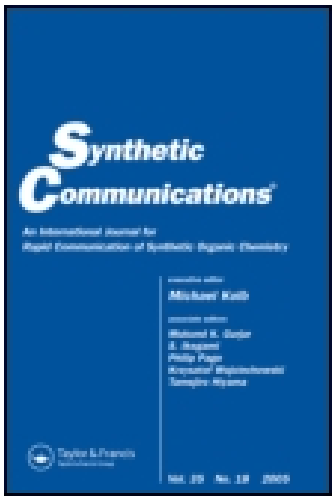

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USEFUL SYNTHESES OF PRENYLATED- AND PYRANO-3-ARYLCOUMARINS

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USEFUL SYNTHESES OF PRENYLATED- AND PYRANO-3-ARYLCOUMARINS

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ABSTRACT

Convenient syntheses of 6-prenyl- and 8-isoprenyl-3-aryl-coumarins (**7a–d** and **8c–d**) from 2-prenyloxy-4-methoxy-benzaldehydes (**5a** and **5b**) and of pyrano-3-arylcoumarins (**10a–b**) from 2-hydroxy-4-(1,1-dimethylpropynyloxy) benzal-dehyde (**9**) using Wittig reaction are described.

Coumarins constitute an important class of naturally occurring oxygen ring compounds.[1] Various simple and 3-substituted coumarins have been isolated[1] from natural sources. A few simple 3-arylcoumarins (**1a–c**), 6-prenyl-3-arylcoumarins (glycyrin **2a** and glycycoumarin **2b**) and 8-isoprenyl-3-arylcoumarin (licoarylcoumarin, **3**) have also been reported[2] from various plant sources. A large number of natural coumarins[1] possess prenyl- or funtionalised prenyl-units at C-6 position. The number of natural 3-arylcoumarins having prenyl unit at C-6 position is small. Some natural 3-arylcoumarins[1] have a pyran ring instead of the prenyl or isoprenyl group.

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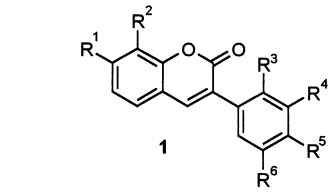
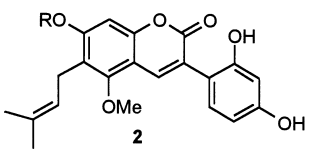
Thus, the pyrano-3-arylcoumarins viz. kanzonol W (**4a**) and its mono methyl ether (**4b**) have been isolated[3] from *Glycyrrhiza glabra*. Apart from their importance as natural products, 3-arylcoumarins are reported to possess interesting biological activities. Thus, glycycoumarin (**2b**) is known to possess anti-HIV[4] and antitumor activities[5] besides being anti-oxidant.[6] It also inhibit xanthine oxidase activity[2d] (an enzyme responsible for formation of gout). Licoarylcoumarin (**3**) exhibits strong inhibition of cAMP phosphodiesterase.[7] Recently,[8] glycyrin (**2a**), glycycoumarin (**2b**) and kanzonol W (**4a**) have been found to be potent antibacterials.



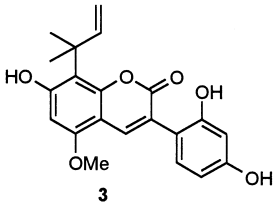
1

	R^1	R^2	R^3	R^4	R^5	R^6
a	OH	H	OH	H	OMe	H
b	OH	H	OH	H	-O-CH_2-O-	
c	H	OH	H	OH	OMe	H



2

	R
a	Me
b	H



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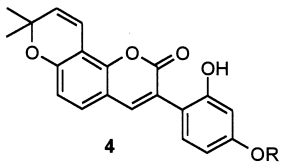

4

	R
a	H
b	Me

In view of the natural occurrence associated with various biological activities, a few methods, making use of the classical Perkin[9] and Knoevenagel[10] reactions, have been reported for the synthesis of simple 3-arylcoumarins of type **1**. The synthesis of 6-prenylcoumarins from naturally occurring 7-hydroxy/alkyloxy coumarins have been reported in the literature,[11] however, the synthesis of 6- and 8-prenylated-3-arylcoumarins of type **2** and **3** remain almost untouched. Pyrano-3-arylcoumarins **4a** and **4b**, however, have been synthesized recently[3b] by making use of the classical Perkin reaction. The overall yields of the final products (**1** and **4**) in these reactions are invariably low and/or involve a multistep sequence of reactions.[3b] The syntheses of prenylated 3-arylcoumarins have not been

