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Research Article

Synthesis, Antimicrobial, and Anticoagulant Activities of 2-(Arylsulfonyl)indane-1,3-diones

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2-(Arylsulfonyl)indane-1,3-diones, earlier synthesized by Claisen condensation involving diethyl phthalate and aryl methyl sulphones, are found to be potent blood anticoagulants. In search of improved analogs of 2-(arylsulfonyl)indane-1,3-dione, we have synthesized them (**7 a-f**) by a different route involving Knoevenagel reaction between phthalic anhydride and arylsulfonylacetates in the presence of pyridine-piperidine medium for the first time. The synthesized 2-(arylsulfonyl)indane-1,3-diones were evaluated for antimicrobial and anticoagulant activities and all of them registered significant activity.

1. Introduction

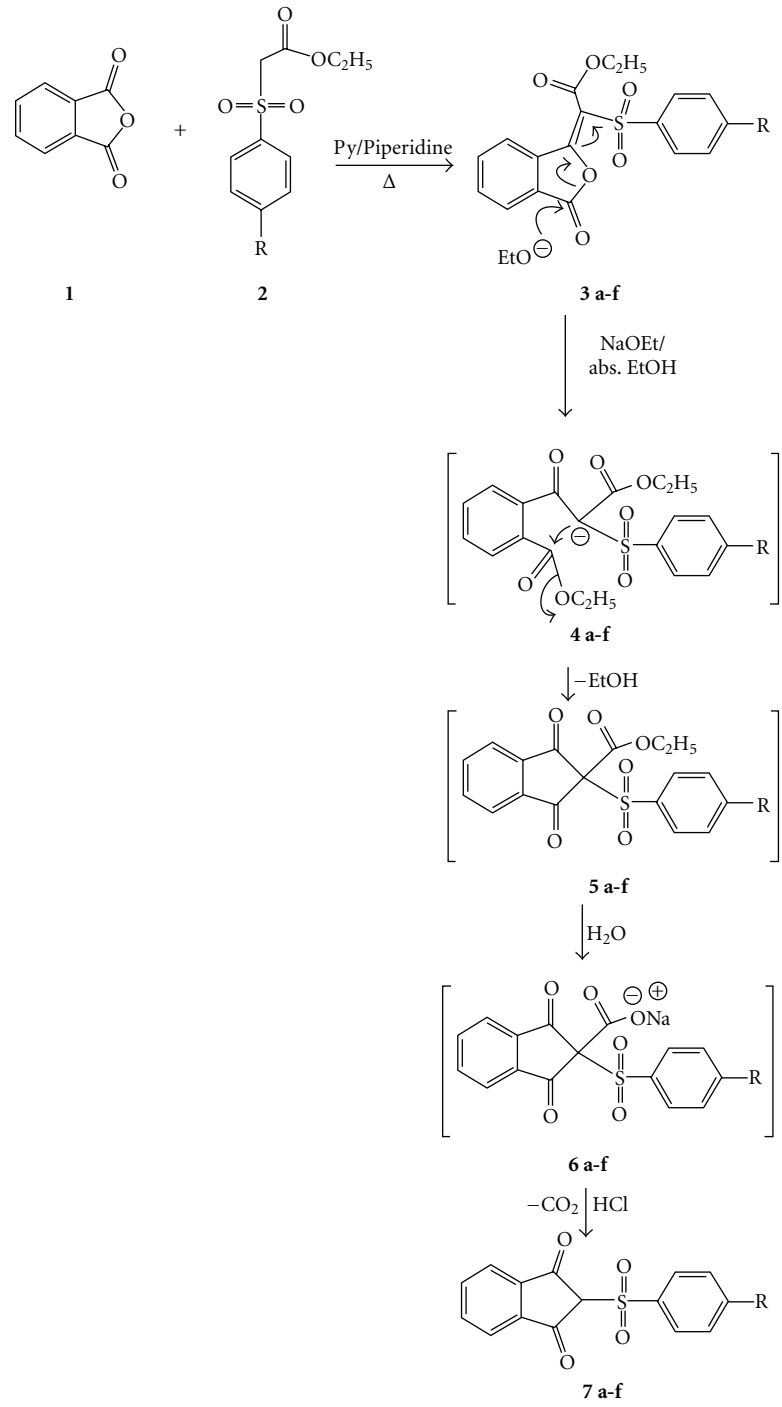
Indane-1,3-dione and its derivatives constitute a unique group of compounds and attracted the attention of organic chemists and biologist due to their three characteristic features [1, 2]. (a) Indane-1,3-diones have enormous synthetic potential due to the presence of β-dicarbonyl moiety which often serves as a synthon for the preparation of more structurally complex compounds *via* condensation, decomposition, reduction, cyclization, rearrangements, and so forth. (b) The molecule offers wide scope for the study of physiochemical properties such as 1,3-indandione tautomerism, dual reactivity, electrochemical redox properties, unique property of polycrystalline films, and quantum mechanical calculations, and so forth [3, 4]. (c) A wide range of biological properties covering antimicrobial, antitumor, anti-inflammatory, antiviral, antihepatitis, anticoagulant, rodenticidal, herbicidal, and insecticidal properties were associated with indane-1,3-dione derivatives [5–10].

