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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 2949–2952

A non-catalytic regioselective approach to the synthesis of (*E*)-stilbenes from suitably functionalized 2*H*-pyran-2-ones☆

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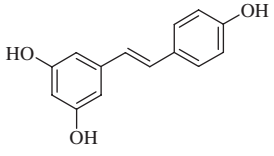
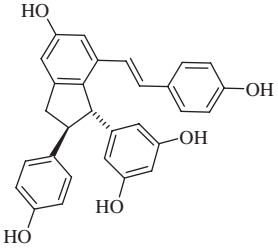
Received 6 January 2006; revised 2 February 2006; accepted 16 February 2006
Available online 6 March 2006

Abstract—Highly functionalized (*E*)-stilbenes **3a**–**m** and 4-aryl-6-styryl-pyran-2-ylidineacetonitriles **4a**–**b** have been prepared and delineated through the ring transformation of 6-aryl-3,4-disubstituted-2*H*-pyran-2-ones **1** with commercially available (*E*/*Z*)-4-phenyl-3-buten-2-one **2** without the use of any catalyst.

Numerous hydroxylated stilbenes are present in Nature, especially in various plant species[1] of the vegetable kingdom. The naturally occurring stilbenoids, polyhydroxy stilbenes and their glycosides have drawn considerable attention due to their wide range of pharmacological activities and therapeutic potential. Resveratrol **I**, a natural polyhydroxy stilbene is reported to be beneficial in the prevention of cardiovascular disease and cancer[2] due to its antioxidant and antimutagenic activities.[3] It also inhibits the dioxygenase activity of lipooxygenase and protects against platelet aggregation.[4,5]



(*E*)-Resveratrol
I



(*E*)-Viniferin
II

Viniferin **II**, an oligomer of resveratrol is recognized as a growth inhibitor of pathogenic fungi. Besides these, various stilbene derivatives are also known to display anti-inflammatory,[6] antiviral and antibacterial properties.[7,8] The non-availability of natural stilbenes in sufficient quantities has necessitated the development of a new efficient synthetic strategy for the preparation of this class of compounds.

The first synthesis of resveratrol **I** was reported[9] in 1941 and thereafter, the synthesis of this class of compounds was further developed using various organometallic reagents. C=C bond formation had always been a sensitive issue prior to the discovery of the Wittig reaction. However, its application was limited to carbonyl compounds only. The first significant breakthrough occurred in 1970 with the discovery of the reductive dimerization of the C=O group of aldehyde and ketones into olefins, using low-valent titanium reagents.[10] Among various catalytic approaches for the construction of stilbenoids, the Heck and Suzuki reactions are prominent and versatile. The Heck reaction[11–13] involves Pd(0) or Pd(II)-complex catalyzed C–C coupling of styrene with an aryl halide. They are also synthesized by Pd(II) catalyzed reaction of aryldiazonium salts with vinyltriethoxysilane.[14] In addition to conventional Heck reactions, nucleophilic organoboron species have been employed for the construction of stilbene derivatives. The palladium catalyzed cross coupling of aryl boronic acids with organic halides or diazonium salts is a highly selective and effective method for preparing stilbenes.[15,16]

They are also synthesized through reduction of benzil, benzoin and deoxybenzoin with zinc under a hydrogen

Keywords: Stilbene; Ring transformation; 2*H*-Pyran-2-ones.
☆CDRI Communication No. 6916.
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0040-4039/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2006.02.103

atmosphere.[17] Oxidative dimerization of methylarenes is another useful approach for the synthesis of this class of compounds.[18] They are generally prepared by the condensation of activated methyl arenes with an aryl aldehyde.[19]

