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Efficient Synthesis of 3-Arylphthalides†

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A convenient method for the synthesis of 3-arylphthalides (**3a**–**q**) involving condensation of phthalaldehydic acids (**1a,b**) with aromatic substrates (**2a**–**k**) in the presence of TFA is described.

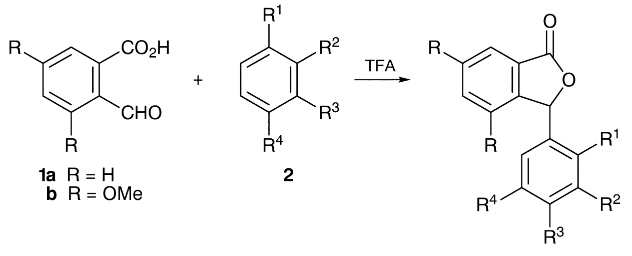
Phthalides, isobenzofuran-1(3*H*)-ones, constitute an important class of naturally occurring oxygen ring compounds, well known for their interesting biological properties.[1] They are also used as intermediates for the synthesis of isocoumarins,[2] anthraquinones[3] and anthracyclines.[4] In view of this, various methods have been reported for their synthesis.

As a part of our ongoing programme directed towards the synthesis of various naturally occurring and biologically active anthraquinones, we needed 3-arylphthalides as precursors for their synthesis. Most methods reported for the synthesis of 3-arylphthalides involve (i) heteroatom-directed lithiation of benzamides, followed by reaction with an appropriate aryl aldehyde as an electrophile,[5] (ii) reaction of phthalaldehydic acids with arylmagnesium halides[6] and (iii) acid-catalysed condensation of phthalaldehydic acids with aromatic substrates.[7–9] Method (iii) in the presence of an acid appeared to us more convenient as it does not involve sensitive organometallic reagents and critical reaction conditions. The acids used were sulfuric acid[7] in different concentrations, concentrated hydrochloric acid[8] and methanesulfonic acid[9] (MSA).

Even though the yields of 3-arylphthalides were moderate by using sulfuric acid, the experimental conditions varied from substrate to substrate; for example, in some cases concentrated sulfuric acid was used while in others a mixture of sulfuric acid with oleum was used. Furthermore in some cases a mixture of isomeric phthalides was obtained. MSA was used for condensation of naphthalene and its monosubstituted derivatives only and the reaction required stirring overnight.

It was therefore decided first to use concentrated hydrochloric acid. Adopting the reported procedure,[8] when hydroquinone dimethyl ether and resorcinol dimethyl ether were treated with phthalaldehydic acid **1a**[10] in the presence of concentrated hydrochloric acid the corresponding phthalides **3b** and **3a** were obtained in 50–55% yield. Both reactions required 2 h for completion and steam distillation to obtain pure products. Hence it was decided to look for another reagent which would be general and could provide the final products in high yields and shorter reaction times.

As trifluoroacetc acid (TFA), having good ionizing power and very low nucleophilicity, has been used as a reagent for electrophilic aromatic substitution reactions,[11] it was thus decided to use TFA (Scheme 1). As a test case, when a solution of phthalaldehydic acid **1a** and resorcinol dimethyl ether **2a** in TFA was heated on water-bath the reaction was complete in 15 min as evident from TLC and the desired phthalide **3a**, mp 105 °C (lit.,[8] 106 °C) was obtained in 90% yield. Similarly when hydroquinone dimethyl ether **2b** was condensed with **1a** it provided the phthalide **3b**, mp 80 °C (lit.,[8] 80 °C) in 85% yield. With these encouraging results, various other aromatic substrates were subjected to condensation with **1a** and the corresponding phthalides **3a**–**k** were obtained in 80–85% yield using TFA. Compound **1b**[12] on similar reaction with aromatic substrates provided the corresponding phthalides **3l**–**q**. The starting acid **1b** was obtained by hydrolysis of ethyl 2-formyl-3,5-dimethoxybenzoate which in turn was obtained by formylation of ethyl 3,5-dimethoxybenzoate using Vilsmeier–Hack reaction.



	R¹	R²	R³	R⁴
2a	OMe	H	OMe	H
2b	OMe	H	H	OMe
2c	H	OMe	OMe	H
2d	OMe	H	H	Me
2e	Me	H	OMe	H
2f	OMe	H	Me	OMe
2g	Me	H	OMe	OMe
2h	OMe	$-CH_2-CH_2-CH_2-CH_2-$		OMe
2i	OMe	$-CH=CH-CH=CH-$		OMe
2j	$-CH=CH-CH=CH-$		H	H
2k	H	H	OMe	H

Scheme 1

To conclude, the present paper describes a simple and efficient method for the synthesis of 3-arylphthalides. The major advantages of TFA over other acid-catalysed methods are (i) the desired phthalides are obtained in high yields, (ii) the work-up procedure is simple and (iii) milder reaction conditions are required.