A survey of literature revealed that derivatives of indane-1,3-dione particularly 2-arylsulfonylindane-1,3-diones have been found to be potent blood anticoagulants [11]. Earlier, these were prepared by the Claisen condensation involving diethyl phthalate and aryl methyl sulphones [12, 13] by a procedure analogous to the preparation of indane-1,3-dione from diethylphthalate and ethyl acetoacetate [14]. In search of improved oral anticoagulants, we have synthesized 2-(arylsulfonyl)indane-1,3-diones **7 a-f** by a different route involving Knoevenagel reaction between phthalic anhydride and arylsulfonylacetates. The reaction is based on the observation that phthalic anhydride can function as a carbonyl compound in Perkin-type reactions [15].

2. Chemistry

In an attempt to prepare improved analogs of 2-(arylsulfonyl)indane-1,3-diones, we have attempted the condensation of arylsulfonylacetic acids with phthalic anhydride under different conditions. Although, the reaction failed with arylsulfonylacetic acids, the corresponding arylsulfonylacetates readily reacted with phthalic anhydride in the presence of pyridine-piperidine medium gave phthalyl arylsulfonylacetates **3**, which on further reaction with sodium ethoxide in dry ethanol and subsequent heating with 1 : 1 HCl afforded 2-(arylsulfonyl)indane-1,3-diones **7 a-f** (Scheme 1).

The structures of the synthesized compounds **7 a-f** were established by IR and NMR spectroscopic data and elemental analysis. Compounds **7 a-f** were homogenous on TLC and contained sulfur. The presence of sulfone moiety in **7 a-f**



Scheme 1

was established by IR bands [15] in the region, 1300–1360 cm^{-1} (unsymmetrical S=O str.) and 1120–1140 cm^{-1} (symmetrical S=O str.), and the presence of intact indane1,3-dione moiety was also confirmed by the IR bands in the region 1640–1670 cm^{-1}.

The ^{1}H NMR spectra of **7 a-f** bear close resemblance and displayed, in addition to complex multiplets due to aromatic protons in the region δ 7.0–7.5, a one proton singlet in the region δ 4.0–5.5 assignable to the lone methine (H-2) of indane-1,3-dione moiety; the exact chemical shift of

Table 1: Antibacterial activity of compounds **7 a-f**.

Compound	Antibacterial activity (zone of inhibition in mm) at 10 μg/mL	
	S. aureus	*E. coli*
7a	11	6
7b	13	5
7c	16	7
7d	15	6
7e	15	5
7f	14	6
Control (DMSO)	**0**	**0**
Ciprofloxacin	**19**	**8**

Table 2: Minimum inhibitory concentrations (MICs in μg/mL).

Compounds	*S. aureus*	*E. coli*
7a	9	8
7b	9	6
7c	7	8
7d	7	6
7e	7	8
7e	8	6
Ciprofloxacin	5	4

H-2 is influenced by the nature of the substituents of the arylsulfonyl group and by the degree of enolization of the indane-1,3-dione moiety.

