldehydes and were then dehydrated to give the 2-arylidenindane-1,3-diones.

Scheme 1 Synthesis of 2-arylideneindan-1,3-diones



1 2 3

Ar = 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 4-ClC_6H_4, 4-HOC_6H_4, 2-HOC_6H_4, 3-HOC_6H_4, 3,4-$(HO)_2C_6H_3$, 4-$CH_3OC_6H_4$, etc.

Table 1 Comparison of different methods

Product	Solvent	Catalyst	Reaction condition	Yield (%)
3d	H_2O	None	r.t. 14 h, 80 °C 3 h	85.2
3d	EtOH	Morpholine	Reflux 12 h	23.2
3d	Toluene	PTSA	Reflux 20 h	83.2

Table 2 Synthesis of arylideneindan-1,3-diones in water

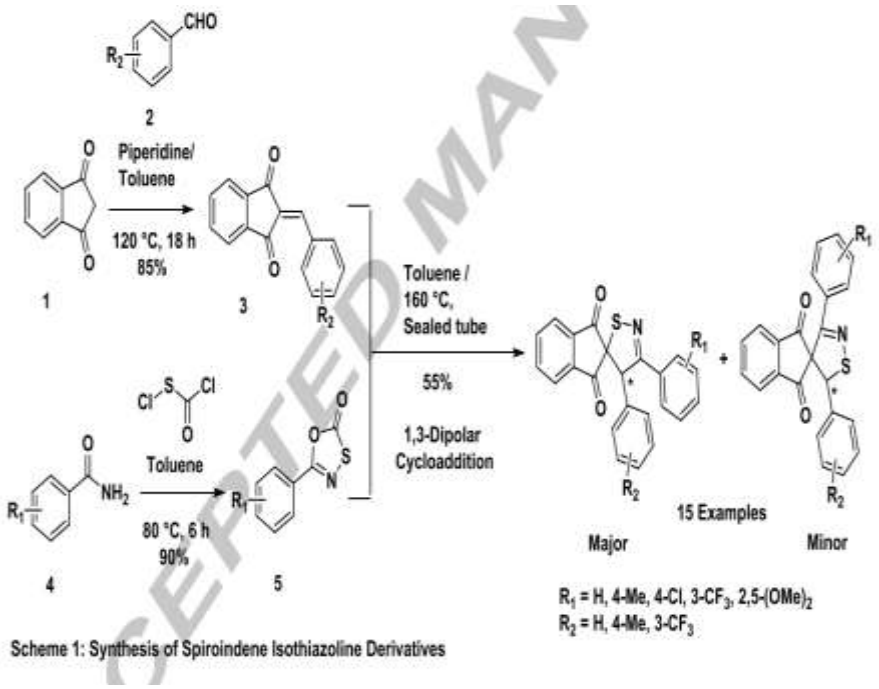
Entry	Ar	Product	Yield (%)
1	4-$NO_2C_6H_4$	**3a**	97.5
2	2-$NO_2C_6H_4$	**3b**	92.5
3	4-ClC_6H_4	**3c**	95.5
4	4-HOC_6H_4	**3d**	85.2
5	2-HOC_6H_4	**3e**	94.4
6	3-HOC_6H_4	**3f**	96.0
7	3,4-$(HO)_2C_6H_3$	**3g**	88.7
8	4-$CH_3OC_6H_4$	**3h**	66.7
9	2-furyl	**3i**	85.3[a]

[a] Stirred at r.t. for 14 h, then at 60 °C for 4 h

In summary, we have developed a new process for the preparation of 2-arylidenindane-1,3-diones in water at ambient temperature without the addition of a catalyst. The process is simple, efficient and environmentally friendly [11].

