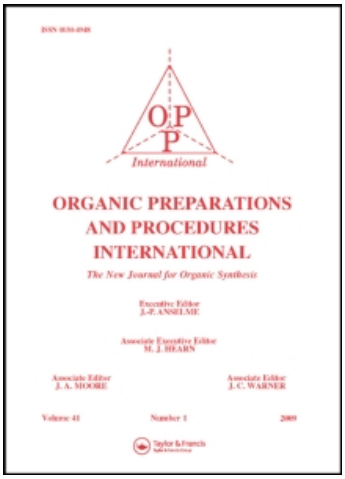

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PREPARATION AND CHARACTERIZATION OF NEW SUBSTITUTJED 5-METHOXY-2-STYRYL-4-PYRONES

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32. E. B. Hersberg, *J. Org. Chem.*, **12**, 541 (1948).

33. J. R. Maloney and R. E. Lyle, *Synthesis*, 212 (**1978**).

34. L Singh and R. N. Ram, *Synth. Commun.*, **23**, 3139 (1962).

35. J. Drabowicz, *Synthesis*, 125 (**1980**).

36. C. G. Rao, A. S. Radhakrishna, B. B. Singh and S. P. Bhatnagar, *ibid.*, 805 (**1983**).

37. S. Satish and N. Kalyanam, *Chem. Ind. (London)*, 809 (**1981**).

38. S. H. Pines, J. M. Chemerda and M. A. Kozlowski, *J. Org. Chem.*, **31**, 3446 (1966).

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PREPARATION AND CHARACTERIZATION OF NEW SUBSTITUTED 5- METHOXY-2-STYRYL-4-PYRONES

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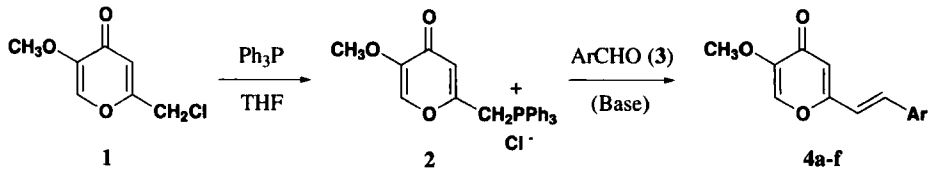
During the last several decades, many 4-pyrones or compounds containing 4-pyrone moieties has been found to be biologically active; bactericidal, insecticidal, herbicidal, fungicidal, antiallergenic, cytotoxic and potential anticancer activity has been reported.[1] Some 4-pyrones with the styryl group possess anticancer activity[2] and 5-hydroxy-2-styryl-4-pyrone has been used in the formulation of skin-lightening cosmetics,[3] and the use of such pyrones in the synthesis of polycondensed heterocyclics has been described.[4] Previous papers of this series described some reactions of 5-hydroxy-4-pyrones.[5] The transformation to corresponding *N*-substituted-5-hydroxy-4-pyridones (useful as chelating agents),[5a-d] photochemical isomerizations[5e] and ring-contraction reactions[5f] have been studied. Our continuing interest in the photochemistry of 4-pyrones, especially in regard to the difference between reactions of 5-hydroxy and its methylated analogues, prompted us to study styryl-substituted 4-pyrones.

Herewith we report the synthesis of several aryl-substituted 5-methoxy-2-ethenyl-4-pyrones (**4a-4f**) presumably capable of exhibiting various photochemical reactions. Several 5-hydroxy-2-

arylethenyl-4-pyrones have been prepared[6] but the reports about the 5-methoxy analogues are scarce. To our best knowledge, the only reported example[4] of such a compound is unsubstituted 5-methoxy-2-styryl-4-pyrone (**4a**), by the condensation of benzaldehyde with allomaltol monomethyl ether, obtainable by a tedious three-step sequence from kojic acid;[4] the overall yield reported did not exceed 12%. To overcome this drawback, we now report the alternative route employing a Wittig reaction, which almost tripled the overall yield.