3. Pharmacological Screening

3.1. Antibacterial Activity. The antimicrobial activity of compounds was determined by the disc diffusion method and minimum inhibitory concentrations (MICs). Minimum inhibitory concentration is the lowest concentration of an antimicrobial agent that inhibits more than 99% of the bacterial population. MICs were determined by the macrodilution broth method following the procedures recommended by the National Committee for Clinical Laboratory Standards for testing purposes [16, 17]. Compounds **7 a-f** were evaluated *in vitro* activity against *S. aureus* and *E. coli* at a concentration of 10 μg/mL in meat peptone agar medium. Ciprofloxacin was used as a standard for antimicrobial screening. For each biological activity test, two to three experiments were performed and the average zone of inhibition is shown in Table 1.

Compounds **7c**, **7d**, **7e**, and **7f** exhibited significant activity against *S. aureus* while **7a**, **7c**, **7d**, and **7f** showed significant activity against *E. coli*. Compounds **7a** and **7b** showed low activity against *S. aureus*, and **7b** and **7e** registered low activity against *E. coli*. Compounds **7c** and **7d** showed significant activity against *S. aureus* and both *E. coli*. The MICs of these two compounds are summarized in Table 2.

3.2. Anticoagulant Activity. Anticoagulant activity of compounds **7 a-f** was assessed against sodium citrate (standard) in albino rats [18, 19]. The blood samples were collected from albino rats by puncturing carotid artery. Compounds **7 a-f** and sodium citrate were added to the blood separately (10 mg/dL). The time required for the formation of the clot was measured, and the results of anticoagulant activity of **7 a-f** are shown in Table 3.

Table 3: Anticoagulant activity of compounds **7 a-f**.

Compound	Clotting time (min)
7a	60
7b	70
7c	65
7d	75
7e	65
7f	75
Sodium citrate (standard)	**80**

Compounds **7b**, **7d**, and **7f** registered high anticoagulant activity compared to that of standard, whereas compounds **7a**, **7c**, and **7e** showed low activity.

4. Conclusions

A scrutiny of the results of antibacterial activity of **7 a-f** reveals (Tables 1 and 2) emphasized that bulky nuclear substituents at 4-position of benzenesulfonyl moiety were found to decrease the antibacterial activity, especially against Gram-positive bacteria (*S. aureus*). Thus there appears to be an empirical inverse relationship between the activity and the size of the nuclear substituents. The observed decreasing order of antibacterial activity of **7 a-f** against Gram-positive bacteria, **7c** (R = OMe, $E_s = -0.55$) > **7e** (R = Cl, $E_s = -0.97$) = **7d** (R = Br, $E_s = -1.16$) > **7b** (R = Me, $E_s = -1.24$)≈**7f** (R = NO_2, $E_s = -2.52$), reflected an empirical inverse correlation between the acidity and Taft's steric factor (E_s) [20] which is a measure of steric bulk of the substituents, and bulky substituents have larger negative values for E_s.

An analysis of the results of anticoagulant activity of **7 a-f** (Table 3) revealed that an opposite trend was observed in this case, that is, there is a direct correlation between the anticoagulant activity and the size of the nuclear substituents. Thus, the observed increasing order of anticoagulant activity, **7f** (R = NO_2, $E_s = -2.52$) = **7d** (R = Br, $E_s = -1.16$) > **7b** (R = Me, $E_s = -1.24$) > **7e** (R = Cl, $E_s = -0.97$)≈**7c** (R = OMe, $E_s = -0.55$), reflected a direct correlation between anticoagulant activity and Taft's steric factor (E_s).

These contrasting results emphasize that bulky groups lower the activity of the compound by preventing it from fitting properly into the binding site of the receptor. On the other hand, bulky substituents may also increase the activity by forcing a compound to adopt the required active conformation at the binding site.

5. Experimental Section

Melting points were determined on a sulphuric acid bath and are uncorrected. IR spectra were recorded on JASCO 470

FT-IR spectrometer, and ^{1}H-NMR spectra were recorded on a 300 MHz on Bruker (Avance) NMR spectrometer using TMS as an internal standard.

5.1. General Procedure for the Synthesis of Ethyl Arylsulfonylacetate (2). To an alkaline solution of thiophenol (0.10 mol in 15% NaOH), ethyl chloroacetate (0.10 mol) was added while stirring and keeping the temperature at 0°C for about 0.5 h. The resulting oily liquid was extracted with chloroform, and the chloroform layer was washed with water and dried. Evaporation of solvent gave ethyl arylmercaptoacetate, which on oxidation with *m*-CPBA (in $CHCl_3$) gave ethyl arylsulfonylacetate **2**.

