Facile synthesis of 3-(diarylmethylene)isobenzofuranones, 4-(diarylmethyl)-1(2*H*)-phthalazinones and diarylmethanes

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Reflux of 2,2-diaryl-1,3-indanediones in ethyleneglycol with a catalytic amount of triethylamine affords 3-(diarylmethylene)isobenzofuranones in very good yields. The latter produces 4-diarymethyl-1(2*H*)-phthalazinones under reflux in hydrazine hydrate (99%), and diarylmethanes upon stirring in ethylenediamine.

Keywords: indane-1,3-diones, isobenzofuranones, phthalazinones, diarylmethanes

Isobenzofuranones are an important class of naturally occuring lactones[1-3] with interesting biological properties, such as antispasmodic, herbicidal, insecticidal,[4] cytotoxic,[5] *etc*., activities. Because of these diverse activities, the development of synthetic methods for suitably substituted isobenzofuranones is important. It is known that 3-(diarylmethylene) isobenzofuranones are not obtained by conventional base catalysed condensation of phthalides with aromatic ketones. Olah and co-workers have shown that stirring ninhydrin with various arenes in superacidic triflic acid (CF_3SO_3H, TfOH) produces 3-(diarylmethylene)isobenzofuranones within 8 h.[6] Since triflic acid is a costly as well as a very drastic reagent, a method involving easily available and mild reagents with short reaction times would be an advantage.

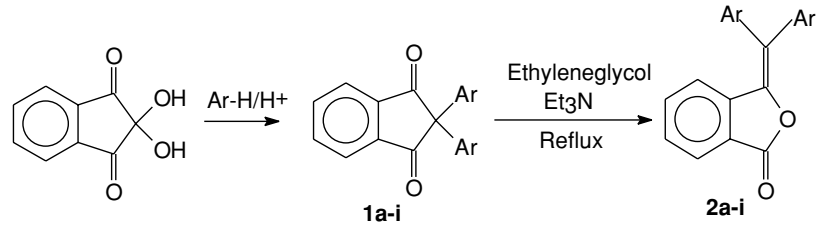
In this paper we report an efficient synthetic method for forming 3-(diarylmethylene)isobenzofuranones from the easily prepared 2,2-diaryl-1,3-indanediones such as **1a–i** (Scheme 1). It is observed that 2,2-diaryl-1,3-indanediones isomerise to 3-(diarylmethylene)isobenzofuranones **2a–i** under reflux in ethyleneglycol with a catalytic amount of triethylamine in very good yields, in a short space of time (Table 1).

Table 1 3-(Diarylmethylene)isobenzofuranones **2a–i** from 2,2-diaryl-1,3-indanediones **1a–i**

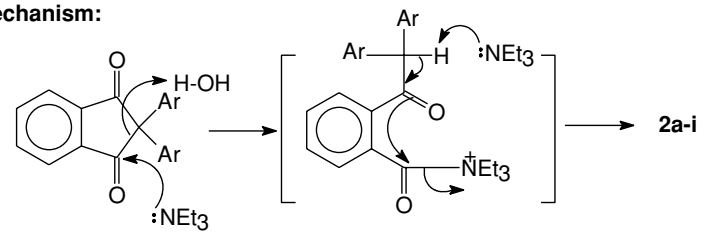
Substrate	Product	Time/ min	Yield[a]/ %	M.p./ °C	Lit.[6] m.p./°C
1a	**2a**	20	82	157–158	159–162
1b	**2b**	15	86	158–159	158–160
1c	**2c**	15	85	171–172	171–173
1d	**2d**	15	83	210–211	211–213
1e	**2e**	15	83	209–210	209–211
1f	**2f**	20	78	136–138	137–139
1g	**2g**	15	82	150–151	152
1h	**2h**	15	80	175–176	178
1i	**2i**	20	76	173–174	–

[a]Yields refer to pure isolated products.

A proposed mechanism for the reaction is depicted in Scheme 1. The nucleophilic attack of triethylamine at either of the carbonyl groups of the 2,2-diaryl-1,3-indanedione (**1a–i**) produces an open chain intermediate, which undergoes a subsequent base-catalysed cyclisation to furnish the 3-(diarylmethylene)isobenzofuranones (**2a–i**). The substrates **1a–i** were derived by condensation of ninhydrin with arenes in acid medium following the reported procedure.[6,7]



Mechanism:



1 and **2**

a: Ar = Ph
b: Ar = *p*-FC_6H_4
c: Ar = *p*-ClC_6H_4
d: Ar = *p*-BrC_6H_4
e: Ar = *p*-IC_6H_4
f: Ar = *p*-CH_3-C_6H_4
g: Ar = *p*-OCH_3-C_6H_4
h: Ar = 3,4-di-OCH_3-C_6H_3
i: Ar = *m*-Cl-*p*-OCH_3-C_6H_3

Scheme 1

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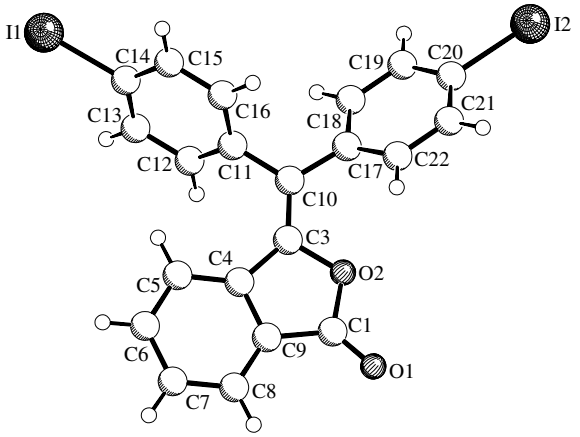


Fig. 1 SCHAKAL-plot with atomic numbering scheme of **2e**.

The formation of products **2a–h** was confirmed by the correspondence of the spectral data (NMR, IR) and melting points with the reported values (Table 1).[6] The X-ray crystal structure of **2e** prepared by the above method is presented in Fig. 1.[8] The X-ray crystal structure of **2a** was reported by Olah *et al*.[6a]

As 3-(diarylmethylene)isobenzofuranones (**2a–i**) are five-membered lactones with an exocyclic methylene group, they are expected to be reactive towards nucleophiles. Predictably, **2a–i** condense with refluxing hydrazine hydrate (99%) to furnish 4-diarylmethyl-1(2*H*)-phthalazinones (**3a–i**) in very high yields (Scheme 2, Table 2) within 15 minutes.

Generally, 4-substituted 1(2*H*)-phthalazinones are found to be biologically active.[9] Surprisingly, **2a–i** produce elimination products diarylmethanes **4a–i** upon stirring in ethylenediamine, corresponding to the diaryl groups at the methylene unit (Table 3). In all these reactions the nucleophilic attack of hydrazine and ethylenediamine on the carbonyl groups of **2a–i** leads to the formation of open chain hydrazides and amides respectively. Subsequently the hydrazides undergo an intramolecular nucleophilic attack on the ketonic CO group, followed by dehydration to furnish 4-diarylmethyl-1(2*H*)-phthalazinones **3a–i**. On the other hand, the open chain amides of ethylenediamine undergo an intramolecular nucleophilic attack on the ketonic CO by the amide NH group to produce the elimination products diarylmethanes **4a–i** and the side product 2-(2-aminoethyl)-1*H*-isoindole-1,3(2*H*)-dione (Scheme 3).[10g] The formation of 4-diarylmethyl-1(2*H*)-phthalazinones[9a,b] **3a, 3c–g** and diarylmethanes[10] **4a–i** was confirmed by comparing the spectral data (NMR, IR) and melting points with the reported values.

In summary, we have developed an efficient method for preparation of 3-(diarylmethylene)isobenzofuranones by refluxing 2,2-diaryl-1,3-indanediones in ethyleneglycol with catalytic amounts of triethylamine. It has also been demonstrated that 3-(diarylmethylene)isobenzofuranones could be easily converted into 4-diarylmethyl-1(2*H*)-phthalazinones and diarylmethanes by reaction with hydrazine hydrate and ethylenediamine respectively.

Table 2 Conversion of 3-(diarylmethylene)isobenzofuranones **2a–i** into 4-diarylmethyl-1(2*H*)-phthalazinones **3a–i**

Substrate	Product	Time/ min	Yield[a]/ %	M.p./ °C	Lit.[9a,b] m.p./°C
2a	**3a**	15	90	218–219	220
2b	**3b**	15	85	215–216	–
2c	**3c**	15	91	227–228	228
2d	**3d**	15	92	254–255	254
2e	**3e**	15	89	277–278	279
2f	**3f**	15	92	228–229	230
2g	**3g**	15	94	225–226	226
2h	**3h**	15	91	227–228	–
2i	**3i**	15	87	214–216	–

[a]Yields refer to pure isolated products.