1 2 4a-f

a) Ar = C_6H_5 b) Ar = p-$CH_3C_6H_4$ c) Ar = p-$CH_3OC_6H_4$

d) Ar = p-ClC_6H_4 e) Ar = o-ClC_6H_4 f) Ar = p-$NO_2C_6H_4$

TABLE 1. Reaction Conditions for the Preparation, Yields, mps. and Analysis of **4a-4f**

Comp.	Solv./Base[a]	Temp. (°C)	Time (hrs)	Yield (%)	mp. (°C)	Anal. Calcd (Found) C	H	N	Cl
4a	A/a	r.t.	6	92	136-138				
	A/b	r.t.	8	83					
	B/d	30	8	58					
	C/c	r.t.	8	57					
	E/e	40	18	48					
	D/e	60	24	38					
4b	A/b	50	6	65	161-162	74.41 (74.68)	5.84 (5.76)		
4c	A/b	50	12	64	143-146	69.75 (69.94)	5.47 (5.34)		
4d	A/a	50	6	88	131-133	64.01 (64.18)	4.23 (4.38)		13.49 (13.29)
4e	A/a	30	6	67	138-140	64.01 (64.21)	4.23 (4.05)		13.49 (13.62)
4f	A/a	30	6	90	198-199	61.54 (61.67)	4.07 (3.89)	5.13 (5.28)	

a) A = ethanol; B = *t*-butanol; C = dimethylformamide; D = tetrahydrofuran; E = dichloromethane; a = potassium ethoxide; b = sodium ethoxide: c = sodium methoxide; d = potassium *t*-butoxide; e = potassium carbonate.

Starting compound **1** was also prepared from kojic acid but in only two steps. The straightforward Wittig reaction[8] gave the products **4a-4f** in satisfactory yield (Table 1). Although the Wittig reaction depends on stabilizing effects of substituents present both in the phosphonium salt and carbonyl compound, the effect of the base used and the solvent should not be neglected. A mixture of *cis*- and *trans*-alkene is to be expected and the ratio of isomers depends on reaction conditions.[7] To

find the optimal conditions for the preparation of the series of styryl derivatives **4b-4f**, the Wittig reaction was performed while the solvent, the base, the reaction temperature and time (Table 1) were changed on the model compound **4a**. The best result was obtained in ethanol using potassium ethoxide as a base. The reaction of phosphonium salt **2** and the appropriate substituted benzaldehyde **3** gave a good yield of mostly the *trans*-isomer of **4** (Table 1); it was purified by column chromatography. Styryl derivatives **4a-4f** were characterized completely by UV, IR, ^1H and ^{13}C NMR spectral data and by elemental analyses for all new compounds (Table 2-4). The IR spectra of all *trans*-isomers show characteristic 4-pyrone carbonyl band at 1640-1620 cm^{-1} and a double bond frequency at 1610-1580 cm^{-1} (Table 2). The UV spectra exhibited maxima at 224-248 and 310-330 nm (Table 2). For the structural determinations of **4a-4f**, ^1H and ^{13}C NMR spectra were the most valuable (Tables 3 and 4). The most significant peaks used to assign the *trans*-configuration were the ^1H NMR signals for ethylenic double bond found as two doublets at δ 6.69-7.31 and δ 7.19-7.80 with the coupling constants $J_{H,H}$ =16.11-16.95 Hz, as expected for *trans*-substituted double bonds.[1b,6]

TABLE 2. UV and IR Spectra for Compounds **4a-4f**

Cmpd	UV[a] λ_{max} (log ε)	IR[b] (cm^{-1})
4a	320 (4.50) 232 (4.25)	3080(w), 2900(vw), 1630(vs), 1610(vs), 1570(m), 1450(w), 1425(w), 1370(m), 1230(s), 100(m), 950(m), 875(m), 820(m), 755(w), 695(w)
4b	328 (4.02) 236 (4.15)	3080(w), 2900(vw), 1625(vs), 1610(vs), 1570(w), 1420(m), 1380(m), 1290(m), 1270(w), 1230(vs), 1190(w), 1180(w), 1160(vw), 1000(s), 960(s), 930(s), 860(s), 800(s), 750(m)
4c	345 (4.19) 228 (3.95)	3050(w), 2810(vw), 1630(vs), 1600(vs), 1580(m), 1500(s), 1435(m), 1420(m), 1380(w), 1270(w), 1250(m), 1230(m), 1170(s), 1110(w), 1015(vw), 1000(m), 950(m), 930(m), 830(m), 810(m), 750(w), 690(w)
4d	324 (4.25) 228 (3.78)	3090(w), 2890(vw), 1645(vs), 1610(vs), 1570(w), 1480(w), 1420(m), 1270(s), 1230(vs), 1080(w), 1000(m), 960(m), 920(m), 850(m), 810(m), 790(w)
4e	312 (4.31) 230 (4.05)	3040(w), 2900(vw), 1640(vs), 1605(vs), 1590(w), 1450(w), 1435(w), 1280(m), 1250(m), 1220(vs), 1000(m), 950(m), 925(m), 860(m), 765(vs), 720(w), 690(s)
4f	335 (4.40) 222 (4.38)	3025(vw), 2920(vw), 1640(vs), 1630(s), 1600(m), 1580(m), 1540(m), 1500(s), 1400(m), 1330(vs),1260(m), 1220(vs), 1180(m), 1100(m), 1000(m), 970(m), 920(m), 840(s), 800(m), 740(m), 680(m)