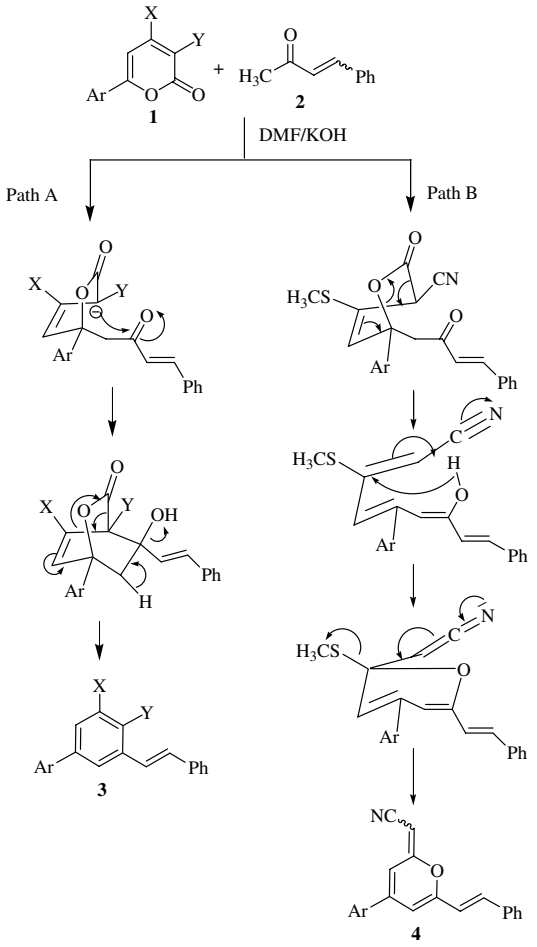
Our approach to the regioselective synthesis of stilbenes **3a**–**m** is based on the ring transformation of (i) 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles **1a**,**b**, (ii) methyl 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carboxylates **1c**–**e** and (iii) 6-aryl-4-piperidin-1-yl-2*H*-pyran-2-one-3-carbonitriles **1f**–**m** with 4-phenyl-3-buten-2-one **2**. The precursors **1a**–**e** used for the synthesis of the stilbenes were prepared[20] from the reaction of aryl methyl ketones and methyl 3,3-dimethylthio-2-cyano/carbomethoxyacrylate. The 6-aryl-4-piperidin-1-yl-2*H*-pyran-2-one-3-carbonitriles **1f**–**m** were obtained[21] by refluxing a mixture of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles with piperidine in ethanol for 5 h.

Thus, an equimolar mixture of 2*H*-pyran-2-one **1**, 4-phenyl-3-buten-2-one **2** and powdered KOH in dry DMF was stirred at room temperature for 6–8 h. Following complete consumption of the starting material (TLC), the reaction mixture was poured into ice water with vigorous stirring. The aqueous solution was neutralized with 10% aqueous HCl, and the precipitate obtained was filtered and dried. The crude product, on purification via column chromatography, yielded various unsymmetrical stilbene derivatives **3a**–**m**. Our approach has shown advantages over earlier reported procedures in terms of regioselectivity as well as an option for functionalization of the aromatic ring.

The selectivity of the reaction depends upon the presence of substituents at C-3 and C-4 on the pyran ring. Thus, the ring transformation of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles **1a**,**b** with **2** may proceed to yield three possible outcomes, (i) 3-methylsulfanyl-5-styryl-biphenyl-4-carbonitriles **3a**,**b** following path A, (ii) 4-phenyl-6-styryl-pyran-2-ylidineacetonitriles **4a**,**b** through path B, exclusively or (iii) a mixture of **3** and **4**. Under our experimental conditions we have been able to isolate and characterize the product as a mixture of **3** (minor) and **4** (major) but the ring transformation of **1c**–**e** with **2** exclusively gave (*E*)-stilbenes **3c**–**e** in excellent yields. Thus, a substituent at C-3 of the pyran ring in reactants **1a**–**e** plays a crucial role in the regioselectivity, possibly due to the difference in electron withdrawing strength of the CN and $COOCH_3$ substituents, which affects the electrophilicity of C-4 of the pyran ring.

The ring transformation of **1f**–**m** with **2** also provides regioselectively unsymmetrical (*E*)-stilbenes **3f**–**m** in good yields even in the presence of a CN substituent at C-3 of the pyran ring, possibly due to the presence of the 4-piperidin-1-yl moiety, which reduces the electrophilicity of C-4.

The topography of 2*H*-pyran-2-ones **1a**–**m** reveals the presence of three electrophilic centres C-2, C-4 and C-6 in which the latter is highly vulnerable to nucleophilic attack due to extended conjugation and the presence of an electron-withdrawing substituent at C-3 of the pyran ring. Thus, the carbanion generated from 4-phenyl-3-buten-2-one **2** attacks C-6 of the pyran ring of **1** with ring closure followed by liberation of carbon dioxide and water to yield products **3**. The ring transformation of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles **1a**,**b** with **2**, led to a mixture of (*E*)-3-methylsulfanyl-5-styryl-biaryl-4-carbonitriles **3a**,**b** as minor products and 4-aryl-6-styryl-pyran-2-ylidineacetonitriles **4a**,**b** as a mixture of (*E*)- and (*Z*)-isomers due to the creation of a new exocyclic C=C bond. The formation of **4** possibly proceeds through the attack of the carbanion