Table 3 Formation of diarylmethanes **4a–i** from 3-(diarylmethylene)isobenzofuranones **2a–i**

Substrate	Product	Time/h	Yield[a]/ %	M.p./ °C	Lit.[6] m.p./°C
2a	**4a**	1.5	81	Liquid	25–26
2b	**4b**	1.5	80	Liquid	29–30
2c	**4c**	1.0	85	52–53	54–56
2d	**4d**	1.0	87	60–62	63–64
2e	**4e**	1.0	85	89–91	91–94
2f	**4f**	1.0	82	Liquid	28
2g	**4g**	1.0	87	48–49	51–52
2h	**4h**	1.0	85	69–70	71
2i	**4i**	1.0	80	80–82	83.5

[a]Yields refer to pure isolated products.

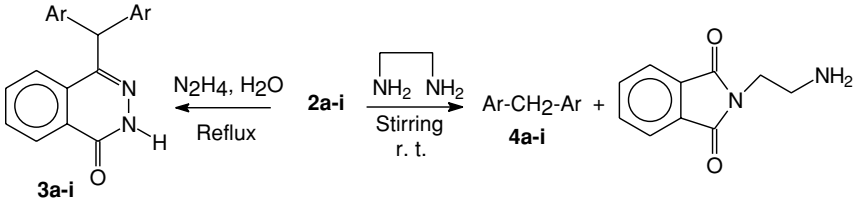
Experimental

Melting points were determined in open capillary tubes. IR spectra were examined in KBr disc on a Perkin Elmer-782 spectrophotometer. Proton magnetic resonance spectra (^{1}H NMR) were recorded on Bruker AM 300L (300 MHz) or a Bruker DRX-500 (500 MHz) spectrometer in the solvents indicated. Elemental analyses were performed on a Perkin-Elmer 240C analyser, at the Indian Association for the Cultivation of Science (IACS), Kolkata.

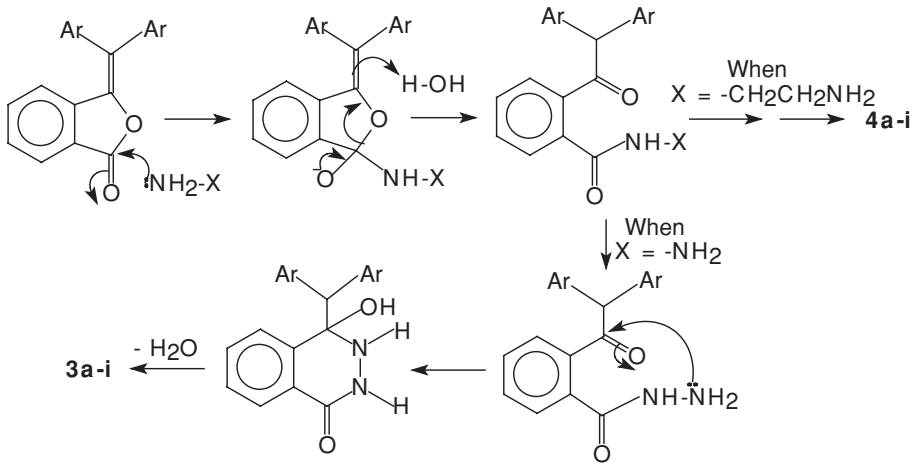
Ninhydrin adducts **1a–i** were prepared following the reported procedure.[6, 7]

3-(Diarylmethylene)isobenzofuranones (**2a–i**): The appropriate substrate **1a–i** (1.4 mmol) was added to 5.0 ml of ethyleneglycol containing 0.5 ml of triethylamine and the mixture refluxed for a specified period (Table 1). The cooled reaction mixture was acidified with 6 N HCl to pH 6. The solid product was extracted with $CHCl_3$ and worked up as usual. Column chromatography of the residue over silica gel using ethyl acetate-petroleum ether as eluent afforded pure solid products **2a–i**. Single crystals of **2e** were grown from $CHCl_3$-petroleum ether.

Bis-(4-iodophenyl)methylene compound (**2i**): Colourless crystals, m.p.173–174 °C. IR (KBr): ν_{max} 1773, 1594, 1501, 1292, 1259, 1003, 753 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 7.92 (1H, d, J = 7.5 Hz), 7.52 (1H, dd, J = 8.7, 2.2 Hz), 7.47–7.39 (3H, m), 7.37 (1H, d, J = 2.1 Hz), 7.23 (1H, dd, J = 8.4, 2.1 Hz), 7.08 (1H, d, J = 8.4 Hz), 6.94 (1H, d, J = 8.7 Hz), 6.45 (1H, d, J = 7.9 Hz), 4.03 (3H, s), 3.93 (3H, s). Anal. Calcd for $C_{23}H_{16}Cl_2O_4$: C, 64.64; H, 3.77; Cl, 16.61. Found: C, 64.75; H, 3.87; Cl, 16.73 %.