Aitha A et al. Investigated that they were previously successfully prepared a 1,2,4-thiadiazole ring system in our laboratory by treating substituted 5-phenyl-1,3,4-oxathiazol-2-one with p-toluenesulfonyl cyanide via 1,3-dipolar cycloaddition reaction. 12 In this work, we used the same substituted 5-phenyl-1,3,4-oxathiazol-2-one that was treated with 2-arylidene-1,3-indanedione to obtain the new chiral spiroinden-1 3 - Dionisothiazoline derivatives according to Michael / 1,3-dipolar [3 + 2] cycloaddition reaction protocol.26 To the best of our knowledge, this is the first example of a Michael / 1,3-dipolar cascade [3+] 2] cycloaddition reaction to obtain spiroindene- 1,3-dionisothiazoline derivatives as two regioisomers. First, the reaction of indan-1,3-dione (1) with aromatic aldehydes (2) in the presence of piperidine as the base in toluene solvent for the synthesis of 2-arylidene-1,3-indanediones (3) was carried out successfully. Although similar condensations with different bases have been reported in the past, we found that in the presence of piperidine as the base, the reaction proceeds easily and in very good yields. The key intermediate 1,3,4-oxathiazol-2-one unit (5) was prepared from compound (4) according to our previously described procedure. The Michael / 1,3-dipolar cycloaddition cascade reaction of 2-arylidene-1,3-indanedione (3) and substituted 5-phenyl-1,3,4-oxathiazol-2-one (5) was examined in toluene solvent at 160 ° C. 180 ° C in sealed tubes and a majority of them are obtained mixtures of two regioisomeric isothiazoline-cyclo-adducts and some of them as individual isomers (Scheme 1). The initial screening of the reaction conditions with and without bases showed that the organic and inorganic bases did not play a major role either for the reactivity or for the ratio of the regioisomer formation. Without base, however, the Michael / alkylation cascade majority products were obtained as a mixture of two regioisomers and a few of them as

individual isomers in moderate to high yields of ~ 50-55%. To get better reaction conditions, we next examined the effects of solvents among the tested solvents toluene, xylene, 1,2-dichlorobenzene, chloroform and dichloromethane. In chloroform and dichloromethane the starting material was as such even after 24 hours of reflux and no reaction occurred. In toluene and xylene, both starting materials consumed at 160-180 oC in the sealed tube and gave similar results. They were found to be the best solvents to give the good yield as a mixture of two regioisomers and individually isomers .With the 1,2-dichlorobenzene as solvent, a somewhat lower yield was observed, but also a similar result ratio. Unexpectedly, the main product is of this reaction was isolated as the main product, which represents the formation of a highly substituted isothiazoline derivative. These two regioisomers had very narrow delay values, and therefore their separation with tetrahedron letters 3 by flash column chromatography was unsuccessful. However, the majority of the regioisomers from their corresponding mixtures were successfully separated by Grace flash column chromatography.26-28 Three of the regioisomers were even separated by Grace- Flash column chromatography separated unsuccessfully due to very narrow delay factor values. The 1,3-dipolar cycloaddition reaction of part of the 2-arylidene-1,3-indanedione (3) reaction with 5-phenyl-1,3,4-oxathiazol-2-one (5) derivatives with dimethoxy substitution compounds gave due to steric effect only individual isomers due to steric effect.

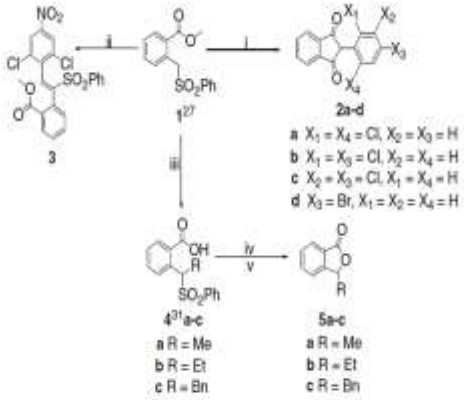


Scheme 1: Synthesis of Spiroindene Isothiazoline Derivatives

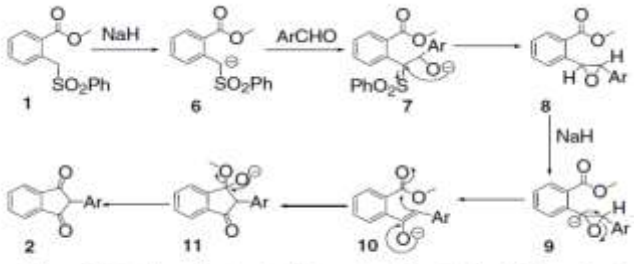
In summary, an efficient approach to the synthesis of chiral spiroindenisothiazoline derivatives as a mixture of two regioisomers in three steps with good yield in toluene as solvent was developed. Although the approach to the formation of chiral spiroindenisothiazoline derivatives was restricted by the use of a 1,3,4-oxathiazol-2-one unit, we report for the first time on the synthesis of chiral spiroindenisothiazoline heterocycles. We have successfully separated the majority from two regioisomers from mixture by Grace column cleaning. One of the regioisomeric compounds 18a was purified by a chiral SFC method and two enantiomers were confirmed. Further applications of this methodology and bioactivity study of these new heterocycles are in progress [12].

