Ultrasound-assisted Wittig reaction and synthesis of 5-alkyl- and 5-alkenyl-resorcinols

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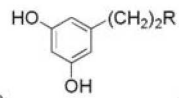
Some 5-alkyl- and 5-alkenyl-resorcinols were synthesised from commercially available 3,5-bis(benzyloxy)benzaldehyde by ultrasound-assisted Wittig reaction with alkyltriphenyl phosphonium bromides in basic aqueous condition, followed by debenzylation and simultaneously reduction of a double bond of the styrene type with Na/*n*-BuOH in overall yields of 62–72%.

Keywords: 5-alkylresorcinol, 3,5-bis(benzyloxy)benzaldehyde, Wittig reaction, ultrasound irradiation, 5-alkenylresorcinols

5-Alkylresorcinols are non-isoprenoid phenolic lipids that carry an *n*-alkyl side chain at C-5 of the resorcinol ring. They are of a great importance owing to their biological activity such as antibacterial and antifungal activity, cytotoxic activity, antioxidant activity and 5-1ipoxygenase inhibitory activity.[1] Olivetol(**1a**),[2] grevillol(**1b**),[3] adipostatin A(**1c**)[4] and 5-heptadecyllresorcinol (**1d**)[5] and the 5-alkenylresorcinols ardisinol II(**1e**)[6] and bilobol (**1f**)[7] (Fig. 1) have been isolated from natural sources.

There are three strategies for synthesis of 5-alkenyl-resorcinols: (i) elaboration of the side-chain on the aromatic ring. This route is complicated and has a lower yield;[8-10] (ii) aromatisation of cyclohexane derivatives. This method is not suitable for synthesis of 5-alkenylresorcinols;[11-12] (iii) direct alkylation of the aromatic ring by Suzuki coupling. The necessity for a terminal alkene as the starting material for the reaction limits the number of compounds available for this kind of approach to 5-alkenylresorcinols synthesis in general.[13] We now report a simple and efficient route to 5-alkylresorcinols and some 5-alkenylresorcinols based on an ultrasound-assisted Wittig reaction.

Compounds **1a–f** were prepared starting from commercially available 3,5-bis(benzyloxy) benzaldehyde, as outlined in Table 1. Ultrasound-assisted Wittig reaction of alkyltriphenyl phosphonium bromides with 3,5-bis(benzyloxy)benzaldehyde, in the presence of K_2CO_3 and using DMSO/water as solvent, afforded the styrenes **2a–f** in 81–90% yields. Cleavage of the benzyl ethers and reduction of the conjugated double bond of compounds **2a–f** were attempted by catalytic hydrogenolysis over Pd/C, but this method was not suitable for synthesis of 5-alkenylresorcinols as the isolated double bond was reduced. However, compounds **2a–f** were treated with metallic sodium in *n*-butanol to obtain the 5-alkyl- and alkenyl-resorcinols in 75–81% yields, where two benzyl ethers functionalities were cleaved and the conjugated double bond was reduced but the isolated one was not affected.[14]



1a R=$CH_3(CH_2)_2$ olivetol
1b R=$CH_3(CH_2)_{10}$ grevillol
1c R=$CH_3(CH_2)_{12}$ adipostatin A
1d R=$CH_3(CH_2)_{14}$ 5-heptadecyllresorcinol
1e R=$CH_3(CH_2)_3CH\overset{Z}{=}CH(CH_2)_5$ ardisinol II
1f R=$CH_3(CH_2)_5CH\overset{Z}{=}CH(CH_2)_5$ bilobol

Fig. 1 Some 5-alkyl- and 5-alkenyl-resorcinols

The Wittig reaction is one of the most versatile synthetic methods for preparation of olefins from carbonyl compounds and it is classically carried out using a hydride or organometallic base in anhydrous aprotic solvents under an inert atmosphere. During synthesis of **2**, we applied the solid–liquid transfer technique to the Wittig reaction. This salt-free system is a more environmentally-friendly strategy than methods utilising lithium bases.[15] Scheme 1 details the solid–liquid phase-transfer process.

To establish simple and suitable conditions for the synthesis of compounds analogous to **2** the reaction of butyltriphenyl phosphonium bromide with 3, 5-bis(benzyloxy) benzaldehyde was chosen as a model, and its behaviour was studied under a variety of conditions by TLC and1 ^{1}H NMR and ^{13}C NMR spectroscopy (Table 2).

According to Table 2, the best result was obtained in the presence of K_2CO_3, ultrasound irradiation and using DMSO/water as solvent (entry 7). The results also emphasised the importance of using ultrasound irradiation (entries 1, 3, 5 and 7), which shortened reaction times and improved yields.

