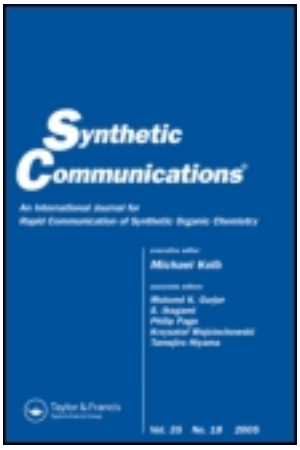

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Convenient Synthesis of 3-Styrylphthalides

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Version of record first published: 22 Aug 2006.

To cite this article: R. S. Mali & Archna Patience Massey (1997): Convenient Synthesis of 3-Styrylphthalides, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 27:6, 1049-1057

To link to this article: http://dx.doi.org/10.1080/00397919708003050

SYNTHETIC COMMUNICATIONS, 27(6), 1049-1057 (1997)

CONVENIENT SYNTHESIS OF 3 - STYRYLPHTHALIDES.

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Abstract : A convenient, high yield, two-step method is described for 3-styrylphthalides (**3a - e**) from 3-phenacylphthalides (**1a - e**)

Although 3-styrylphthalide ring system does not occur in natural products, these compounds are very useful as colour formers for thermal and pressure sensitive recording materials.[1] Mainly two approaches have been developed for the synthesis of substituted 3-styrylphthalides.[2,3] The reaction of 1,1-bis-diarylethylene with ortho-benzoylbenzoic acids is involved in one method,[2] while in the other, it is treated with phthalic anhydrides.[3] The syntheses of styryl and 4,5,6,7-tetrahydrostyrylphthalides have also been achieved using lithiation approaches.[4,5]

We report herein a useful method for the synthesis of 3-styrylphthalides **(3a - e)** from 3-phenacylphthalides (**1a - e**) as shown in **Scheme 1**.

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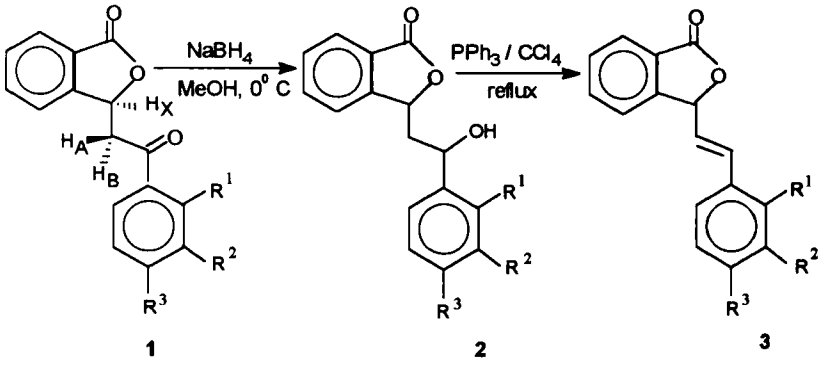
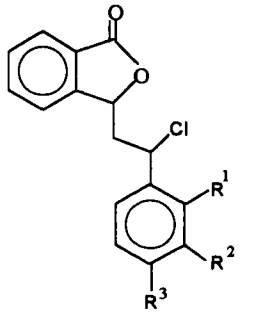


1 - 3	R^1	R^2	R^3
a	H	H	OCH_3
b	H	OCH_3	OCH_3
c	OCH_3	H	OCH_3
d	H	CH_3	OCH_3
e	H	H	H



Scheme 1

The 3-phenacylphthalides (**1a, 1b** and **1e**) were prepared using literature procedure,[6-8] while the remaining two new phthalides (**1c** and **1d**) were obtained in 80 and 84 % yields by condensing phthalaldehydic acid with 2,4-dimethoxyacetophenone and 4-methoxy-3- methyl acetophenone respectively. 3-Phenacylphthalides (**1a - e**) on reduction with sodium borohydride provided the hydroxyphthalides (**2a - e**) in 76-93 % yield. Treatment of **2a -d** with triphenyl-phosphine - tetrachloromethane gave the 3-styrylphthalides (**3a - d**) in 63-80 % yield. The hydroxyphthalide (**2e**) on similar reaction did not give the corresponding

3-styrylphthalide (**3e**), however, the chlorocompound (**4**) was isolated from this reaction in 62 % yield. Dehydrochlorination of **4** was achieved by reacting it with s-collidine in presence of lithium bromide, under refluxing conditions to give 3-styrylphthalide (**3e**) in 69 % yield.

Although there are a large number of reports on the application of triphenylphosphine-tetrachloromethane for the conversion of alcohols to the corresponding chlorides,[9] there are very few instances, wherein, dehydration of alcohols has been observed, when this reagent was used in presence of base.[10]

The present two-step method developed for the synthesis of 3-styryl-phthalides (**3a - e**) is very convenient and general one. It provides the final products in high overall yields.

EXPERIMENTAL.