1,3,4	Ar	X	Y	Yield (%) 3	4
a	C_6H_5	SCH_3	CN	30	60
b	4-CH_3.C_6H_4	SCH_3	CN	26	65
c	C_6H_5	SCH_3	$COOCH_3$	70	-
d	4-Br.C_6H_4	SCH_3	$COOCH_3$	76	-
e	4-CH_3.C_6H_4	SCH_3	$COOCH_3$	81	-
f	C_6H_5	Piperidin-1-yl	CN	79	-
g	4-F.C_6H_4	Piperidin-1-yl	CN	71	-
h	4-Cl.C_6H_4	Piperidin-1-yl	CN	79	-
i	4-Br.C_6H_4	Piperidin-1-yl	CN	78	-
j	4-CH_3.C_6H_4	Piperidin-1-yl	CN	76	-
k	4-CH_3O.C_6H_4	Piperidin-1-yl	CN	77	-
l	3,4-CH_2O_2.C_6H_3	Piperidin-1-yl	CN	79	-
m	1-Naphthyl	Piperidin-1-yl	CN	73	-

Scheme 1.

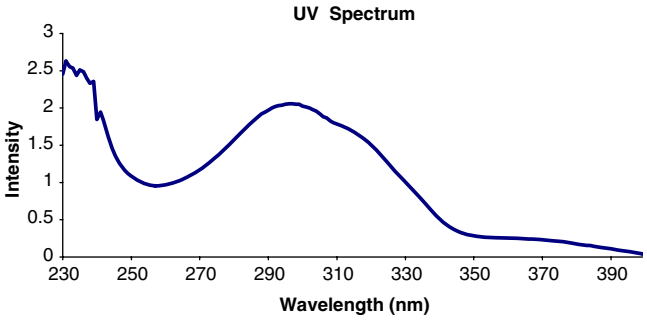


Figure 1. UV spectrum ($CHCl_3$) of **3d**.

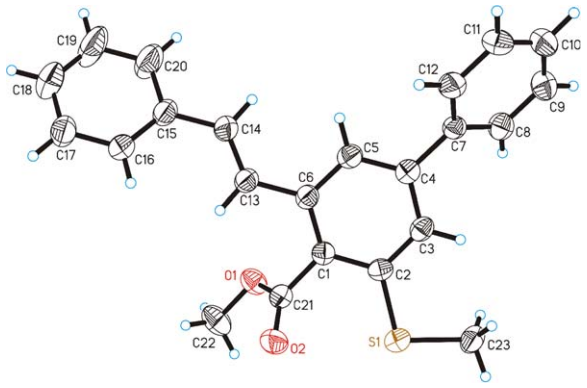


Figure 2. ORTEP diagram of **3c**.

from **2** at C-6 followed by decarboxylation and recyclization involving C-4 of the pyran ring and the enolic OH of the intermediate as depicted in Scheme 1. All the synthesized compounds were characterized by spectroscopic and elemental analysis.[22]

The stereochemistry of the highly functionalized stilbenes was determined on the basis of UV and NMR spectroscopy. The UV spectrum of **3d** in chloroform showed absorption maxima at ~292 nm, which is in proximity to the reported λ_{max} for (*E*)-stilbenes[23] at 293.8 nm (Fig. 1).

Finally, the geometry of the products was ascertained by a single crystal X-ray diffraction study.[24] The ORTEP diagram of **3c** is depicted in Figure 2.

Our methodology provides a regioselective approach to the synthesis of highly functionalized (*E*)-stilbenes in one-step from the reaction of suitably functionalized 2*H*-pyran-2-ones **1** and 4-phenyl-3-buten-2-one **2** without the need for a catalyst. The synthesis is very economical and the work-up is very simple.

Acknowledgement

V.J.R. and R.P. thank the CSIR for financial support.

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22. *General procedure for the synthesis of 3,4-disubstituted-5-styryl-biaryls and 4-aryl-6-styryl-pyran-2-ylidine acetonitriles:* The typical experimental procedure is as reported in the text. The crude products were purified through column chromatography using 1:1 chloroform–hexane yielding various unsymmetrical (*E*)-stilbene derivatives **3a**–**m**, while **1a** and **1b** under similar reaction conditions yielded 4-aryl-6-styryl-pyran-2-ylidine acetonitriles **4a**,**b** as a mixture of (*E*)- and (*Z*)-isomers as major products and 3-methylsulfanyl-5-styryl-biaryl-4-carbonitriles **3a**,**b** as minor constituents. Compound (**3a**). Yield 30%; mp 116–118 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.61 (s, 3H, SCH_3), 6.76–6.96 (m, 2H, CH), 7.23–7.25 (m, 2H, ArH), 7.30–7.71 (m, 10H, ArH); IR (KBr) 2214 cm^{-1} (CN); MS *m*/*z* 328 (M^++1); $C_{22}H_{17}NS$ (327.11) calcd: C, 80.70; H, 5.23; N, 4.28. Found: C, 80.89; H, 5.49; N, 4.10. Compound (**3b**). Yield 26%; mp 110–112 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.43 (s, 3H, CH_3), 2.57 (s, 3H, SCH_3), 6.52–6.56 (m, 1H, ArH), 6.97–7.02 (m, 1H, ArH), 7.07–7.11 (m, 1H, CH), 7.22–7.25 (m, 2H, ArH), 7.34–7.37 (m, 1H, CH), 7.49–7.53 (m, 2H, ArH), 7.80–7.86 (m, 5H, ArH); IR (KBr) 2212 cm^{-1} (CN); MS *m*/*z* 342 (M^++1);

