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Preparation of vinylphenols from 2- and 4-hydroxybenzaldehydes

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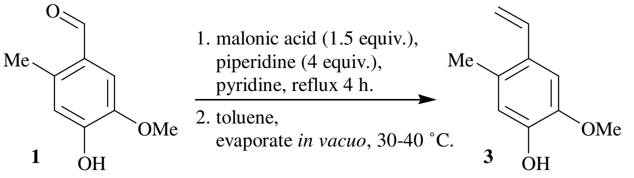
Abstract—A straightforward, high-yielding procedure has been developed for the manufacture of substituted vinylphenols from 2- and 4-hydroxybenzaldehydes utilising classical Knoevenagel condensation reaction conditions.

Reactions of aldehydes or ketones with active methylene compounds in the presence of a weak base to give alkylidene-dicarbonyls or analogous compounds are generally termed Knoevenagel condensations.[1] In a valuable variation of the reaction, in which malonic acid is used as the active methylene compound, the reaction is accompanied by decarboxylation to give the corresponding α,β-unsaturated monocarboxylic acid. Where condensations with malonic acid are performed in the presence of aromatic aldehydes, the product obtained is exclusively the *trans*-cinnamic acid.

During the construction of a substituted 4-hydroxy-*trans*-cinnamic acid related to our research (4-hydroxy-5-methoxy-2-methyl-*trans*-cinnamic acid, **2**) we observed the formation of a single new compound which was plainly not the expected *trans*-cinnamic acid.[2] Indeed, the ^{1}H NMR spectrum clearly indicated the presence of an *ABX* system characteristic of a styrene and further analysis of the purified compound confirmed that we had generated 2-methoxy-5-methyl-4-vinylphenol **3** directly from the corresponding aldehyde **1** (Scheme 1).



Scheme 1.

The reaction conditions utilised for the preparation of 2-methoxy-5-methyl-4-vinylphenol **3** were identical to those of classical Knoevenagel reactions. However, instead of quenching the reaction by pouring it into concentrated HCl on ice, the pyridine reaction solvent was removed in vacuo in the presence of toluene to afford the crude product.[3] In order to establish the generality and utility of this phenomenon, we decided to test a range of aldehyde substrates bearing variations of all substituents of the 4-hydroxy-5-methoxy-2-methyl-benzaldehyde **1** utilised in our original preparation using both the classical and new work-up conditions (Table 1).

These results demonstrate that styrene formation occurs only in reactions where a 2- or 4-hydroxybenzaldehyde substrate is utilised in conjunction with the new work-up conditions. The product in all other cases, regardless of the conditions utilised, was the expected *trans*-cinnamic acid. With 2-hydroxybenzaldehyde **4**, both the expected *trans*-cinnamic acid **5** and the corresponding vinylphenol **6** were generated in the same reaction.

When utilising benzaldehydes and malonic acid, the Knoevenagel reaction is accompanied by decarboxylation to give the corresponding substituted *trans*-cinnamic acid (Scheme 2).[1] In the presence of 1° and 2° amines, the reaction proceeds via the Knoevenagel mechanism.[4] Following initial addition of the activated methylene, the decarboxylated intermediate (R = piperidine) outlined in Scheme 2 is most likely generated in the reaction. Subsequent β-elimination of the amine

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Keywords: Organic synthesis methodology mechanism.

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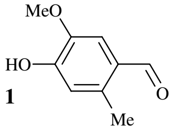
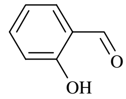
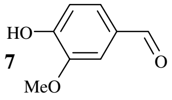
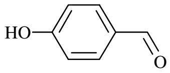
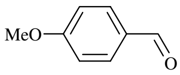
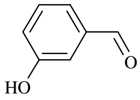
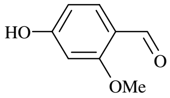
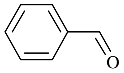
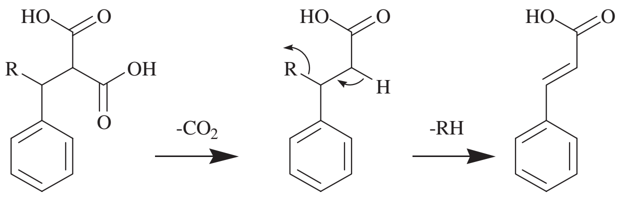
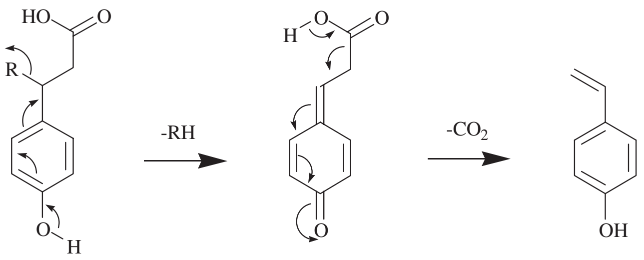
Table 1. Products and yields following Knoevenagel condensation of benzaldehydes and malonic acid (reactions were not optimised)

Substrate	HCl/H_2O		Toluene	
	Product	Yield (%)	Product	Yield (%)
 **1**	Acrylic acid **2**	56	Vinylphenol **3**	50
4 	Acrylic acid **5**	48	Acrylic acid **5** and vinylphenol **6**	50 and 38
 **7**	Acrylic acid **8**	35	Vinylphenol **9**	67
	Acrylic acid	35	Vinylphenol	86
	Acrylic acid	87	Acrylic acid	23
	Acrylic acid	78	Acrylic acid	82
	Acrylic acid	27	Vinylphenol	58
	Acrylic acid	61	Acrylic acid	96



Scheme 2.



Scheme 3.

from this intermediate generates only the expected *trans*-cinnamic acid.

The addition of 4-hydroxy-3-methoxy-*trans*-cinnamic acid **8** to Knoevenagel condensation reaction conditions and subsequent removal of the pyridine solvent in vacuo in the presence of toluene did not lead to the corresponding vinylphenol. This suggests that formation of the *trans*-cinnamic acid through elimination of water during the Knoevenagel reaction is effectively non-reversible under these conditions. Therefore, the second decarboxylation must occur prior to formation of an α,β-unsaturated carboxylic acid.

The fact that only 2- and 4-hydroxybenzaldehydes generate the unexpected vinylphenols strongly suggests the participation of a quinone in the double decarboxylation necessary to afford a vinylphenol. We propose that following the initial decarboxylation, the phenolic oxygen participates in elimination of the amine function in the condensation product through the generation of a quinone methide (Scheme 3). This intermediate is identical to that invoked for the decarboxylation of 4-hydroxy-*trans*-cinnamic acid in aqueous weak alkali solution.[5] Decarboxylation then proceeds readily to give the corresponding vinyl phenol either through conjugate addition to give the unstable β-lactone or more likely by direct decarboxylation (as shown).

Interestingly, the generation of the *ortho*-quinone methide competes with β-elimination leading to the generation of both the corresponding vinylphenol and

Table 2. Solvent variation[a]

Solvent	Products observed[b]			
	Reflux		50 °C	
	Styrene	Acid	Styrene	Acid
Toluene	100	0	0	100
Pyridine	100	0	0	100
Water	33	67	0	100
Acetonitrile	0	100	0	100
THF	0	100	0	100

[a] The reaction conditions described are for the initial Knoevenagel addition conditions. The work-up for all reactions followed solvent removal in vacuo in the presence of toluene at 30–40 °C.

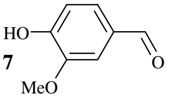
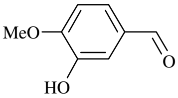
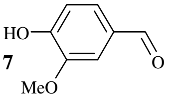
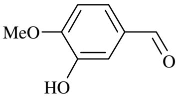
[b] As a percentage of total product observed in the reaction. Analyses of reactions were carried out using the ^{1}H NMR spectra of crude products. Product ratios were obtained from comparative integration of the protons furthest downfield in the exocyclic double bonds of the α,β-unsaturated carboxylic acid and vinylphenol.

Table 3. Variation of the ratio of catalyst to substrate

Ratio of starting material to piperidine	Time (h)	Products observed[a]	
		Styrene	Acid
1:0.0	4	0	100
1:0.1	4	14	86
1:0.5	4	58	42
1:1	4	100	0
1:5	4	100	0
1:10	3	100	0

[a] As a percentage of total product observed in the reaction. Analyses of reactions were carried out using the ^{1}H NMR spectra of crude products. Product ratios were obtained from comparative integration of the protons furthest downfield in the exocyclic double bonds of the α,β-unsaturated carboxylic acid and vinylphenol.

Table 4. Variation of base in the reaction[a]

Base	Starting material	Products observed[b]	
		Styrene	Acid
DBU	 7	100	0
DBU		0	100
TEA	 7	40.5	59.5
TEA		0	100

[a] The ratio of base to aldehyde in each reaction was 1:1.