Scheme 2



Scheme 3

4-Diarylmethyl-1(2H)-phthalazinones (**3a–i**): The appropriate substrate **2a–i** (1.4 mmol) was added to hydrazine hydrate (10 ml, 99%) and the mixture was refluxed for about 15 minutes (Table 2). The usual work up and purification (as in the case of **2a–i**) furnished solid products **3a–i**.

4-[Bis-(4-fluorophenyl)methyl]-1(2H)-phthalazinone (**3b**): Colourless crystals, m.p. 215–216 °C. IR: ν_{max} 3047, 1660, 1506, 1226, 823 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 10.23 (1H, s, N–H), 8.47 (1H, m), 7.74 (3H, m), 7.18–7.13 (4H, m), 7.03–6.98 (4H, m), 5.93 (1H, s).

4-[Bis-(3,4-dimethoxyphenyl)methyl]-1(2H)-phthalazinone (**3h**): Colourless crystals, m.p. 227–228 °C. IR: ν_{max} 2921, 1668, 1515, 1462, 1245, 774 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 9.89 (1H, s, N–H), 8.45 (1H, m), 7.81 (1H, m), 7.73 (2H, m), 6.81 (2H, d, J = 8.1 Hz), 6.74 (2H, br. s), 6.69 (2H, d, J = 8.2 Hz), 5.87 (1H, s), 3.85 (6H, s), 3.79 (6H, s); Anal. Calcd for $C_{25}H_{24}N_2O_5$: C, 69.43; H, 5.59; N, 6.48. Found: C, 69.54; H, 5.71; N, 6.59 %.

4-[Bis-(3-chloro-4-methoxyphenyl)methyl]-1(2H)-phthalazinone (**3i**): Colourless crystals, m.p. 214–216 °C. IR: ν_{max} 3009, 2906, 1659, 1497, 1258, 779 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 10.24 (1H, s, N–H), 8.46 (1H, m), 7.74 (3H, m), 7.21 (2H, br. s), 7.02 (2H, d, J = 8.3 Hz), 6.86 (2H, d, J = 8.7 Hz), 5.80 (1H, s), 3.87 (6H, s). Anal. Calcd for $C_{23}H_{18}Cl_2N_2O_3$: C, 62.58; H, 4.11; Cl, 16.08; N, 6.35. Found: C, 62.64; H, 4.19; Cl, 16.16; N, 6.44 %.

Diarylmethanes (**4a–i**): The appropriate substrate **2a–i** (1.4 mmol) was added to ethylenediamine (10 ml, 99%) and the mixture was stirred for about 1 h at room temperature (Table 3). The usual work up and purification (as in the case of **2a–i**) furnished products **4a–i**.

Crystal data for **2e**[8]: X-ray crystal structure analysis for **2e**: formula $C_{21}H_{12}I_2O_2$, M = 550.11, colourless crystal 0.20 × 0.20 × 0.10 mm, a = 14.996(1), b = 13.667(1), c = 9.254(1) Å, V = 1896.6(3) Å^3, ρ_{calc} = 1.927 g cm^{-3}, μ = 33.27 cm^{-1}, empirical absorption correction (0.556 ≤ T ≤ 0.732), Z = 4, orthorhombic, space group $Pna2_1$ (No. 33), λ = 0.71073 Å, T = 198 K, ω and φ scans, 15625 reflections collected (±h, ±k, ±l), [(sinθ)/λ] = 0.66 Å^{-1}, 4387 independent (R_{int} = 0.045) and 3841 observed reflections [$I \geq 2\ \sigma(I)$], 226 refined parameters, R = 0.029, wR^2 = 0.066, max. residual electron density 0.46 (–0.5) e Å^{-3}, Flack parameter -0.02(2), hydrogens calculated and refined as riding atoms. The data set was collected with a Nonius Kappa CCD diffractometer equipped with a rotating anode Nonius FR591.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-268331. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, CambridgeCB2 1EZ, UK [fax: int. code +44 1223 336 033, e-mail: deposit@ccdc.cam.ac.uk].

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