All melting points are uncorrected. The IR spectra were recorded on a Perkin-Elmer FTIR-615 spectrophotometer and NMR spectra in $CDCl_3$ solutions on Jeol FX 90 Q instrument. Chemical shifts are expressed in δ (ppm) downfield from TMS as an internal standard and coupling constants in Hertz. Phenacylphthalides **1a** , **1b** and **1e** were prepared by known methods.[6-8]

General procedure for preparation of 3-phenacylphthalides 1c and 1d :

A solution of 0.870 g potassium hydroxide in 1.02 mL water and 50 % ethanol (2.54 mL) was added dropwise to a stirred solution of phthalaldehydic acid (0.990 g, 6.6 mmol) and corresponding acetophenone (6.6 mmol) in ethanol (25 mL), maintained at room temperature. The reaction mixture was stirred at

room temperature for 24 h and poured in water (20 mL).It was acidified with ice cold 1:1 HCl and the solid product obtained was extracted with chloroform (3 x 10 mL). The organic layer was washed successively with a solution of sodium bicarbonate and water. It was dried ($Na_2 SO_4$) and evaporated to give the corresponding 3-phenacylphthalides **1c** and **1d** respectively.

1c : Yield 80 %; m.p. 140^0 C; IR : 1752, 1650 cm^{-1} ; ^{1}H-NMR : 3.31 (dd, 1H, J_{AB}=17.5 Hz, J_{AX}=7.5 Hz, H_A),3.81 (dd, 1H, J_{AB} = 17.5 Hz, J_{BX}=6.5Hz ,H_B),3.83 (s,6H, 2xOMe),6.16 (bt, 1H, H_x),6.35 - 6.62 (m, 2H, ArH),7.43 - 7.67(m,3H, ArH),7.81 -8.01 (m, 2H, ArH); Anal. Calcd for C_{18} $H_{16}O_5$: C, 69.22; H, 5.16. Found : C, 69.34 ; H, 4.97.

1d : Yield 83 %; m.p. 145^0 C; IR :1754, 1671 cm^{-1}; ^{1}H- NMR :2.22 (s,3H, Me), 3.28 (dd, 1H, J_{AB} =17.5 Hz, J_{AX}=7.5 Hz, H_A), 3.77 (dd, 1H, J_{AB} =17.5 Hz, J_{BX}=6.5 Hz ,H_B), 3.88 (s,3H, OMe), 6.16 (bt, 1H, H_x), 6.84 (d, 1H, J=8.8 Hz, ArH), 7.33 -7.96 (m, 6H, ArH); Anal. Calcd for C_{18} $H_{16}O_4$: C, 72.96; H, 5.44. Found : C,73.03; H, 5.58.

General procedure for preparation of 3-(2-hydroxy 2- phenylethyl) phthalides (2a - e) :

Sodium borohydride (0.132 g, 3.5 mmol) was added to a stirred solution of 3-phenacylphthalides (**1a - e**, 3.5 mmol) in methanol (3 mL) at 0^0 C. The reaction mixture was stirred at 0^0 C for 1-2 h (monitored by TLC) and poured in ice cold water (10 mL). It was extracted with chloroform (2 x 10 mL) and the organic layer was washed with water, dried ($Na_2 SO_4$) and evaporated to give the

corresponding 3-(2-hydroxy 2-phenylethyl) phthalides (**2a - e**).

2a: Yield 93 %; m.p. 130^{0}C; IR : 3480, 1745 cm^{-1}; ^{1}H- NMR : 2.28 (app t, 3H, 1H exchangeable with D_2O, OH, -CH_2), 3.79 (s, 3H, OMe), 4.94 -5.41 (m, 2H, CH-OH, ArCH), 6.81 - 6.97(m, 2H, ArH), 7.28 - 7.66 (m, 5H, ArH), 7.77 - 7.93 (bd, 1H, J = 7.8 Hz, ArH); Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found : C,72.05; H, 5.77.

2b: Yield 87 %; m.p. 121^{0}C; IR : 3472, 1741 cm^{-1}; ^{1}H- NMR : 2.15 - 2.37 (m, 3H, 1H exchangeable with D_2O, OH, -CH_2), 3.89 (s, 6H, 2 x OMe), 4.94 -5.44 (m, 2H, CH-OH, ArCH), 6.76 - 7.04 (m, 3H, ArH), 7.37 - 7.70 (m, 3H, ArH), 7.92 (bd, 1H, J = 7.6 Hz, ArH); Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found : C, 68.99; H, 5.73.

2c: Yield 92 %; thick liquid; IR (neat) : 3481, 1751 cm^{-1}; ^{1}H-NMR : 2.3 (app t, 2H, -CH_2), 2.61 (bs, 1H exchangeable with D_2O, OH); 4.02 (s, 6H, 2 x OMe), 5.16-5.69 (m, 2H, CH-OH, ArCH), 7.11 - 7.47 (m, 3H, ArH), 7.77 - 8.11 (m, 3H, ArH), 8.33 (bd, 1H, J=7.6 Hz, ArH); Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found : C,68.60; H, 5.89.

2d: Yield 87 %; m.p. 118^0 C; IR : 3478, 3429, 1745, 1726 cm^{-1}; ^{1}H-NMR : 2.05 (bs,1H exchangeable with D_2O, OH), 2.25- 2.52 (m, 5H, Me, $ArCH_2$), 4.02 (s, 3H, OMe), 5.33 (t, 1H, J=7 Hz, -CH-OH), 5.63 (t, 1H, J = 7 Hz, ArCH), 6.94 -7.33 (m, 1H, ArH), 7.52 - 8.16 (m, 5H, ArH), 8.36 (bd, 1H, J = 7.7 Hz, ArH); Anal.Calcd for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found : C,72.24; H, 6.27.

2e: Yield 75 %; m.p. 80^0 C; IR : 3493, 1746 cm^{-1}; ^{1}H- NMR : 2.05 - 2.25 (m, 3H, 1H exchangeable with D_2O, OH, -CH_2), 4.88 - 5.36 (m, 2H, CH-OH, ArCH), 7.13 - 7.61 (m, 8H, ArH), 7.75 - 7.91 (m, 1H, ArH); Anal.Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found : C,75.48; H, 5.73.

General procedure for preparation of 3-styrylphthalides (3a - d) :

A mixture of triphenylphosphine (0.262 g,1 mmol), 3-(2-hydroxy 2-phenyl ethyl) phthalides (**2a - d**, 1 mmol) was refluxed in tetrachloromethane (0.5 mL) for 2.5 -5 h (monitored by TLC).Tetrachloromethane was distilled off and the solid obtained was chromatographed over silica gel using n-hexane: ethyl acetate (99:1) as an eluent to give the corresponding 3-styrylphthalides (**3a-d**).

3a : Yield 69 %; m.p. 99^0 C; IR: 1755, 1651 cm^{-1}; ^{1}H- NMR : 3.8 (s, 3H, OMe), 6.02 - 6.40 (m, 2H, C_3H, -CH=), 7.02 - 7.37 (m, 3H, -CH=, 2 x ArH), 7.6 - 8.17 (m, 5H, 5 x ArH), 8.40 (bd, 1H, J=7.71 Hz, ArH); Anal.Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found : C,76.43; H, 5.48.

3b : Yield 80 %; m.p. 117^0 C; IR: 1756, 1645 cm^{-1}; ^{1}H- NMR : 3.82 (s, 6H, 2 x OMe), 5.83 - 6.09 (m, 2H, C_3H, -CH=), 6.72 -7.03 (m, 4H, -CH=, 3 x ArH), 7.35 -7.75 (m, 3H, ArH), 7.96 (bd, 1H, J=8.3 Hz, ArH); Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found : C,72.88; H, 5.45.

3c : Yield 80 %; m.p. 115^0 C; IR: 1759, 1647 cm^{-1}; ^{1}H- NMR : 3.88 (s, 6H, 2 x OMe), 5.77 - 6.17 (m, 2H, C_3H, -CH=), 6.68 -7.11 (m, 4H, -CH=, 3 x ArH), 7.33 -7.73 (m, 3H, ArH), 7.93 (bd, 1H, J=7.9 Hz, ArH); Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found : C,72.85; H, 5.63.

3d : Yield 78 %; m.p.106^0 C; IR; 1749,1648 cm^{-1}; ^{1}H-NMR : 2.23 (s, 3H, Me), 3.89 (s, 3H, OMe), 5.94 - 6.26 (m, 2H, C_3H, -CH =), 6.78 - 7.10 (m, 2H, -CH =, ArH), 7.26-7.44 (m, 2H, ArH), 7.55 - 7.94 (m, 3H, ArH), 8.10 (bd, 1H, J=8 Hz, ArH); Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found : C,72.25; H, 5.92.

Procedure for the preparation of 3-styrylphthalide (3e):

A mixture of chlorophthalide **4** (0.250 g ,1 mmol), lithium bromide(0.121 g, 1.4 mmol) and s-collidine (10 mL) was refluxed for 5 h . The reaction mixure was cooled to room temperature, poured in ice cold 1:1 HCl (10 mL) and extracted with chloroform (2 x 10 mL). The organic layer was washed with water, dried (Na_2SO_4) and evaporated to give a thick liquid, which was chromatographed over silica gel using n-hexane: ethyl acetate (97:3) as an eluent to give 3-styrylphthalide **3e** (0.150g, 69%). It was identical with authentic sample[4](TLC ,m.p., superposable IR).

ACKNOWLEDGEMENT : We thank Mrs. J. P.Chaudhari and Mr. A. P. Gadgil for spectral and analytical data. One of us (APM) thanks CSIR, New Delhi for the award of a Senior Research Fellowship.

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(Received in the UK 16th August 1996)