Experimental

All melting points are uncorrected. ^1H NMR spectra were recorded on a JEOL FX 90 Q instrument in $CDCl_3$ using TMS as internal standard, IR spectra on a Perkin Elmer FT IR 1600 spectrophotometer. All compounds gave satisfactory microanalysis (±0.2% for C and H).

General Procedure.—A solution of phthalaldehydic acid **1** (0.002 mol), aromatic substrate **2** (0.002 mol) and TFA (1 ml) was heated on water-bath for 15 min. The reaction mixture was cooled and poured on crushed ice. The solid thus obtained was filtered off and purified by column chromatography using hexane–ethyl acetate (9:1) as an eluent.

3a. $R=R^2=R^4=H$; $R^1=R^3=OCH_3$ (90% yield); mp 105 °C (lit.,[8] 106 °C); $\tilde{\nu}_{max}/cm^{-1}$ (Nujol) 1750 (lactone carbonyl); δ_H 3.70 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 6.55 (s, 1 H, CH), 6.85 (s, 1 H, H-Ar), 7.10 (m, 1 H, H-Ar), 7.60–8.00 (m, 4 H, H-Ar), 8.20 [br d 1 H ($J=8$ Hz), H-Ar].

3b. $R=R^2=R^3=H$; $R^1=R^4=OCH_3$ (75% yield); mp 80 °C (lit.,[8] 80 °C); $\tilde{\nu}_{max}/cm^{-1}$ (Nujol) 1750 (lactone carbonyl); δ_H 3.70 (s, 3 H, OCH_3) 3.90 (s, 3 H, OCH_3), 6.65 (s, 1 H, CH), 6.80–7.00 (m, 3H, H-Ar), 7.40–7.70 (m, 3 H, H-Ar), 7.95 [br d 1 H ($J=8$ Hz), H-Ar].

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3c. $R = R^1 = R^4 = H$; $R^2 = R^3 = OCH_3$ (90% yield); mp 146 °C (lit.,[13] 148 °C); $\tilde{\nu}_{max}$/cm^{-1} (Nujol) 1760 (lactone carbonyl); δ_H 3.90 (s, 3 H, OCH_3) 4.00 (s, 3 H, OCH_3), 6.55 (s, 1 H, CH), 6.90 (br s, 1 H, H-Ar), 7.05 (m, 1 H, H-Ar), 7.30–8.00 (m, 4 H, H-Ar), 8.15 [br d 1 H (J = 8 Hz), H-Ar].

3d. $R = R^2 = R^3 = H$; $R^1 = OCH_3$; $R^4 = CH_3$ (85% yield); mp 118 °C (lit.,[7b] 121 °C); $\tilde{\nu}_{max}$/cm^{-1} (Nujol) 1755 (lactone carbonyl); δ_H 2.20 (s, 3 H, CH_3), 3.90 (s, 3 H, OCH_3), 6.80–6.90 (m, 2 H, CH, H-Ar), 7.10 [d (J = 2), 1 H, H-Ar], 7.30–7.65 (m, 4 H, H-Ar), 7.95 [br d (J = 8 Hz), H-Ar].

3e. $R = R^2 = R^4 = H$; $R^1 = CH_3$; $R^3 = OCH_3$ (75% yield); mp 121 °C; $\tilde{\nu}_{max}$/cm^{-1} (Nujol) 1750 (lactone carbonyl); δ_H 2.50 (s, 3 H, CH_3) 3.85 (s, 3 H, OCH_3), 6.55–7.05 (m, 3 H, CH, H-Ar), 7.45 [d (J = 8), 1 H, H-Ar], 7.55–7.95 (m, 3 H, H-Ar), 8.10 [br d (J = 8 Hz), 1 H, H-Ar].

3f. $R = R^2 = H$; $R^1 = R^4 = OCH_3$; $R^3 = CH_3$ (85% yield); mp 138 °C; $\tilde{\nu}_{max}$/cm^{-1} (Nujol) 1765 (lactone carbonyl); δ_H 2.25 (s, 3 H, CH_3) 3.85 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 6.65 (s, 1 H, CH), 6.95 (br s, 2 H, H-Ar), 7.50–7.85 (m, 3 H, H-Ar), 8.20 [br d (J = 8 Hz), 1 H, H-Ar].

3g. $R = R^2 = H$; $R^1 = CH_3$; $R^3 = R^4 = OCH_3$ (80% yield); mp 102 °C; $\tilde{\nu}_{max}$/cm^{-1} (Nujol) 1765 (lactone carbonyl); δ_H 2.50 (s, 3 H, CH_3), 3.70 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 6.30 (s, 1 H, CH), 6.65 (s, 1 H, H-Ar), 6.75 (s, 1 H, H-Ar), 7.35 [br d (J = 8), 1 H, H-Ar], 7.55–7.75 (m, 2 H, H-Ar), 8.00 [br d (J = 8 Hz), 1 H, H-Ar].

3h. $R = H$; $R^1 = R^4 = OCH_3$; R^2, $R^3 = [CH_2]_4$ (75% yield); oil; $\tilde{\nu}_{max}$/cm^{-1} (Nujol) 1755 (lactone carbonyl); δ_H 1.80–2.10 (m, 4 H, $2 \times CH_2$), 2.50–3.00 (m, 4 H, $2 \times CH_2$), 3.70 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 6.25 (s, 1 H, CH), 6.90 (s, 1 H, H-Ar), 7.40–7.80 (m, 3 H, H-Ar), 8.05 [br d (J = Hz), 1 H, H-Ar].

3i. $R = H$; $R^1 = R^4 = OCH_3$; $R^2 = R^3 = CH{=}CH{-}CH{=}CH$ (80% yield); mp 143 °C $\tilde{\nu}_{max}$/cm^{-1} (Nujol) 1750 (lactone carbonyl); δ_H 3.75 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 6.15 (s, 1 H, CH), 7.05 (s, 1 H, H-Ar), 7.35–7.70 (m, 5 H, H-Ar), 7.90–8.15 (m, 2 H, H-Ar), 8.25 [br d (J = 8 Hz), 1 H, H-Ar].

3j. $R = R^3 = R^4 = H$; R^1, $R^2 = CH{=}CH{-}CH{=}CH$ (85% yield); mp 135 °C (lit.,[9] 137 °C); $\tilde{\nu}_{max}$/cm^{-1} (Nujol) 1750 (lactone carbonyl); δ_H 6.50 (s, 1 H, CH), 7.10–8.00 (complex multiplet, 10 H, H-Ar), 8.20 [br d (J = 8 Hz), 1 H, H-Ar].

3k. $R = R^1 = R^2 = R^4 = H$; $R^3 = OCH_3$ (85% yield); mp 117 °C (lit.,[13] 118 °C); $\tilde{\nu}_{max}$/cm^{-1} (Nujol) 1760 (lactone carbonyl); δ_H 3.90 (s, 3 H, OCH_3), 6.50 (s, 1 H, CH), 7.10–7.90 (m, 7 H, H-Ar), 8.15 [br d (J = 8 Hz), 1 H, H-Ar].

3l. $R = R^2 = R^3 = OCH_3$; $R^1 = R^4 = H$ (85% yield); mp 119 °C; $\tilde{\nu}_{max}$/cm^{-1} (Nujol) 1760 (lactone carbonyl); δ_H 3.85 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.95 (s, 6 H, $2 \times OCH_3$), 6.40 (s, 1 H, CH), 6.65–7.05 (m, 4 H, H-Ar), 7.10 [d (J = 2 Hz), 1 H, H-Ar].

3m. $R = R^1 = R^3 = OCH_3$; $R^2 = R^4 = H$ (85% yield); mp 162 °C; $\tilde{\nu}_{max}$/cm^{-1} (Nujol) 1750 (lactone carbonyl); δ_H 3.75 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 6.30–6.60 (m, 2 H, CH, H-Ar), 6.65–6.90 (m, 3 H, H-Ar), 7.05 [d (J = 2 Hz), 1 H, H-Ar].

3n. $R = R^1 = R^4 = OCH_3$; $R^2 = R^3 = H$ (80% yield); mp 149 °C; $\tilde{\nu}_{max}$/cm^{-1} (Nujol) 1760 (lactone carbonyl); δ_H 3.70 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH), 6.55 (s, 1 H, CH), 6.65–7.05 (m, 4 H, H-Ar), 7.10 [d (J = 2 Hz), 1 H, H-Ar].

3o. $R = R^1 = R^4 = OCH_3$; $R^2 = H$; $R^3 = CH_3$ (80% yield); mp 149 °C; $\tilde{\nu}_{max}$/cm^{-1} (Nujol) 1765 (lactone carbonyl); δ_H 2.25 (s, 3 H, CH_3), 3.65 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 6.40 (s, 1 H, CH), 6.70–7.00 (m, 3 H, H-Ar), 7.10 [d (J = 2 Hz), 1 H, H-Ar].

3p. $R = R^3 = R^4 = OCH_3$; $R^1 = CH_3$; $R^2 = H$ (80% yield); mp 172 °C; $\tilde{\nu}_{max}$/cm^{-1} (Nujol) 1760 (lactone carbonyl); δ_H 2.50 (s, 3 H, CH_3), 3.70 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.95 (s, 6 H, $2 \times OCH_3$), 6.35 (s, 1 H, CH), 6.60 (s, 1 H, H-Ar), 6.70–6.90 (m, 2 H, H-Ar), 7.10 [d (J = 2 Hz), 1 H, H-Ar].

3q. $R = R^1 = R^4 = OCH_3$; R^2, $R^3 = [CH_2]_4$ (75% yield); mp 193 °C; $\tilde{\nu}_{max}$/cm^{-1} (Nujol) 1755 (lactone carbonyl); δ_H 1.50–2.05 (m, 4 H, $2 \times CH_2$), 2.45–3.00 (m, 4 H, $2 \times CH_2$), 3.60 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 6.15 (s, 1 H, CH), 6.70–7.00 (m, 2 H, H-Ar), 7.15 [d (J = 2 Hz), 1 H, H-Ar].

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