a) In methanol. b) Peak intensity is represented as very strong (vs), strong (s), medium (m), weak (w) or very weak (vw).

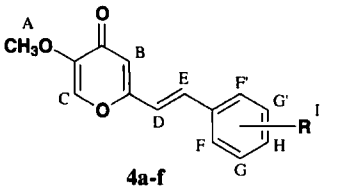
EXPERIMENTAL SECTION

Melting points were determined on an Original Kofler Mikroheitztisch apparatus (Reichardt, Wien) and are not corrected. The IR spectra were obtained as potassium bromide pellets on a Perkin-Elmer Model 297 instrument. The UV spectra were recorded on a Hitachi-Perkin-Elmer Model 124 spectrophotometer using methanolic solutions. The ^1H NMR spectra and ^{13}C NMR spectra were recorded on a Varian GEMINI 300 spectrometer in DMSO-d_6 with TMS as internal standard. The starting 2-chloromethyl-5-methoxy-4-pyrone was prepared from kojic acid ('Fluka') *via* 2-chloromethyl-5-

hydroxy-4-pyrone according to reported procedures.[9, 10]

Preparation of Phosphonium Salt (2).[11]- A mixture of 2-chloromethyl-5-methoxy-4-pyrone (**1**) (11.7 g, 0.067 mole) and triphenylphosphine (31.9 g, 0.079 mole) in 300 mL of dry tetrahydrofuran was heated under reflux temperature for 4 days. After cooling to room temperature the precipitate (14.7 g) was removed by filtration. Continued reflux of the filtrate for another 6 days gave a second crop of **1** (7.2 g); total yield 21.9 g (82%).

TABLE 3. ^{1}H NMR spectra[a] of compounds **4a-4f**



4a-f

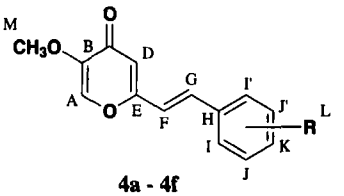
Cmpd	**4a** (R = H)	**4b** (R = *p*-CH_3)	**4c** (R = *p*-OCH_3)	**4d** (R = *p*-Cl)	**4e** (R = *o*-Cl)	**4f** (R = *p*-NO_2)
H^A	3.69 (s, 3H)	3.79 (s, 3H)	3.70 (s, 3H)	3.82 (s, 3H)	3.79 (s, 3H)	3.72 (s, 3H)
H^B	6.49 (s, 1H)	6.55 (s, 1H)	6.27 (s, 1H)	6.59 (s, 1H)	6.39 (s, 1H)	6.56 (s, 1H)
H^C	8.09 (s, 1H)	8.17 (s, 1H)	7.80 (s, 1H)	8.19 (s, 1H)	7.61 (s, 1H)	8.12 (s, 1H)
H^D	7.12 (d, 1H) *J* = 16.38 Hz	7.18 (d, 1H) *J* = 16.41 Hz	7.08 (d, 1H) *J* = 16.42 Hz	7.26 (d, 1H) *J* = 16.11 Hz	6.69 (d, 1H) *J* = 16.95 Hz	7.31 (d, 1H) *J* = 16.42 Hz
H^E	7.43 - 7.38 (m)[b]	7.60 (d, 1H) *J* = 16.40 Hz	7.19 (d, 1H) *J* = 16.42 Hz	7.44 (d, 1H) *J* = 16.11 Hz	7.80 (d, 1H) *J* = 16.95 Hz	7.58 (d, 1H) *J*= 16.42 Hz
$H^{F, F'}$	7.68 (d, 2 H) *J* = 6.98 Hz	7.70 (d, 2 H) *J* = 8,40 Hz	7.29 (d, 2 H) *J* = 8.42 Hz	7.63 (d, 2 H) *J* = 8.79 Hz	7.65 (d, 1H) *J* = 5.89 Hz	7.92 (d, 2H) *J* = 8.78 Hz
$H^{G, G'}$	7.43 - 7.38 (m)[c]	7.38 (d, 2 H) *J* = 8.40 Hz	6.87 (d, 2 H) *J* = 8.42 Hz	7.86 (d, 2 H) *J* = 8.79 Hz	7.29 (dd, 1H) *J* = 5.90 Hz 7.42 (d, 1H) *J* = 5.95 Hz	8.26 (d, 2 H) *J* = 8.78 Hz
H^H					7.42 (dd, 1H) *J* = 5.90 Hz)	
H^I		2.43 (s, 3H)	3.54 (s, 3H)			