*5.2. General Procedure for the Synthesis of 2-(Arylsulfonyl)Indane-1,3-Diones (**7 a-f**).* A mixture of ethyl arylsulfonylacetate **2** (0.10 mol), dry pyridine (15.0 mL), piperidine (2.0 mL), and powdered phthalic anhydride **1** (0.10 mol) was refluxed for 3 h. The reaction mixture was poured into ice water and neutralized with dil. HCl. The solid **3** that separated was filtered, washed with water, and dried. It was then refluxed with sodium ethoxide (0.20 mol) in absolute ethanol for 1 h, and the excess of solvent was removed *in vacuo,* and the residue was dissolved in hot water and neutralized while hot with 1 : 1 HCl. The product **7 a-f** that separated on cooling was filtered, dried, and crystallized.

*2-(Phenylsulfonyl)-1H-indene-1,3(2H)-dione (**7a**).* M.p. 185°C (benzene), yield: 40%. IR (KBr): 1664 (CO), 1336 (S=O unsym. str.), 1141 (S=O sym. str.) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.60 (s, 1H, CH-SO_2-); 7.24–7.99 (m, 9H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 29.79, 122.04, 127.19, 127.49, 129.12, 132.10, 137.10, 151.04, 179.09. Anal. Cald. for $C_{15}H_{10}O_4S$: C, 62.93; H, 3.52. Found: C, 62.96; H, 3.54.

*2-(4-Methylphenylsulfonyl)-1H-indene-1,3(2H)-dione (**7b**).* M.p. 160°C (benzene), yield 45%. IR (KBr): 1672 (CO), 1338 (S=O unsym. str.), 1138 (S=O sym. str.) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.57 (s, 3H, -CH_3), 3.15 (s, 1H, CH-SO_2-), 7.19–7.52 (m, 8H, Ar-H). Anal. Calcd. for $C_{16}H_{12}O_4S$: C, 63.99; H, 4.03. Found: 63.97; H, 4.00.

*2-(4-Methoxyphenylsulfonyl)-1H-indene-1,3(2H)-dione (**7c**).* M.p. 153°C (pet. ether-benzene), yield 43%; IR (KBr): 1668 (CO), 1335 (S=O unsym. str.), 1129 (S=O sym. str.) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.82 (s, 3H, -OCH_3), 5.86 (s, 1H, CH-SO_2-), 6.75–7.49 (m, 8H, Ar-H). Anal. Calcd. for $C_{16}H_{12}O_5S$: C, 60.75; H, 3.82. Found: C, 60.77; H, 3.84.

*2-(4-Bromophenyl-sulfonyl)-1H-indene-1,3(2H)-dione (**7d**).* M.p. 145°C (pet. ether-chloroform), yield 40%. IR (KBr): 1656 (CO), 1346 (S=O unsym. str.), 1136 (S=O sym. str.) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.03 (s, 1H, CH-SO_2-), 7.23–7.55 (m, 8H, Ar-H). Anal. Calcd. for $C_{15}H_9BrO_4S$: C, 49.33; H, 2.48. Found: C, 49.37; H, 2.51.

*2-(4-Chlorophenylsulfonyl)-1H-indene-1,3(2H)-dione (**7e**).* M.p. 131°C (pet. ether-chloroform), yield 42%. IR (KBr): 1666 (CO), 1333 (S=O unsym. str.), 1125 (S=O sym. str.) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.03 (s, 1H, CH-SO_2-), 7.25–7.58 (m, 8H, Ar-H). Anal. Calcd. for $C_{15}H_9ClO_4S$: C, 56.17; H, 2.83. Found: C, 56.14; H, 2.81.

*2-(4-Nitrophenylsulfonyl)-1H-indene-1,3(2H)-dione (**7f**).* M.p. 142°C (aq. ethanol), yield 41%. IR (KBr): 1662 (CO), 1328 (S=O unsym. str.), 1119 (S=O sym. str.) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.91 (s, 1H, CH-SO_2-), 6.83–7.66 (m, 8H, Ar-H). Anal. Calcd. for $C_{15}H_9NO_6S$: C, 54.38; H, 2.74; N, 4.23. Found: C, 54.41; H, 2.77; N, 4.19.

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