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Formation of 2-arylindane-1,3-diones and 3-alkylphthalides from methyl *o*-[α-phenylsulfonyl]toluate

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Abstract

2-Aryl-1,3-indanedione and phthalide derivatives have attracted considerable interest due to their anticoagulant, parasiticidal and a range of biological activities. The synthesis of 2-aryl-1,3-indanedione by the condensation of the title sulfone with aryl aldehydes through an interesting pathway and a previously unreported approach to 3-alkylphthalide from C-alkylated derivatives of **1** under microwave and conventional heating conditions are described.

Keywords: 2-Aryl-1,3-indanedione; Anticoagulant; 3-Alkylphthalide

The synthesis of natural products[1] and several other significant heterocyclic compounds such as benzofuroisocoumarins,[2] 4-diarylmethyl-1-(2*H*)phthalazinones,[3] indeno[1,2-*b*]pyridines,[4] 4-azafluorenones,[5] 4-aza-podophyllotoxin derivatives[6] and calixpyrroles with push–pull chromophores,[7] are made possible via the intermediates 2-aryl-1,3-indanedione and phthalide derivatives. In addition, these intermediates also have a range of biological activities[8] such as anticoagulant,[9] antioxidant, antiplatelet aggregation, antithrombosis, antiangina, antimicrobial, antifungal,[10] antiproliferative[11] and antiinflammatory.[12] The synthesis of 2-aryl substituted indanedione and alkylated phthalides have been extensively reported.[13,14] The most well-known method for the synthesis of 2-arylindandione derivatives is via a condensation reaction of assorted phenols/naphthols with ninhydrin in acetic acid medium.[15] However, although substituted indane-1,3-dione and phthalide derivatives are made possible by several common reactions, the formation of the 2-aryl-1,3-indanedione and alkylated phthalide compounds from easily available sulfones as the starting material has not been studied or researched.

Sulfone is a vital functional group in organic chemistry which have valuable synthetic capabilities.[16] In particular, sulfones can necessitate new potentials for drug design and medicinal chemistry.[17–20] Of special interests are alkyl sulfones which act as potent analgesic–antiinflammatory agents.[21] An compelling report about the anti-HIV activity of indolylarylsulfones has also been revealed.[22] In effort to continue our research[23–26] interests in the synthesis of medicinally important compounds, two novel and effective methods for the synthesis of 2-aryl substituted indane-1,3-dione and alkylated phthalides from easily prepared methyl-*o*-[α-phenylsulfonyl]toluate **1** have been proposed.

Scheme 1 presents the strategies for the synthesis of the compounds of interest. Indanediones **2a–d** were prepared by a simple condensation of sulfone **1**[27] with the corresponding halobenzaldehydes. Reaction of 1 equiv of sulfone **1** with 1 equiv of 2,6-dichlorobenzaldehyde in DMSO in the presence of 5 equiv of NaH afforded 2-(2′,6′-dichlorophenyl)indane-1,3-dione **2a** in 50% yield after chromatographic purification (SiO_2) using hexanes/ethylacetate, (7:3) as the eluting solvent. In ^{1}H NMR

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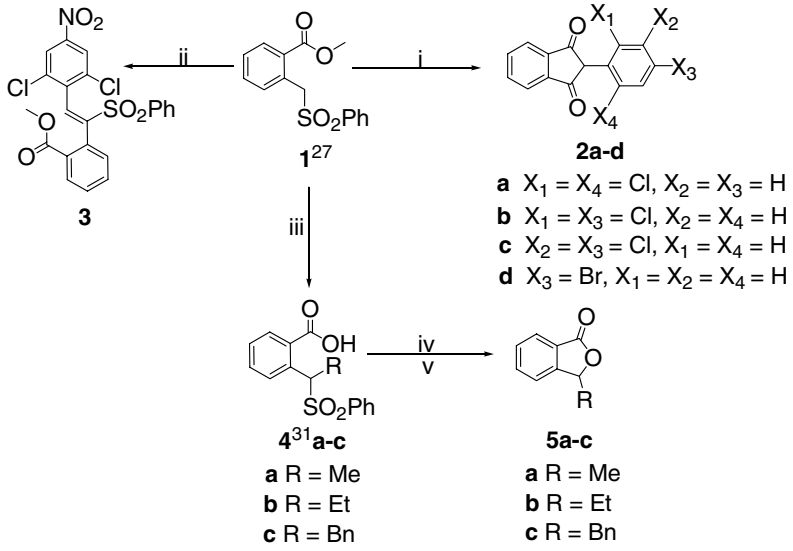
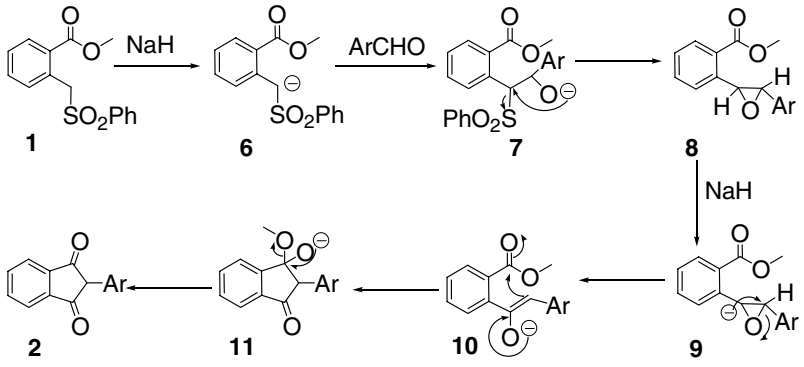