B. T. S. Thirumamagal et al. Investigated that sulfone is an important functional group in organic chemistry that has valuable synthetic capabilities. Sulfones, in particular, may require new potential for drug design and medicinal chemistry. Of particular interest are alkyl sulfones, which act as strong analgesics against inflammation. A compelling report on the anti-HIV activity of indolylarylsulfones has also been published. In an effort to continue our research interests in the synthesis of medically important compounds, two new and effective methods for the synthesis of 2-aryl-substituted indan-1,3-dione and alkylated phthalides from easy-to-prepare methyl-o- [a-phenylsulfonyl] developed. Toluate 1 was suggested. Scheme 1 shows the strategies for the synthesis of the compounds of interest. The indandiones 2a - d were prepared by simple condensation of sulfone 127 with the corresponding halobenzaldehydes. The reaction of 1 equivalent of sulfone 1 with 1 equivalent of 2,6-dichlorobenzaldehyde in DMSO in the presence of 5 equivalents of NaH gave

2- (20,60-dichlorophenyl) indan-1,3-dione 2a in 50% yield chromatographic purification (SiO 2) Using hexanes / ethyl acetate (7: 3) as the elution solvent. In the 1H NMR spectrum of indanedione, 2a CH proton appeared as a singlet alongside the aromatic one. In the 13c NMR spectrum of indandione, 2a CH proton appeared alongside the aromatic singlet on protons. In the 13C NMR spectrum CH, aromatic and carbonyl carbons appeared at d 59.1, 123.5, 128.3, 128.4, 130.0, 135.7, 138.1, 141.3 and 196.0, respectively. The molecular ion appeared at m / z 289.7280 with isotope clusters at 291.8120 and 293.8010 in HR-EI-MS. Reactions of sulfone 1 with other halobenzaldehydes, i.e. 2,4-dichlorobenzaldehyde, 3,4-dichlorobenzaldehyde and 4-bromobenzaldehyde gave the indanediones 2b - d under the same reaction conditions. The structures of indandiones 2a - d have been confirmed from spectral data and their melting points are consistent with those described in the literature. The mechanism is given in Scheme 2. In our view, the formation of indandiones 2a - d is probably related to oxirane 8 as a possible intermediate, although no such intermediates have been isolated. Due to its higher carbonyl reactivity, a similar reaction of 2,6-dichloro-4-nitrobenzaldehyde with sulfone 1 in the presence of 1 equivalent of NaH in DMSO gave the regular condensation product 3 in 60% yield after chromatographic purification (SiO 2) using hexanes / ethyl acetate (9: 1) as elution solvent. The reaction was unsuccessful with simple benzaldehyde and veratraldehyde and the starting materials were isolated in 70% yield. For the synthesis of the 3-methylphthalide 5a - c the alkylated sulfones o- [a-phenylsulfonyl] ethylbenzoic acid 4a, o- [a-phenylsulfonyl] propylbenzoic acid 4b and o- [aphenylsulfonyl-b-phenyl] ethylbenzoic acid 4c were used after a previously published one Method manufactured. In addition to the aromatic protons, the 1H-NMR spectrum of the alkylated sulfone 4a showed the CH3 and CH (SO2Ph) protons as doublets and quartets at d 2.2 and d 6.1, respectively. In the 13C NMR spectrum of SO2Ph-CH, methyl and carbonyl carbon appeared at d 58.80, 14.29 and 171.47. The structures of other alkylated sulfones 4b and 4c were thoroughly characterized by spectral and analytical data and then heated with o-phosphoric acid to synthesize 3-alkylphthalides 5a - c under conventional and microwave conditions [13].



Scheme 1. Synthesis of 2-arylindane-1,3-diones (2a-d) and 3-alkylphthalides (5a-c). Reagents and conditions: (i) ArCHO, NaH, DMSO, RT(N2), 24 h 30-50%; (ii) 2,6-dichloro-4-nitrobenzaldehyde, NaH, DMSO, RT(N2), 10 h, 60%; (iii) R-X, NaH, DMSO, RT(N2), 12 h, 60-75%; (iv) H_3PO_4, 140 °C 12 h, 45-50%; (v) H_3PO_4, microwave irradiation, 90 s-1 min, 60-70%



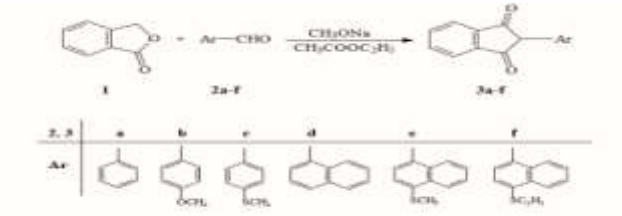
Scheme 2. Plausible mechanism for the formation of 2-arylindane-1,3-diones 2a-d.

Marianne Formiller has investigated that many reports of changes in the activity of anticoagulants by other drugs have appeared in the literature in recent years. As a result, it is possible to summarize information about those drugs that have been clinically shown to affect the activity and effectiveness of the oral coumarin and indione anticoagulants. Although the mechanisms of such reactions are largely hypothetical, these proposed mechanisms can provide information on how the treatment of each patient with anticoagulant drugs is very

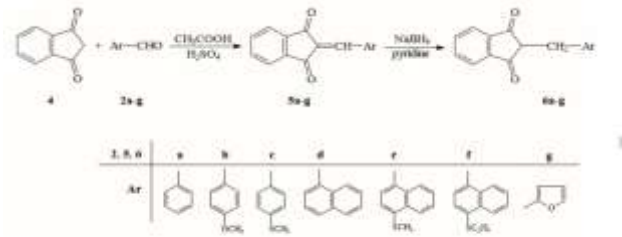
different and the dosage of such drugs can only be determined by regularly monitoring the prothrombin time. The prothrombin time can be changed significantly by endogenous and exogenous factors. This article examines the endogenous and exogenous factors that change the response to anticoagulants, both theoretically and clinically. The pharmacology, use, and side effects of anticoagulants and clotting mechanisms are extensively studied in other literature sources [14].

K. Mitka et al. Investigated the synthesis of 2-arylmethylene indan-1,3-diones (5a-g) using substituents.2-benzylidenindan-1,3-dione (5a),2- (4-methoxybenzylidene) indan-1,3-dione (5b),2- (4-methylsulfanylbenzylidene) indan-1,3-dione (5c)2- (1-naphthylmethylene) indan-1,3-dione (5d),2- [1- (4-methylsulfanyl) naphthylmethylene] indan-1,3-dione (5e),2- [1- (4-ethylsulfanyl) naphthylmethylene] indan-1,3-dione (5f),2- (2-furylmethylene) indan-1,3-dione (5 g) [14].

The reaction of phthalide with suitable aryl aldehydes gave 2-arylindane-1,3-diones (3). 2-Arylmethylene indan-1,3-diones (5) were prepared by condensing indan-1,3-dione with the corresponding aryl aldehydes. Compounds 5 were converted to their methyl analogues 6 by reduction with sodium tetrahydroborate [15].



Scheme 1.



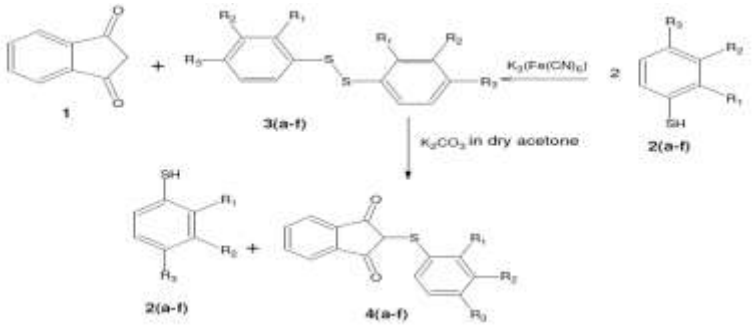
Scheme 2.

2-Arylindan-1,3-diones (3a - f) were prepared by condensing phthalide (1) with suitable aryl aldehydes (2a - f) in the presence of sodium methoxide in ethyl acetate (Scheme 1). With this method, 2-arylindane-1,3-diones (3a, c - f) and the anisindione (3b) approved as an anticoagulant were obtained.12, 13 In order to check the influence of the modification of 2-arylindane-13 1,3 - Diones (3a - f) also had 2-arylmethylene- (5a-g) and 2-arylmethylindan-1,3-diones (6a - g) due to their anticoagulant properties, which received additional methine and methylene units, respectively (Scheme 2). The compounds 5a - g were prepared by condensation of indan-1,3-dione (4) with the corresponding aryl aldehydes 2a - g. The reactions were carried out in glacial acetic acid with the presence of concentrated sulfuric acid, as a catalyst at room temperature. The 2-arylmethylene indan-1,3-diones (5a - g) were prepared in acceptable yields (Scheme 2) .14 All 2-arylmethylene indan-1,3-diones were colored crystalline solids with sharp melting points.

The compounds 5a - g were converted into their saturated analogues 6a - g by reduction of the same with sodium tetrahydroborate in pyridine at 50 ° C (Scheme 2) . It should be noted that the reduction of C = C bonds in 5a - g occurred without affecting the C = O bonds. It is well known that NaBH4 tends to double reduce conjugated CC = O systems. In addition, the product of C = O bond reduction is usually formed in a larger amount even in the case of a single reduction. In our investigations we never isolated products of the C = O bond reduction. The structure of compounds 5a - g and 6a - g was identified by analytical and spectroscopic data. In all 1H NMR spectra of 5a - g, protons of –CH = were in the aromatic region. Unexpectedly, protons of CH - CH2 units as singlets were observed in the 1H NMR spectra of 6a - c as singlets at δ 3.29–3.34 ppm. This phenomenon can be attributed to the structural symmetry of 6a - c. Examination of the heteronuclear 1H-13C correlation spectra from 6a - c revealed cross peaks between protons at two different C atoms. For example, Figure 1 shows the 1H-13C-COZY spectrum of 6b - the proton signal at

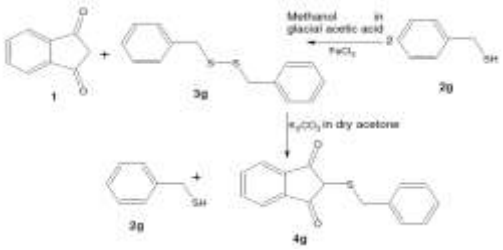
δ 3.29 ppm gives a cross peak with the composite signal of carbons in CH2 (δ 31.42 ppm) and CH (δ 55.26 ppm) , In the 1H NMR spectra of structurally asymmetrical derivatives, 6d-g protons in CH-CH2 units appear in an ABX pattern.

D. Giles et al. Examined that aromatic amines were diazotized and treated with potassium ethyl xanthate, which was prepared by reacting carbon disulfide, ethanol in potassium hydroxide, to give aromatic thiols (2). It was oxidized using potassium ferricyanide in sodium hydroxide to give disulfide (3) in good yield. After treatment with 3 using potassium carbonate in dry acetone, indane-1,3-dione5,6 gave derivatives of indane-1,3-dione (4a-g) substituted dithiodibenzene (3a-f)1,1 '-[dithiobis (methylene)] dibenzene (3 g),2-substituted indan-1,3-dione (4a-g),2 - [(2-methylphenyl) thio] indan-1,3-dione (4a),- [(4-methylphenyl) thio] indan-1,3-dione (4b),2 - [(3-chlorophenyl) thio] indan-1,3-dione (4c),2 - [(4-chlorophenyl) thio] indan-1,3-dione (4d),2 - [(4-methoxyphenyl) thio] indan-1,3-dione (4e),2-(phenylthio) indan-1,3-dione (4f),2- (benzylthio) indan-1,3-dione (4 g)



	R_1	R_2	R_3
a	CH_3	H	H
b	H	H	CH_3
c	H	Cl	H
d	H	H	Cl
e	H	H	OCH_3
f	H	H	H

Scheme 1



Anticoagulant Activity Indan-1,3-dione procedures used primarily as anticoagulant activity and performed for 1,4a-g using the procedure used by Miller7. The time required for clotting was measured under these substitutions of methyl (4a, b), chlorine (4c, d) and hydrogen (4 g) in the thiophenyl group and showed good anticoagulant activity compared to indan-1,3-dione [16].

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Nil

CONFLICT OF INTEREST

Nil

REFERENCE

1. Asadi S and Ziarani GM. The molecular diversity scope of 1,3-indandione in organic synthesis. *Mol Divers*, 20(1), 2016, 111-152.
2. Anticoagulant medicines. *nhs.uk. 2018-02-06*. Retrieved 2020-01-23
3. Warfarin. *Stat Pearls. Stat Pearls Publishing. 2019.*
4. Dieter BH. 2-[p-(Phenylsulfonyl)phenyl]-1,3-indandione and its tautomer," US 3356732, 1967, 3.
5. Gabriel B and O. Katsuyuki O. Ethyl (Phenylsulfonyl)acetate," in Encyclopedia of Reagents for Organic Synthesis. JohnWiley & Sons, Chichester, UK, 12, 2001, 1639,
6. Horst and Heinrich P. 1,3-Indandione derivatives. Ger. Patent DE 2045466, 172, 4.
7. Furniss BS, Hannaford AJ, Rogers V, Smith PWG and Tatchell AR. Vogel's Text Book of Practical Organic Chemistry including Qualatitative Organic Analysis, The English Language Book Society and Longman, London, UK, 4th ed., 1978.
8. Fiesher IL and Fiesher M. Advanced Organic Chemistry, Van Nostrand Reinhold Company, New York, NY, USA, 1961

9. Malaichamy J and Penugonda R. Synthesis, Antimicrobial, and Anticoagulant Activities of 2-(Arylsulfonyl)indane-1,3-diones. *Organic chemistry international*, Article ID 360810, 2011, 5.
10. Jubie S, Meena S, Rameseshu KV, Jawahar N, Vijayakumar. Synthesis and biological evaluation of some hydrazones and carbazones of indane-1,3-dione. *Indian journal of chemistry*, 49B, 2010, 1261-1263
11. Pen HY, Qun ZZ, Wei S. Clean synthesis of 2-arylideneindan-1,3-diones in water. springer link, 38(3–5),2012, 1063–1068.
12. Anjaiah A, Satyanarayana Y, Manoranjan B, Jayashree A. 3,4,Synthesis of spiroindene-1,3-dione isothiazolines via a cascade michael/1,3-dipolar cycloaddition reaction of 1,-oxathiazol-2-one and 2-arylidene-1,3-indandiones. *Tetrahedron Letters*, 58(6), 2017, 578-581.
13. Thirumamagal BTS, Sureshbabu N. Formation of 2-arylindane-1,3-diones and 3-alkylphthalides from methyl *o*-[α-phenylsulfonyl]toluate. Elsevier, 49(3), 512-515.
14. Marianne Formiller, Monte.s.cohol, Coumarin and Indandione Anticoagulants: Potentiators and Antagonists. *American journal of health - system pharmacy*, 26(10), 1969, 574–582
15. Mitka K, Kowalski, Pawelec D, Majka Z. Synthesis of Novel Indane-1,3-dione Derivatives and Their Biological Evaluation as Anticoagulant Agents. *Croatica chemical acta*, 2009, 3, 613-618.
16. (a) Giles D, Prakash MS, Ramaseshu KV. *E-J Chem*, 4, 2007, 428; (b) Robert-Piessard S, Leblois D, Kumar P, Robert JM, Baut GL, Sparfel L. *J. Med. Chem*., 35, 1990, 737; (c) Robert-Piessard S, Leblois D, Courant J, Baut GL, Petit JY. *Ann .Pharm Fr*, 56, 1998, 160; (d) Meena S, Shankar D, Ramaseshu, KV, Giles D, Prakash MS, Venkataraman S. *Indian J. Chem*., 45, 2006, 1572; (e) Giles D, Roopa K, Sheeba FR, Gurubasavarajaswamy PM, Divakar G, Vidhya T. *Eur J. Med. Chem*., 58, 2012, 478; (f) Giles D, Roopa K, Sheeba FR, Venkatesh DP, Gurubasavarajaswamy PM. *J. Pharm. Sci. & Res*., 2011, 3, 1253.