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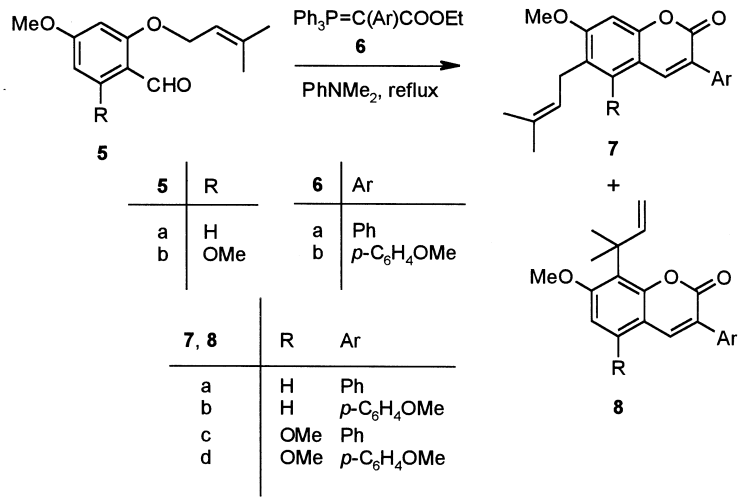
reported in the literature. Hence, it was decided to develop convenient methods for the syntheses of prenylated-3-arylcoumarins of type **2** and **3** and pyrano-3-arylcoumarins of type **4**.



Scheme 1.

In continuation of our work[12,13] on the synthesis of naturally occurring coumarins, we report herein a simple and convenient method (Scheme 1) for the synthesis of 6-prenyl-3-arylcoumarins (**7a–d**) and 8-isoprenyl-3-arylcoumarins (**8c–d**) from the corresponding 2-prenyloxy-4-methoxybenzaldehydes (**5a** and **5b**).

The synthesis of angular pyrano-3-arylcoumarins (**10a–b**) has been achieved (Scheme 2) starting from 2-hydroxy-4-(1,1-dimethylpropynyloxy) benzaldehyde[13] (**9**). The literature method for the synthesis of pyrano-3-arylcoumarin requires several steps and provide the final product in low overall yield.[3b]

In our approach 2-prenyloxy-4-methoxybenzaldehyde[14] (**5a**) was refluxed with phosphoranes (**6a** and **6b**) in N,N-dimethylaniline, to give 7-methoxy-6-prenyl-3-phenylcoumarin (**7a**) and 2′,5-dideoxy-4′-O-methylglycyrin (**7b**) respectively. 4,6-Dimethoxy-2-prenyloxybenzaldehyde[12] (**5b**) when reacted similarly with phosphoranes **6a** and **6b**, provided 5,7-dimethoxy-6-prenyl-3-phenylcoumarin (**7c**) and 2′-deoxy-4′-O-methylglycyrin (**7d**) along with minor amounts of 5,7-dimethoxy-8-isoprenyl-3-phenylcoumarin (**8c**) and 2′-deoxy-7,4′-di-O-methyl licoarylcoumarin (**8d**)

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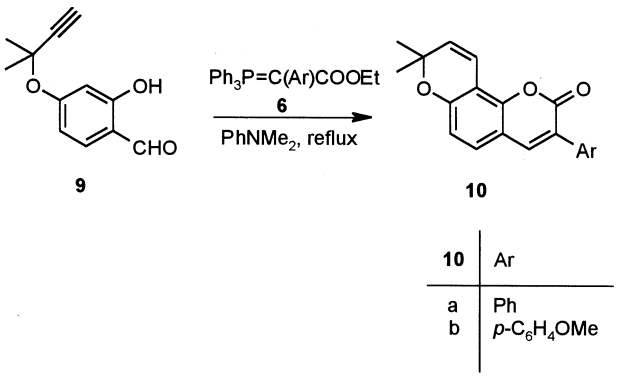

Scheme 2.

respectively. 2-Hydroxy-4-(1,1-dimethylpropynyloxy) benzaldehyde[13] (**9**) on similar reaction with phosphoranes **6a** and **6b** gave the desired pyrano-3-phenylcoumarin (**10a**) and 2′-deoxy-4′-O-methyl kanzonol W (**10b**) respectively. The synthesis of pyrano-3-phenylcoumarin (**10a**) has been reported[15] in the literature starting from 7-hydroxy-3-phenylcoumarin.

The syntheses of 6- and 8-prenylated-3-arylcoumarins (**7a–d** and **8c–d**) have been reported here for the first time. The approaches (Schemes 1 and 2) described here for the syntheses of prenylated-3-arylcoumarins (**7a–d** and **8c–d**) and pyrano-3-arylcoumarins (**10a** and **10b**) do not require preformed coumarins. In both the approaches the Claisen rearrangement, Wittig reaction and cyclization occur in one-pot.

EXPERIMENTAL

All mps are uncorrected. The IR spectra were recorded on a Perkin-Elmer model 337 IR spectrophotometer. ^{1}H NMR (300 MHz) spectra were recorded on Varian VXR 300S instrument in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) downfield from TMS and coupling constants are in Hertz. Analyses were obtained on a Hosli's rapid carbon-hydrogen analyzer.