Table 1 The synthesis of 5-alkyl- and 5-alkenyl-resorcinols

2 1

Entry	R	2	Yield/%[a]	1	Yield/%[b]
1	$CH_3(CH_2)_2$	**2a**	89	**1a**	81
2	$CH_3(CH_2)_{10}$	**2b**	85	**1b**	76
3	$CH_3(CH_2)_{12}$	**2c**	86	**1c**	79
4	$CH_3(CH_2)_{14}$	**2d**	90	**1d**	77
5	$CH_3(CH_2)_3CH\overset{Z}{=}CH(CH_2)_5$	**2e**	82	**1e**	75
6	$CH_3(CH_2)_5CH\overset{Z}{=}CH(CH_2)_5$	**2f**	81	**1f**	77

[a]Total yield of the *Z* and *E* mixture.
[b]Isolated yield.

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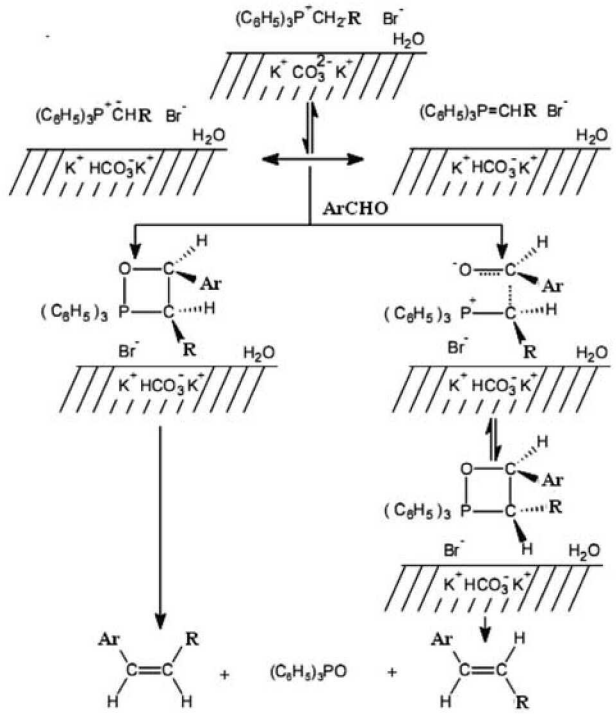

Scheme 1 Solid–liquid phase-transfer process.

Table 2 The reactions of butyltriphenylphosphonium bromide and 3,5-bis(benzyloxy)benzaldehyde under different conditions[a]

Entry	Base	Solvent	Time/h	Ultrasound	Yield/%[b]
1	NaOH	Dioxane/water	1	+	26
2	NaOH	Dioxane/water	5	–	<10
3	NaOH	DMSO/water	1	+	28
4	NaOH	DMSO/water	5	–	<10
5	K_2CO_3	Dioxane/water	1	+	38
6	K_2CO_3	Dioxane/water	5	–	30
7	K_2CO_3	DMSO/water	1	+	85
8	K_2CO_3	DMSO/water	5	–	55

[a]3,5-Bis(benzyloxy)benzaldehyde: alkyltriphenylphosphonium bromide: K_2CO_3: water = 1:1: 1.3:2; the reaction carried out at 90–100 °C.
[b]Total yield of the *Z* and *E* mixture.

In summary, we have developed a general methodology to synthesise a number of 5-alkyl- and 5-alkenyl–resorcinols in excellent yield. The key steps include ultrasound-accelerated Wittig reaction, followed by debenzylation and simultaneous reduction of the conjugated double bond with Na/*n*-BuOH.

Experimental

NMR spectra were determined on FT-NMR Avance 400 spectrometer in $CDCl_3$ or DMSO-d_6 and were expressed in delta values relative to tetramethylsilane, coupling constants (*J*) were measured in Hz; Elemental analyses were recorded on a Vario EL III elemental analyser; melting points were determined on a Mel-Temp capillary tube apparatus and were uncorrected; ultrasound irradiation was effected in a water bath of a CQ250 ultrasonic cleaner (frequency: 40 kHz, power 250 W); Commercially available reagents were used throughout without further purification unless otherwise stated; Dioxane and DMSO were freshly distilled from sodium.

Preparation of **1***: General procedure*

The alkyltriphenylphosphonium bromide (15 mmol), potassium carbonate (20 mmol), DMSO (10 mL) containing water (0.5 mL), and 3,5-bis(benzyloxy)benzaldehyde (15 mmol) were successively introduced into a 100 mL reaction vessel. The mixture was irradiated in a water bath of the ultrasonic cleaner at 90–100 °C for 1 h, then cooled to 25 °C, treated with 10 mL of water and extracted with two 15 mL portions of ether. The combined organic layer was washed successively with water and brine and then dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was chromatographed on silica gel eluting using hexane:ethyl acetate (10:1) to yield **2** as colourless oil.