a) Chemical shift (δ) in ppm (TMS), solvent: DMSO-d_6. b) Overlapped with aromatic protons G, G'and H; c) Overlapped with ethylene proton E.

Preparation of 5-Methoxy-2-styryl-4-pyrones (4a-4f). General Procedure.- To a warm solution (50-55°) of (5-methoxy-4-pyron-2-yl)methyltriphenylphosphonium chloride (2.4 g, 6.0 mmol) and an equimolar quantity of the arylaldehyde (**3a-3f**) in 200 mL of the dried solvent, a 10% excess of the base (6.6 mmol) in 15 mL of the same solvent was added dropwise with stirring at room temperature. The reaction mixture was then heated at 25-60° with stirring for 6-24 h (Table 1). After removal of the

solvent under reduced pressure, 100 mL of water was added, the mixture acidified with 1 M hydrochloric acid and extracted with chloroform (3x50 mL). After drying, the solvent was evaporated. The residue was taken into dichloromethane and passed through a silica-gel column to separate most of the triphenylphosphonium oxide. After evaporation of dichloromethane, the organic residue was rechromatographed on an alumina column using petroleum ether/acetone 5:1 as eluent. After separation of a small amount of the corresponding *cis*-alkene, pure *trans*-**4a-4f** (Table 1) was obtained.

TABLE 4. ^{13}C NMR spectra[a] for compounds **4a-4f**



4a - 4f

Cmpd	4a	4b	4c	4d	4e	4f
C^A	135.29	134.99	135.56	134.43	131.81	133.14
C^B	148.36	147.97	147.97	148.37	148.62	148.79
C^C	173.26	172.85	174.10	173.93	172.26	174.02
C^D	113.08	112.42	112.08	113.05	113.64	114.54
C^E	161.17	160.95	161.57	160.67	160.78	159.87
C^F	120.16	118.74	116.54	119.53	121.53	123.41
C^G	138.98	139.34	136.63	136.80	137.06	137.12
C^H	135.22	132.17	127.26	133.07	134.37	140.91
$C^{I, I'}$	127.82	127.32	128.78	128.90	132.89[b]	127.91
$C^{J, J'}$	129.16	129.29	114.11	128.33	130.42[c]	124.14
C^K	129.79	139.17	160.61	135.22	130.06	147.89
C^L		20.71	55.08			
C^M	56.28	56.32	56.04	56.10	56.42	56.35

a) Chemical shift (δ) in ppm (TMS), solvent: DMSO-d_6; b) Signal for C^I (carrying halogen), signal for $C^{I'}$ at 127.06 ppm; c) Signal for C^J, signal for $C^{J'}$at 126.82.