The preparation of phosphorane **6a** is reported[16] in the literature. Phosphorane **6b** was prepared from ethyl-α-bromo-4-methoxyphenyl-acetate[17] following the procedure reported for **6a**.

General procedure for the syntheses of 6-prenyl- and 8-isoprenyl-3-arylcoumarins (7a–d and 8c–d). A mixture of 2-prenyloxy-4-methoxy benzaldehyde (**5a**,[14] **5b**,[12] 1.2 mmol) and phosphorane[16] (**6a** and **6b**, 1.8 mmol)

in N,N-dimethylaniline (15 ml) was refluxed, under nitrogen atmosphere, for 4–12 h (monitored by TLC). Excess of N,N-dimethylaniline was removed under reduced pressure. The residue was extracted with ethyl acetate (3×15 ml), washed first with dilute hydrochloric acid and finally with water. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed over silica gel using pet. ether–ethyl acetate (98:2) as an eluent to provide 6-prenyl-3-arylcoumarins (**7a–d**) in initial fractions. In the reaction of 4,6-dimethoxy-2-prenyloxybenzaldehyde (**5b**) with phosphoranes **6a** and **6b**, the 6-prenyl-3-arylcoumarins **7c** and **7d** were obtained in the initial fractions and the 8-isoprenyl-3-arylcoumarins **8c** and **8d** in later fractions. All these solid products were recrystallized from pet. ether–ethyl acetate.

7-Methoxy-6-prenyl-3-phenylcoumarin (7a). A mixture of **5a** and **6a** was refluxed for 12 h to give **7a** in 37% yield, mp 77–78°C, ν_{max}/cm^{-1} (Nujol) 1716 (C=O); δ_H 1.71 (3H, s, CH_3), 1.78 (3H, s, CH_3), 3.33 (2H, d, *J* 7.3 Hz, Ar*CH*$_2$CH=), 3.91 (3H, s, OCH_3), 5.3 (1H, m, ArCH$_2$*CH*=), 6.81 (1H, s, 8-H), 7.24 (1H, s, 5-H), 7.4–7.46 (3H, m, Ar-H), 7.67–7.7 (2H, m, Ar-H), 7.76 (1H, s, 4-H) (Found: C, 78.58; H, 6.42. $C_{21}H_{20}O_3$ requires C, 78.72; H 6.29%).

2′,5-Dideoxy-4′-O-methylglycyrin (7b). A mixture of **5a** and **6b** was refluxed for 11 h to give **7b** in 38% yield, mp 97–99°C, ν_{max}/cm^{-1} (Nujol) 1717 (C=O); δ_H 1.71 (3H, s, CH_3), 1.77 (3H, s, CH_3), 3.32 (2H, d, *J* 7.3 Hz, Ar*CH*$_2$CH=), 3.85 (3H, s, OCH_3), 3.9 (3H, s, OCH_3), 5.3 (1H, m, ArCH$_2$*CH*=), 6.8 (1H, s, 8-H), 6.96 (2H, d, *J* 8.8 Hz, Ar-H), 7.23 (1H, s, 5-H), 7.65 (2H, d, *J* 8.8 Hz, Ar-H), 7.7 (1H, s, 4-H) (Found: C, 75.64; H, 6.22. $C_{22}H_{22}O_4$ requires C, 75.41; H, 6.33%).

5,7-Dimethoxy-6-prenyl-3-phenylcoumarin (7c). A mixture of **5b** and **6a** was refluxed for 4 h to give **7c** (20% yield) in the initial fractions, mp 133–135°C, ν_{max}/cm^{-1} (Nujol) 1720 (C=O); δ_H 1.69 (3H, s, CH_3), 1.79 (3H, s, CH_3), 3.37 (2H, d, *J* 6.8 Hz, Ar*CH*$_2$CH=), 3.85 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 5.16 (1H, m, ArCH$_2$*CH*=), 6.66 (1H, s, 8-H), 7.38–7.48 (3H, m, Ar-H), 7.68–7.76 (2H, m, Ar-H), 7.98 (1H, s, 4-H) (Found: C, 75.21; H, 6.55. $C_{22}H_{22}O_4$ requires C, 75.41; H 6.33%).

Further elution with the same solvent gave **8c** in 10% yield.

5,7-Dimethoxy-8-(isoprenyl)-3-phenylcoumarin (8c). Mp 158–160°C, ν_{max}/cm^{-1} (Nujol) 1708 (C=O); δ_H 1.67 (6H, s, 2 × CH_3), 3.85 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.87 (1H, dd, *J* 1.1 and 10.4 Hz, CH_2=), 4.89 (1H, dd, *J* 1.1 and 17.4 Hz, CH_2=), 6.3 (1H, dd, *J* 17.4 and 10.4 Hz, CH=), 6.33 (1H, s, 6-H), 7.34–7.46 (3H, m, Ar-H), 7.72–7.76 (2H, m, Ar-H), 8.15 (1H, s, 4-H) (Found: C, 75.38; H, 6.47. $C_{22}H_{22}O_4$ requires C, 75.41; H, 6.33%).

2′-Deoxy-4′-O-methylglycyrin (7d). A mixture of **5b** and **6b** was refluxed for 10 h to give **7d** in (27% yield) in the initial fractions, mp 102–104°C,

ν_{max}/cm^{-1} (Nujol) 1716 (C=O); δ_H 1.68 (3H, s, CH_3), 1.79 (3H, s, CH_3), 3.37 (2H, d, *J* 6.6 Hz, Ar*CH*$_2$CH=), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 5.16 (1H, m, ArCH$_2$*CH*=), 6.65 (1H, s, 8-H), 6.97 (2H, d, *J* 8.8 Hz, Ar-H), 7.67 (2H, d, *J* 8.8 Hz, Ar-H), 7.92 (1H, s, 4-H) (Found: C, 72.53; H, 6.6. $C_{23}H_{24}O_5$ requires C, 72.61; H, 6.36%).

Further elution with the same solvent furnished **8d** in 10% yield.

2′-Deoxy-7,4′-di-O-methyllicoarylcoumarin (8d). Mp 147–151°C, ν_{max}/cm^{-1} (Nujol) 1702 (C=O); δ_H 1.67 (6H, s, $2 \times CH_3$), 3.84 (6H, s, $2 \times OCH_3$), 3.93 (3H, s, OCH_3), 4.86 (1H, dd, *J* 1.5 and 10.4 Hz, CH_2=), 4.88 (1H, dd, *J* 1.5 and 17.4 Hz, CH_2=), 6.3 (1H, dd, *J* 17.4 and 10.4 Hz, CH=), 6.33 (1H, s, 6-H), 6.95 (2H, d, *J* 8.8 Hz, Ar-H), 7.7 (2H, d, *J* 8.8 Hz, Ar-H), 8.09 (1H, s, 4-H) (Found: C, 72.46; H, 6.48. $C_{23}H_{24}O_5$ requires C, 72.61; H, 6.36%).

General procedure for the synthesis of pyrano-3-arylcoumarins (10a and 10b). A mixture of 2-hydroxy-4-(1,1-dimethylpropynyloxy)benzaldehyde[13] (**9**, 1.5 mmol) and appropriate phosphorane[16] (**6a** and **6b**, 2.2 mmol) in N,N-dimethylaniline was refluxed, under nitrogen atmosphere, for 4–9 h (monitored by TLC). The residue obtained on usual work up, was chromatographed over silica gel using pet. ether–ethyl acetate (98:2) as an eluent to give a solid product which was recrystallized from pet. ether–ethyl acetate to provide pyrano-3-arylcoumarin **10a** and **10b** respectively.

Pyrano-3-phenylcoumarin (10a). A mixture or **9** and **6a** was refluxed for 4 h to give **10a** in 45% yield, mp 139–141°C (lit.,[15] 143–144°C), ν_{max}/cm^{-1} (Nujol) 1717 (C=O); 1.48 (6H, s, $2 \times CH_3$), 5.74 (1H, d, *J* 10 Hz, 9-H), 6.74 (1H, d, *J* 8.8 Hz, 6-H), 6.94 (1H, d, *J* 10 Hz, 10-H), 7.27 (1H, d, *J* 8.8 Hz, 5-H), 7.39–7.49 (3H, m, Ar-H), 7.66–7.69 (2H, m, Ar-H), 7.71 (1H, s, 4-H) (Found: C, 79.02; H, 5.4. $C_{20}H_{16}O_3$ requires C, 78.93; H, 5.3%).

2′-Deoxy-4′-O-methylkanzonol W (10b). A mixture of **9** and **6b** was refluxed for 9 h to give **10b** in 57% yield, mp 152–153°C, ν_{max}/cm^{-1} (Nujol) 1712 (C=O); δ_H 1.48 (6H, s, $2 \times CH_3$), 3.85 (3H, s, OCH_3), 5.73 (1H, d, *J* 10 Hz, 9-H), 6.73 (1H, d, *J* 8.4 Hz, 6-H), 6.94 (1H, d, *J* 10 Hz, 10-H), 6.96 (2H, d, *J* 8.7 Hz, Ar-H), 7.25 (1H, d, *J* 8.4 Hz, 5-H), 7.64 (2H, d, *J* 8.7 Hz, Ar-H), 7.66 (1H, s, 4-H) (Found: C, 75.54; H, 5.58. $C_{21}H_{18}O_4$ requires C, 75.43; H, 5.43%).

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