Sodium metal (9.2 g, 400 mmol) was added to a solution of **2** in anhydrous *n*-BuOH (100 mL) at room temperature. The resulting mixture was heated at 80–90 °C and stirred for 1 h. The reaction was quenched by addition of 20% aqueous HOAc (50 mL). After hexane (100 mL) was added to this mixture, it was heated at reflux and the aqueous layer was removed with a Dean–Stark trap overnight. The organic layer then was filtered and concentrated under reduced pressure. The crude product was chromatographed on silica gel eluting using hexane:ethyl acetate (4 : 1) to yield **1**.

Olivetol (**1a**): Colourless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.07 (brs, exch. D_2O, 2H), 6.22 (d, 2H, J = 2.0 Hz), 6.15 (t, 1H, J = 2.0 Hz), 2.42 (t, J = 7.6 Hz, 2H), 1.55–1.50 (m, 2H), 1.33–1.26 (m, 4H), 0.85 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.6 (2C), 146.2, 108.3 (2C), 100.2, 35.8, 31.5, 30.5, 22.5, 14.1. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.38; H, 8.89%.

Grevillol (**1b**): Colourless solid, m.p. 85–86 °C (lit.[10], m.p. 81–83 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.07 (brs, exch. D_2O, 2H), 6.20 (d, 2H, J = 2.1 Hz), 6.15 (t, 1H, J = 2.1 Hz), 2.30 (t, J = 7.4 Hz, 2H), 1.53–1.46 (m, 2H), 1.30–1.25 (m, 20H), 0.87 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.4 (2C), 147.2, 108.6 (2C),

100.2, 35.8, 31.9, 31.0, 29.7-29.0 (8C), 22.7, 14.1. Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 78.00; H, 11.01%.

Adipostatin A (**1c**): Colourless solid, m.p. 88–89 °C (lit.[4], m.p. 91–92 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.02 (brs, exch. D_2O, 2H), 6.05 (d, 2H, J = 2.0 Hz), 6.00 (t, 1H, J = 2.0 Hz), 2.35 (t, J = 7.4 Hz, 2H), 1.60–1.55 (m, 2H), 1.25–1.20 (m, 24H), 0.87 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.8 (2C), 146.8, 108.1 (2C), 100.7, 35.6, 31.9, 31.0, 29.7-29.0 (10C), 22.7, 14.1. Anal. Calcd for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.56; H, 11.35%.

5-Heptadecylresorcinol (**1d**): Colourless solid, m.p. 91–93 °C (lit.[8], m.p. 92–93 °C). ^{1}H NMR (400 MHz, DMSO-d_6,) δ: 8.97 (brs, exch. D_2O, 2H), 6.14 (d, 2H, J = 2.2 Hz), 6.09 (t, 1H, J = 2.2 Hz), 2.45 (t, J = 7.5 Hz, 2H), 1.55–1.50 (m, 2H), 1.30–1.20 (m, 28H), 0.88 (t, 3H, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.7 (2C), 146.2, 107.9 (2C), 100.8, 35.8, 31.9, 31.0, 29.7-29.0 (12C), 22.8, 14.1. Anal. Calcd for $C_{23}H_{40}O_2$: C, 79.25; H, 11.57. Found: C, 79.29; H, 11.56%.

Ardisinol II (**1e**): Colourless solid, m.p. 30–31 °C (lit.[6] m.p. 28–29 °C).^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.59 (d, 2H, J = 2.2 Hz), 6.30 (t, 1H, J = 2.2 Hz), 5.85 (brs, exch. D_2O, 2H), 5.42 (t, 2H, J = 4.8 Hz), 2.60–2.55 (m, 2H), 2.10–2.05 (m, 4H), 1.55–1.20 (m, 14H), 0.88 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.6 (2C), 142.5, 130.9, 130.6, 107.3 (2C), 104.1, 36.2, 32.1, 31.1, 29.9-29.0 (4C), 27.5, 27.4, 22.8, 14.5; Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.58; H, 10.41. Found: C, 78.26; H, 10.35%.

Bilobol (**1f**): Colourless solid, m.p. 31–32 °C (lit.[8] m.p. 31–33 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.55 (d, 2H, J = 2.2 Hz), 6.28 (t, 1H, J = 2.2 Hz), 5.80 (brs, exch. D_2O, 2H), 5.45 (t, 2H, J = 4.7 Hz), 2.58–2.51 (m, 2H), 2.05–1.98 (m, 4H), 1.52–1.20 (m, 18H), 0.90 (t, 3H, J = 7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.4 (2C), 144.2, 130.9, 129.8, 108.9 (2C), 102.3, 35.8, 31.9, 31.0, 29.7–29.0 (6C), 27.5, 27.4, 22.8, 14.5; Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.88; H, 10.73%.

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