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REFERENCES

1. See e. g.: a) S. Yamamura and S. Nishiyama, *Bull. Chem. Soc. Jpn*, **70**, 2025 (1997); b) D. C. G. A. Pinto A. M. S. Silva and J. A. S. Cavaleiro, *J. Heterocycl. Chem.*, **33**, 1887 (1996); c) J. D. Brion, G. Le Baut, F. Zammatio, A. Pierre, G. Atassi and L. Belachmi, *Eur. Pat. Appl.*, EP

454,587 (1991); *Chem. Abstr.*, **116**, 106092k (1992); d) W. H. Gerwick, A. Lopez, G. D. Van Duyne, J. Clardy, W. Ortiz and A. Baez, *Tetrahedron Lett.*, **27**, 1979 (1986); e) G. Atassi, P. Briet, J. P. Berthelon and F. Collonges, *J. Med. Chem., Chim. Ther.*, **20**, 393 (1985); f) Y. Endo and H. Takao, *Ger. Offen.*, D.E. 3,527,305 AI, 6. Feb. 1986; *Chem. Abstr.*, **105**, 97680u (1986); g) B. P. Clark, W. J. Ross and A. Todd, *Ger. Offen.*, 3,012,584 (Cl. C07D 309/306) 16. Oct. 1980, Brit. Appl., 79/12, 062, 05. Apr. 1979; *Chem. Abstr.*, **94**, P 121322f (1981); h) Kurary Co. Ltd., Institute of Physical and Chemical Research, *Jpn Kokai Tokkyo Koho* 80,102,504 (Cl. A01N43/08), 05. Aug. 1980, Appl. 79/9, 315, 29. Jan. 1979; *Chem. Abstr.*, **93**, P 1999231z (1980).

2. a) W. A. Price, A. M. S. Silva and J. A. S. Cavaleiro, *Heterocycles*, **36**, 2601 (1993); b) W. Gerwick, *J. Nat. Prod.*, **52**, 252 (1989); c) H. Nishino, Y. Kodera, T. Sumida, S. Yoshida, H. Matsura and Y. Itakura, Watunaga Pharmaceutical Co. Ltd., *Jpn Kokai Tokkyo Koho*, JP 02,311,462 (90,311,462) (Cl. C07D 213/69), 27. Dec. 1990., Appl. 89/134, 027, 26. May 1989; *Chem. Abstr.*, **115**, 35706 (1991).

3. M. Mimura and Y. Torri, *Jpn Kokai Tokkyo Koho*, JP 63,275,577 (88,275,517) (Cl. C07D 309/40) 14. Nov. 1988, Appl. 87/110, 280, 06. May 1987; *Chem. Abstr.*, 236968m (1989).

4. B. Veera Mallaiah and G. Srimannarayama, *Curr. Sci.* **51**, 513 (1982).

5. a) M. J. Herak, B. Tamhina and K. Jakopčić, *J. Inorg. Nucl. Chem.*, **35**, 1665 (1973); b) B. Tamhina, K. Jakopčić, F. Zorko and M. J. Herak, *ibid.*, **36**, 1855 (1974); c) K. Jakopčić, B. Tamhina, F. Zorko and M. J. Herak, *ibid.*, **39**, 1201 (1977); d) V. Vojković and B. Tamhina, *Solvent Extr. Ion Exch.*, **5**, 245 (1987) and preceding papers; e) Z. Stiplošek, M. Šindler-Kulyk, K. Jakopčić, Z. Meić and D.Vikić-Topić, *J. Heterocycl. Chem.*, **26**, 1707 (1989); f) K. Jakopčić, J. Kojić, Z. Orhanović, Z. Stiplošek, A. Nagl and A. Hergold, *ibid.*, **29**, 107 (1992); g) K. Jakopčić, M. Mintas and I. Isufi, *ibid.*, **30**, 429 (1993); h) M. Kožul, Z. Stiplošek J. Kojić, Z. Orhanović and K. Jakopčić, *Synth. Commun.*, **27**, 3711 (1997) and references cited therein.

6. H. Besso, K. Imafuku and P. Matsumura, *Bull. Chem. Soc. Jpn*, **50**, 2161 (1977).

7. a) R. M. Boden, *Synthesis*, 784 (**1975**); b) M. Schlosser, G. Müller and K. F. Christmann, *Angew. Chem.*, **78**, 677 (1966).

8. Similar procedure has been reported for the preparation of 5-hydroxy derivatives.[6]

9. T. Yabuta, *J. Chem. Soc. Japan*, **125**, 575 (1924).

10. C. N. Campbell, J. F. Ackerman and B. K. Campbell, *J. Org. Chem.*, **15**, 221 (1950).

11. Similarly as for 5-hydroxy Analogue.[12]

12. D. H. R. Barton and L. A. Hulshof, *J. C. S. Perkins I*, 1103 (**1977**).

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