$C_{23}H_{19}NS$ (341.12) calcd: C, 80.90; H, 5.61; N, 4.10. Found: C, 80.73; H, 5.45; N, 4.30. Compound (**3c**). Yield 70%; mp 144–146 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.45 (s, 3H, SCH_3), 3.91 (s, 3H, OCH_3), 7.06 (s, 2H, ArH), 7.23–7.25 (m, 2H, CH), 7.28–7.43 (m, 6H, ArH), 7.51–7.61 (m, 4H, ArH); IR (KBr) 1725 cm^{-1} (CO); MS *m*/*z* 361 (M^++1); $C_{23}H_{20}O_2S$ (360.12) calcd: C, 76.64; H, 5.59. Found: C, 76.85; H, 5.78. Compound (**3d**). Yield 76%; mp 136–138 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.52 (s, 3H, SCH_3), 3.99 (s, 3H, OCH_3), 7.10–7.14 (m, 2H, ArH), 7.32–7.40 (m, 2H, CH), 7.45–7.63 (m, 9H, ArH); IR (KBr) 1723 cm^{-1} (CO); MS *m*/*z* 440 (M^++2); $C_{23}H_{19}BrO_2S$ (438.03) calcd: C, 62.87; H, 4.36. Found: C, 63.03; H, 4.52. Compound (**4a**). Yield 60%; mp 122–124 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.34 (s, 1H, CH), 6.15–6.18 (m, 1H, CH), 6.59–6.61 (m, 1H, CH), 7.22 (s, 1H, ArH), 7.30–7.55 (m, 11H, ArH); IR (KBr) 2198 cm^{-1} (CN); MS *m*/*z* 298 (M^++1); $C_{21}H_{15}NO$ (297.12) calcd: C, 84.82; H, 5.08; N, 4.71. Found: C, 85.03; H, 5.25; N, 4.58. Compound (**4b**). Yield 65%; mp 130–132 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.39 (s, 3H, CH_3), 4.30 (s, 1H, CH), 6.10 (s, 1H, ArH), 6.40–6.70 (m, 2H, CH), 6.88 (s, 1H, ArH), 7.19–7.27 (m, 4H, ArH), 7.33–7.54 (m, 5H, ArH); IR (KBr) 2195 cm^{-1} (CN); MS *m*/*z* 312 (M^++1); $C_{22}H_{17}NO$ (311.13) calcd: C, 84.86; H, 5.50; N, 4.50. Found: C, 85.03; H, 5.35; N, 4.30.

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24. Crystal data for **3c**: $C_{24}H_{21}N_3O_3S$, $M = 431.5$, triclinic, space group P (−1), $a = 10.228(1)$ Å, $b = 10.325(1)$ Å, $c = 11.575(2)$ Å, $\alpha = 101.05(1)°$, $\beta = 109.1(1)°$, $\gamma = 102.63(1)°$, $V = 1080.1(2)$ Å^3, $Z = 2$, $D_c = 1.327$ gcm^{-3}, μ (Mo-Kα) = 0.181 mm^{-1}, $F(000) = 452$, light yellow rectangular block, crystal size = 0.225 × 0.2 × 0.1 mm, 4374 reflections measured ($R_{int} = 0.0385$), 3717 unique, $wR_2 = 0.1419$ for all data, conventional $R = 0.0487$ [$(\Delta/\sigma)_{max} = 000$] on *F*-values of 2064 reflections with $I > 2\sigma(I)$, $S = 1.022$ for all data and 284 parameters. Unit cell determination and intensity data collection ($2\theta = 50°$) was performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: XSCANS [Siemens Analytical X-ray Instrument Inc.: Madison, WI, USA, 1996], SHELXTL-NT [Bruker AXS Inc.: Madison, WI, USA, 1997]. CCDC No. 297102, contains the supplementary crystallographic data. These data can be obtained free of charge from www.ccdc.cam.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: (internat.) +44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk.