# New route synthesis of styryl pyrones:High yield synthesis, reactions and spectral properties of 2-phenyl-6-styryl-4-pyrones

**Abdel Moneim El-Ghanam**

*Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Ibrahimia P.O. Box 426, Alexandria 21321, Egypt*

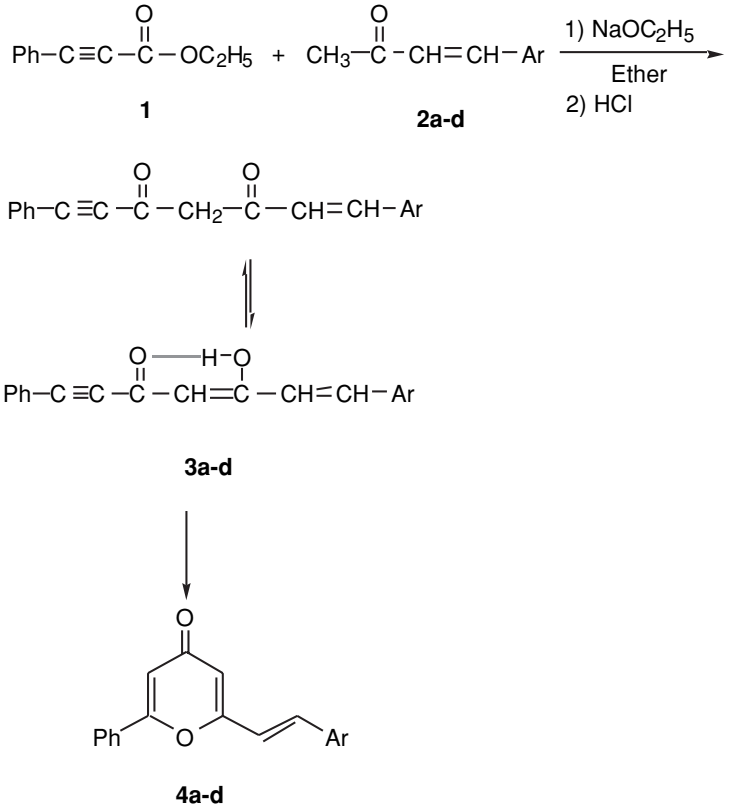
2-Phenyl-6-styryl-4-pyrone derivatives have been synthesised from the reaction of ethyl phenylpropiolate with benzylideneacetone derivatives in the presence of sodium ethoxide. Treatment of styrylpyrone with phosphorus pentasulfide gave the corresponding styrylpyran-4-thione which on treatment with hydroxylamine hydrochloride and aqueous methylamine afforded the corresponding oxime and 1-methyl-2-phenyl-6-styrylpyridine-4(1*H*)-thione, respectively. On the other hand, styrylpyran-4-thione reacted with malononitrile to give pyrolylidenemalononitrile which on treatment with bidentate reagents, hydrazine hydrate, hydroxylamine hydrochloride, thiourea, and thiosemicarbazide afforded the corresponding styrylspiropyran derivatives of pyrazole, 1,2-oxazole or 1,3-thiazine, respectively.

**Keywords:** styrylpyrones, spectral properties

Many 4-pyrones or compounds containing 4-pyrone moieties has been synthesised during the last several decades, which have biological activities, such as herbicidal, fungicidal, antiallergenic as well as anticancer activity.[1-3] The 4-pyrones containing styryl groups attached to the pyrone ring has been reported to have anticancer activity.[4,5] Also, 2-hydroxy-5-styryl-4-pyrone has been used in the formulation of skin-lightening cosmetic[6] as well as in the synthesis of polycondensed heterocyclic compounds.[7] Several 2-hydroxy-5-arylethenyl-4-pyrones as well as 5-methoxy analogues have been prepared by condensation of benzaldehyde with allomaltol monomethyl ether[8] or by Wittig reaction of 2-chloromethyl-5-methoxy-4-pyrone with triphenylphosphine[9] followed by the reaction with aryl aldehydes, respectively. The yields of these reactions did not exceed 36%. The purpose of the present work was to find a new synthetic procedure to prepare and optimised the yields of a series of 6-styryl-4-pyrones due to their importance in biological activity, specially as anticancer activities.

## Results and discussion

The titled compound has been synthesised by stirring a mixture of ethyl phenylpropiolate **1** and benzylideneacetone derivatives **2a–d** in dry ether at 0°C in 1:1 molar ratio using sodium ethoxide as a base for 5 h. The reaction mixture was




**1** **2a-d** **3a-d** **4a-d**

Ar: a = $C_6H_5$, b = *p*-$CH_3C_6H_4$, c = *p*–$CH_3OC_6H_4$, d = *p*–$ClC_6H_4$

**Scheme 1**

* Correspondent. E-mail: delghanam@yahoo.com

poured in ice water and acidified with concentrated HCl to give 2-phenyl-6-styryl-4*H*-pyran-4-ones **4a–d** (Scheme 1). The products, 2-phenyl-6-styryl-4-pyrones, probably formed through the intermediates **3**.[10] The structure of these styryl derivatives **4a–d** were elucidated from their spectral and analytical data (see Experimental). The IR spectra showed bands for the carbonyl of 4-pyrones at 1668–1638 $cm^{-1}$ and a band at 1615–1592 $cm^{-1}$ characteristic to a double bonds of side chain styryl groups. $^1$H NMR spectra, showed beside other characteristics two doublets at δ 6.49–6.92 and δ 6.84–7.62 with the coupling constants 16.2–16.7 Hz proving the *trans*-configuration for the ethylenic double bonds of the styryl moiety at position 2.[8]

Treatment of **4a** with phosphorus pentasulfide afforded 2-phenyl-6-styryl-4*H*-pyran-4-thione **5** which on treatment with hydroxylamine hydrochloride and aqueous methylamine afforded the oxime **6** and 1-methyl-2-phenyl-6-styrylpyridine-4(1*H*)-thione **7**, respectively (Scheme 2). While the treatment of thione **5** with malononitrile in the presence of triethylamine gave (2-phenyl-6-styryl-4*H*-pyran-4-ylidene)malononitrile **8** in moderate yield (Scheme 2). The $^1$H NMR spectrum of the thione **5** showed an downfield shift in the resonance of the H-3 and H-5 protons, δ 7.92 and δ 8.36, respectively comparing to the parent styryl pyran **4a**. Similar deshielding on replacement of carbonyl with thiocarbonyl were also observed for other 4*H*-pyran-4-thiones.[11] Such significant deshielding in the resonance of H-3 and H-5 protons of **5** can be attributed to the increased magnetic anisotropy of the thione over carbonyl.[12]

The structure of 4-pyrolylidenemalononitrile **8** is confirmed from its spectral and analytical data (Experimental). The IR spectrum showed a moderately C≡N absorption at 2188 $cm^{-1}$ while its $^1$H NMR spectrum showed singlets at δ 6.82 and δ 7.22 for H-3 and H-5 protons of pyran ring besides two doublets at δ 7.06 and δ 7.26 for styryl moiety.

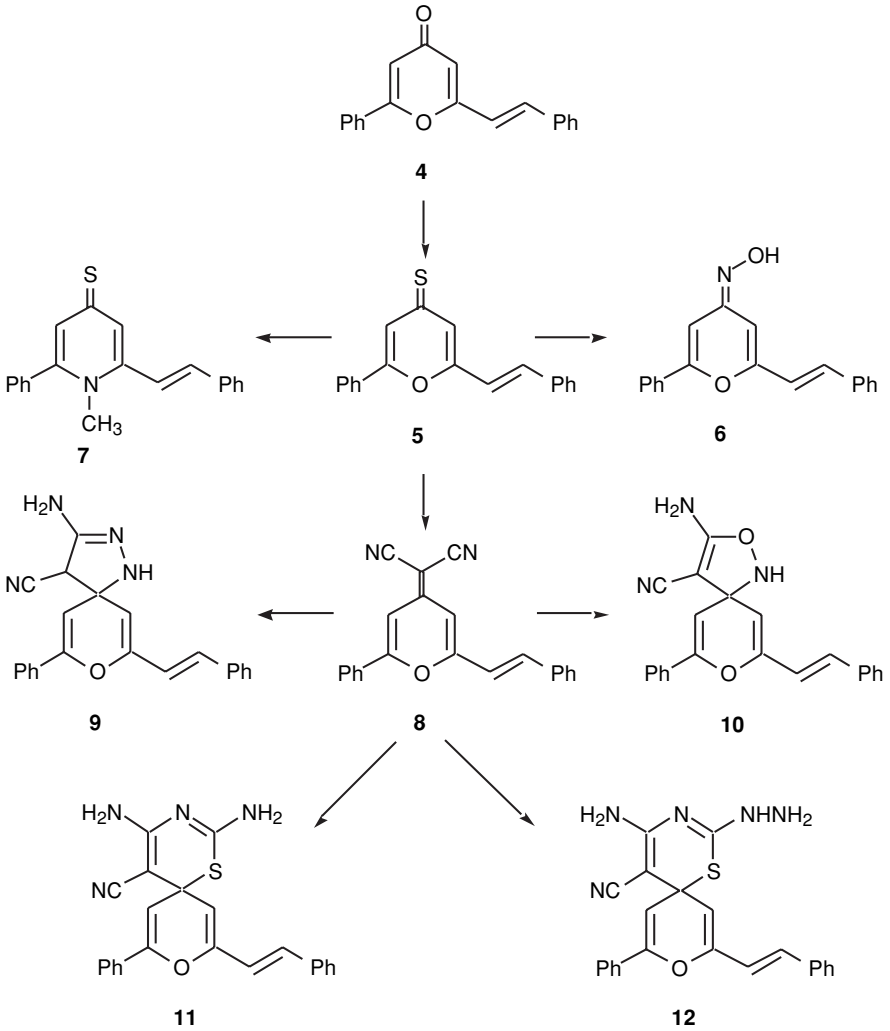
Treatment of **8** with hydrazine hydrate, hydroxylamine hydrochloride, thiourea and thiosemecarbazide in absolute ethanol in the presence of pipredine afforded the corresponding styryl spiropyran derivatives of pyrazole, isoxazole, 1,3-thiazine, **9–12**, respectively (Scheme 2). The reaction involve the addition of the amino or mercapto groups at the ethylenic double bond and nucleophilic attack of the amino group to give the cyclised spiro compounds.[13,14] All styryl spiropyran derivatives **9–12** are confirmed from their spectral and analytical data (Experimental).

## Experimental

Elemental analysis were preformed on a Perkin-Elmer 240 microanalyser. Melting points were recorded on a Kofler Block and are uncorrected. IR spectra were measured with a Unicam SP 1025 spectrophotometer for KBr pellets. The $^1$H NMR spectra were recorded on Jeol ECA 500 MHz spectrometer using TMS as internal standard. Mass spectra were recorded on a Varian Mat CH-7 instrument at 70 eV.

*Preparation of 2-phenyl-6-styryl-4H-pyran-4-ones* **4a–d**. *General procedure*

An ethereal solution of benzylidene acetone derivatives **2a–d** (0.0842 mol) and ethyl phenylpropiolate **1** (0.0842 mol) were added dropwise




**Scheme 2**

to an ice cold suspension of sodium ethoxide (0.0286 mol) in dry ether (120 ml). The reaction mixture was stirred at 08°C for 5 h and then poured to an ice cold water and then acidified with concentrated HCl to give 2-phenyl-6-styryl-4*H*-pyran-4-ones **4a–d** as yellow solid which crystallised from methanol.

*2-Phenyl-6-styryl-4H-pyran-4-one* (**4a**): Yield, 83 %, m.p. 146–148 °C ; IR (KBr, $cm^{-1}$): 3096, 1652, 1588; $^1$H NMR (DMSO-$d_6$, δ): 6.48 (s, 1H, C-3 of pyrone), 6.66 (s, 1H, C-5 of pyrone), 7.08 (d,1H, *J* = 16.2 Hz, styrene proton), 7.42 (d, 1H, *J* = 16.2 Hz, styrene proton), 7.36–7.72 (m, 10H, aromatic); MS: *m/z* (relative abundance): $M^+$ 274 (24), 258 (36), 246 (51) 197 (42), 143 (100), 120 (26), 94 (32), 77 (46). Anal. Calcd. For $C_{19}H_{14}O_2$: C, 83.21; H, 5.11. Found: C, 83.42; H, 5.02.

*2-Phenyl-6-[2-(4-methylphenyl)ethenyl]-4H-pyran-4-one* (**4b**): Yield, 79 %, m.p. 166–167 °C; IR (KBr, $cm^{-1}$): 3112, 2896, 1648, 1592; $^1$H NMR (DMSO-$d_6$, δ): 2.44 (s, 3H, $CH_3$), 6.42 (s, 1H, C-3 of pyrone), 6.82 (s, 1H, C-5 of pyrone), 7.16 (d, 1H, *J* = 16.5 Hz, styrene proton), 7.62 (d, 1H, *J* = 16.5 Hz, styrene proton), 7.26–7.64 (m, 9H, aromatic); MS: *m/z* (relative abundance): $M^+$ 288 (28), 273 (12), 260 (38), 211 (28), 143 (100), 94 ( 36), 77 (42), 91 (22). Anal. Calcd. For $C_{20}H_{16}O_2$: C, 83.33; H, 5.56. Found: C, 83.42; H, 5.38.

*2-Phenyl-6-[2-(4-methoxyphenyl)ethenyl]-4H-pyran-4-one* (**4c**): Yield, 88 %, m.p. 196–198 °C; IR (KBr, $cm^{-1}$): 3118, 2904, 1638, 1615; $^1$H NMR ( DMSO-$d_6$, δ): 3.72 (s, 3H, $OCH_3$), 6.46 (s, 1H, C-3 of pyrone), 6.68 (s, 1H, C-5 of pyrone), 7.14 (d, 1H, *J* = 16.4 Hz, styrene proton), 7.54 (d, 1H, *J* = 16.4 Hz, styrene proton), 7.42–7.86 ( m, 9H, aromatic); MS: *m/z* (relative abundance): $M^+$ 304 (28), 273 (32), 143 (100), 107 (52), 94 (62), 77 (66). Anal. Calc. For $C_{20}H_{16}O_3$: C, 78.95; H, 5.26. Found: C, 78.82; H, 5.30.

*2-Phenyl-6-[2-(4-chlorophenyl)ethenyl]-4H-pyran-4-one* (**4d**): Yield, 82 %, m.p. 170–172 °C; IR( KBr, $cm^{-1}$) 3102, 2896, 1668, 1615; $^1$H NMR (DMSO-$d_6$, δ): 6.38 (s, 1H, H-3 of pyrone), 6.64 (s, 1H, H-5 of pyrone), 7.12 ( d, 1H, *J* = 16.7 Hz, styrene proton), 7.38–7.82 ( m, 10H, 1H of styrene + 9H aromatic). MS: *m/z* (relative abundance): $M^+$ 310 (6), 308 (19), 280 (36), 231 (26), 143 ( 100), 112 (42), 94 (48), 77 (28). Anal. Calc. For $C_{19}H_{13}O_2Cl$: C, 73.91; H, 4.21. Found: C, 73.96; H, 4.12.

*2-Phenyl-6-styryl-4H-pyran-4-thione* (**5**): This compound was prepared from 2-phenyl-6-styryl-4*H*-pyran-4-one **4a** and phosphorus pentasulfide as described earlier.[12]

Yield, 71%, m.p. 182–183 °C; IR (KBr, $cm^{-1}$): 3042, 1648, 1082; $^1$H NMR ($CDCl_3$, δ): 8.36, 7.92 (s, 2H, H-3 and H-5 of pyran), 7.12 (d, 1H, *J* = 16.2 Hz), 7.38–7.78 (m, 11H, 10H aromatic + 1H styrene); MS: *m/z* (relative abundance): $M^+$ 290 (20), 246 (30), 197 (36), 143 (100), 120 (18), 94 (46), 77 (52). Anal. Calc. For $C_{19}H_{14}OS$: C, 78.62; H, 4.83. Found: C, 78.54; H, 4.92.

*2-Phenyl-6-styryl-4H-pyran-4-one oxime* (**6**): This compound was prepared from 2-phenyl-6-styryl-4*H*-pyran-4-thione **5** and hydroxylamine hydrochloride and sodium acetate in ethanol as described earlier.[12]

Yield, 71%, m.p. 168 °C; IR (KBr, $cm^{-1}$): 3528 (br), 3086, 1652; $^1$H NMR ($CDCl_3$, δ): 7.58 (m, 10H, aromatic), 7.14, 6.72 (s, 2H, C-3 and C-5 pyran protons) 7.02 (d, 1H, *J* = 16.2 Hz), 7.22 (d, 1H, *J* = 16.2 Hz). Anal. Calc. For $C_{19}H_{15}NO_2$: C, 78.89; H, 5.19; N, 4.84. Found: C, 78.71; H, 5.02; N, 4.96.

*1-Methyl-2-phenyl-6-styrylpyridine-4(1H)-thione* (**7**): This compound was prepared from styrylpyranthione **5** and 33% aqueous methylamine solution as described earlier.[10]

Yield, 73%, m.p. 156 °C; IR (KBr, $cm^{-1}$): 3088, 2976, 1634, 1076; $^1$H NMR ($CDCl_3$, δ): 7.62 (m, 10H, aromatic), 7.08 (d, 1H, *J* = 16.2 Hz), 7.22 (d, 1H, *J* = 16.2 Hz), 3.36 (s, 3H, $CH_3$). Anal. Calc. For $C_{20}H_{17}NS$: C, 79.21; H, 5.61; N, 4.62; S, 10.56. Found: C, 79.26; H, 5.72; N, 4.70; S, 10.38.

*(2-Phenyl-6-styryl-4H-pyran-4-ylidene)malononitrile* (**8**): 0.023 mol of 2-phenyl-6-styryl-4*H*-pyran-4-one **4a** was added to an equimoler amount of malononitrile in 40 ml ethanol and few drops of trimethylamine. The reaction mixture was refluxed for 4 h, concentrated and cooled to give **8** , which collected by filtration and crystallised from ethanol.

Yield, 71%, m.p. 166–168 °C; IR (KBr, $cm^{-1}$): 3082, 2188, 1646: $^1$H NMR (DMSO-$d_6$, δ): 7.22, 6.82 ( s, 2H, for H-3 and H-5 of pyran), 7.06 (d, 1H, *J* = 16.2 Hz), 7.26 (d, 1H, *J* = 16.2 Hz), 7.38–7.82 ( m, 10H, aromatic). Anal. Calc. For $C_{22}H_{14}N_2O$: C, 81.99; H, 4.35; N, 8.70. Found: C, 81.82; H, 4.32; N, 8.82.

*Synthesis of spiro compounds* **9–12**. *General procedure*

A solution of (2-phenyl-6-styryl-4*H*-pyran-4-ylidene)malononitrile **8** (0.023 mol) in 40 ml absolute ethanol was treated with equimolar amount of hydrazine hydrate, or hydroxylamine hydrochloride or thiourea or thiosemecarbazide and few drops of piperidine. The reaction mixture was refluxed for 4 hours, concentrated, cooled, and the separated compound was filtered off and recrystallised from ethanol.

*5'-amino-2-phenyl-6-styryl-2',4'-dihydrospiro[pyran-4,3'-pyrazole]-4'-carbonitrile* (**9**): Yield, 62 %, m.p. 217–219 °C; IR (KBr, $cm^{-1}$): 3391, 3326, 3214, 3094, 2198, 1642; $^1$H NMR (DMSO-$d_6$, δ): 10.82 (br, 1H, NH), 6.92 and 7.20 ( s, 2H for H-3 and H-5 of pyran), 7.08 (d, 1H, *J* = 16.2 Hz), 7.28 (d, 1H, *J* = 16.2 Hz), 7.40–7.78 (m, 10H, aromatic), 5.42 (br, 2H, $NH_2$). Anal. Calc. For $C_{22}H_{18}N_4O$: C, 74.58; H, 5.08; N, 15.82. Found: C, 74.42; H, 5.16; N, 15.66.

*5-Amino-2'-phenyl-6'-styrylspiro[[1,2]oxazole-3,4'-pyran]-4-carbonitrile* (**10**): Yield, 60 %, m.p. 196–198 °C; IR (KBr, $cm^{-1}$): 3398, 3322, 3196, 3092, 2186, 1642; $^1$H NMR (DMSO-$d_6$, δ): 11.24 (br, 1H, NH), 7.62 (m, 10H, aromatic), 7.20, 6.88 ( s, 2H, H-3 and H-5 of pyran), 7.12 (d, 1H, *J* = 16.2 Hz), 7.30 (d, 1H, *J* = 16.2 Hz), 5.62 (br, 2H, $NH_2$). Anal. Calc. For $C_{22}H_{17}N_3O_2$: C, 74.37; H, 4.79; N, 11.83. Found: C, 74.42; H, 4.86; N, 11.74.

*2',4'-Diamino2-phenyl-6-styrylspiro[pyran-4,6'-[1,3]thiazine]-5'-carbonitrile* (**11**): Yield, 68 %, m.p. 182–183 °C; IR (KBr, $cm^{-1}$): 3390, 3336, 2202, 1638; $^1$H NMR (DMSO-$d_6$, δ): 7.62 (m, 10H, aromatic), 7.22, 6.84 ( s, 2H, C-3 and C-5 of pyran), 7.08 (d, 1H, *J* = 16.2 Hz), 7.14 ( d, 1H, *J* = 16.2 Hz), 5.46–5.82 (br, 4H, $2NH_2$). Anal. Calc. For $C_{23}H_{18}N_4OS$: C, 69.35; H, 4.52; N,14.07; S, 8.04. Found: C,69.28; H, 4.56; N, 14.12; S, 8.26.

*4'-Amino-2'-hydrazino-2-phenyl-6-styrylspiro[pyran-4,6'-[1,3]thiazine]-5'-carbonitrile* (**12**): Yield, 62 %, m.p. 242–244 °C; IR (KBr, $cm^{-1}$): 3408, 3332, 3236, 3092, 2936, 2196, 1636; $^1$H NMR (DMSO-$d_6$, δ): 10.82 (br, 1H, NH), 7.68 (m, 10H, aromatic), 7.26, 6.88 (s, 2H, C-3 and C-4 of pyran), 7.06 ( d, 1H, *J* = 16.2 Hz), 7.18 (d, 1H, *J* = 16.2 Hz), 4.88–5.46 ( br, 4H, $2NH_2$). Anal. Calc. For $C_{23}H_{19}N_5OS$: C, 66.83; H, 4.60; N, 16.95; S, 7.75. Found: C; 66.68; H, 4.62; N, 16.80; S, 7.82.

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