Scheme 1. Synthesis of 2-arylindane-1,3-diones (**2a**–**d**) and 3-alkylphthalides (**5a**–**c**). Reagents and conditions: (i) ArCHO, NaH, DMSO, RT(N_2), 24 h, 30–50%; (ii) 2,6-dichloro-4-nitrobenzaldehyde, NaH, DMSO, RT(N_2), 10 h, 60%; (iii) R–X, NaH, DMSO, RT(N_2), 12 h, 60–75%; (iv) H_3PO_4, 140 °C, 12 h, 45–50%; (v) H_3PO_4, microwave irradiation, 50 s–1 min, 60–70%.

spectrum of indanedione **2a** C*H* proton appeared at δ 5.2 as a singlet besides the aromatic protons. In ^{13}C NMR spectrum CH, aromatic and carbonyl carbons appeared at δ 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 isotopic clusters at 291.8120 and 293.8010 in HR-EI MS. Reactions of sulfone **1** with other halobenzaldehydes viz. 2,4-dichlorobenzaldehyde, 3,4-dichlorobenzaldehyde, 4-bromobenzaldehyde under the same reaction conditions gave indanediones **2b**–**d**. The structures of indanediones **2a**–**d** were confirmed from spectral data[28] and their melting points concur with those described in the literature.[29] The plausible mechanism is given in Scheme 2. In our view the formation of indanediones **2a**–**d** probably involves oxirane **8** as the possible intermediate although no such intermediates were isolated. Owing to its higher carbonyl reactivity a similar reaction of 2,6-dichloro-4-nitrobenzaldehyde with sulfone **1** in the presence of 1 equiv of NaH in DMSO afforded regular condensation product **3**[30] in 60% yield after chromatographic purification (SiO_2) using hexanes/ethylacetate (9:1) as the eluting solvent. The reaction was unsuccessful with simple benzaldehyde and veratraldehyde and the starting materials were isolated in 70% yield.

With a view to synthesize 3-methylphthalides **5a**–**c**, the alkylated sulfones *o*-[α-phenylsulfonyl]ethylbenzoic acid **4a**, *o*-[α-phenylsulfonyl]propylbenzoic acid **4b** and *o*-[α-phenylsulfonyl-β-phenyl]ethylbenzoic acid **4c** were prepared via a previously published method.[31] The ^{1}H NMR spectrum of the alkylated sulfone **4a** displayed the CH_3 and C*H* (SO_2Ph) protons as doublet and quartet at δ 2.2 and δ 6.1, respectively, besides the aromatic protons. In the ^{13}C NMR spectrum of SO_2Ph–*C*H, methyl and the carbonyl carbons appeared at δ 58.80, 14.29 and 171.47, respectively. The structures of other alkylated sulfones **4b** and **4c** were thoroughly characterized by spectral and analytical data[32] and were subsequently heated with *o*-phosphoric acid for the synthesis of 3-alkylphthalides **5a**–**c**[33]



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

under conventional and microwave conditions. Both the percent yield and the reaction duration were considerably improved under microwave irradiation (Scheme 1).

Though it was perceived that methyl-*o*-[α-phenylsulfonyl]toluate **1** could lead to the vinylsulfones with substituted benzaldehydes, our present study has demonstrated a novel mode of condensation of 4-bromobenzaldehye and dichlorobenzaldehydes with sulfone leading to the formation of 2-arylindanediones which have attracted considerable interest due to their anticoagulant and parasiticidal activities. A new and previously unreported approach to 3-alkylatedphthalide under microwave and conventional heating has also been presented.

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33. *3-Methylphthalide* (**5a**): IR (KBr) 760, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.8–6.9 (m, 4H), 5.5 (q, $J = 9.1$ Hz, 1H), 1.6 (d, $J = 9.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4, 151.1, 134.0, 129.0, 129.0, 125.7, 125.7, 75.3, 20.3; exact mass (EI) calcd for $C_9H_8O_2$: *m/z* 148.0517; found, *m/z*

148.1130. *3-Ethylphthalide* (**5b**) IR (KBr) 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.7–6.8 (m, 4H), 5.4 (t, $J = 7.4$ Hz, 1H), 2.0 (m, 2H), 1.0 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.6, 149.7, 136.5, 133.9, 129.4, 126.3, 121.7, 82.2, 27.6, 8.8; exact mass (EI) calcd for $C_{10}H_{10}O_2$: *m*/*z* 162.0712; found, *m*/*z* 162.1189. *3-Benzylphthalide* (**5c**): IR (KBr) 760, 1274, 1762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9–7.1 (m, 9H), 5.7 (t, $J = 7.9$ Hz, 1H), 3.5 (d, $J = 7.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 169.2, 141.2, 133.6, 129.9, 129.6, 128.5, 127.3, 127.2, 127.2, 127.1, 125.5, 75.9, 35.5; exact mass (EI) calcd for $C_{15}H_{12}O_2$: *m*/*z* 224.1226; found, *m*/*z* 224.1237.