[b] As a percentage of total product observed in the reaction. Analyses of reactions were carried out using the ^{1}H NMR spectra of crude products. Product ratios were obtained from comparative integration of the protons furthest downfield in the exocyclic double bonds of the α,β-unsaturated carboxylic acid and vinylphenol.

trans-cinnamic acid in this reaction. In this case, it is quite likely that formation of the *ortho*-quinone methide is less easy than formation of the *para*-quinone methide. In the latter reaction, the formation of products from competing side reactions was not observed.

The effect of solvent on the reaction was also investigated (Table 2). It was found that whilst the preparation of 4-hydroxy-3-methoxy vinylphenol **9** from 4-hydroxy-3-methoxy benzaldehyde **7** was effective using toluene, water or pyridine during the Knoevenagel condensation, the only observed product from the reaction performed in acetonitrile or tetrahydrofuran was the corresponding α,β-unsaturated monocarboxylic acid **8**. In addition, the only product observed when the condensation reaction was performed at 50 °C was the carboxylic acid **8** regardless of the solvent used.

As stated, in the presence of 1° and 2° amines, the reaction proceeds via the Knoevenagel mechanism.[4] In their absence, the transformation is known to proceed via the Hann–Lapworth mechanism with the development of a β-hydroxy intermediate generated directly from the aldehyde.[6,7] However, under conditions that favour the Knoevenagel mechanism, the Hann–Lapworth mechanism may also compete.[7]

In order to investigate the effect of piperidine on the reaction, a study on the variation of the ratio of catalyst to substrate was performed (Table 3). From these results, it is apparent that the piperidine catalyst is critical for vinylphenol formation under these reaction conditions and that a Hann–Lapworth mechanism intermediate does not enable a secondary decarboxylation.

Nonetheless, it was discovered that if a strong hindered base, such as DBU or TEA, is substituted for piperidine in the reaction, then a secondary decarboxylation affording the corresponding vinylphenol was observed (Table 4). Again, the formation of the corresponding vinylphenol was only achieved if the substrate was 4-hydroxybenzaldehyde. In this case, the reaction intermediate must necessarily be a β-hydroxy carboxylic acid. This strongly suggests that a strong hindered base enables the phenolic oxygen to participate in elimination of the hydroxyl function through the generation of a quinone methide. Decarboxylation then proceeds readily to give the corresponding vinylphenol.

To evaluate the scope of this reaction, a range of alternative substrates was utilised. In these investigations, both 4-hydroxybenzophenone and 3-thiophene carboxaldehyde gave only the α,β-unsaturated monocarboxylic acid as a product. On the other hand, trace amounts of isoeugenol were detected by NMR analysis of reactions performed with vanillin **7** and methyl malonic acid.

Common methods for the synthesis of vinylphenols utilise the enzymic decarboxylation[8] of *trans*-cinnamic acids, the synthetic decarboxylation of *trans*-cinnamic acids at elevated temperature in the presence of a metal,[9] Grignard addition[9] to an aldehyde, Wittig synthesis[10] or the catalytic dehydrogenation[11] of ethyl phenols. Moreover, in at least two of these reactions, prior protection of the phenolic oxygen is generally required.

A very brief description of the preparation of 1,2-dihydroxy-4-vinylbenzene through the repeated distillation of products of a Knoevenagel condensation, has previously been reported.[12] Furthermore, since the completion of this work, others have also reported the formation of vinylphenols from 4-hydroxybenzaldehydes in much lower yields using microwave heating.[13] However, in this report we present for the first time the systematic investigation of this straightforward, high-yielding and clean procedure for the manufacture of substituted vinylphenols directly from 2- and 4-hydroxybenzaldehydes utilising classical Knoevenagel condensation reaction conditions.

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References and notes

1. For general reviews on the Knoevenagel reaction: Jones, G. *Org. React.* **1967**, *15*, 204–599; Tietze, L. F.; Beifuss, U. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, pp 341–394.
2. Simpson, C. J. Ph.D. Dissertation, University of East Anglia, 2003.
3. A general procedure was followed for all Knoevenagel condensation reactions. To a solution of aldehyde (5 mmol) and malonic acid (20 mmol) in pyridine (21 mL) was added piperidine (0.75 mL, 7.6 mmol). The stirred reaction solution was heated at reflux (115 °C) for 4 h, then cooled to room temperature. For standard work-up to afford the corresponding acrylic acid, the cooled reaction mixture was poured into a solution (50 mL) of concentrated HCl and ice (50% by volume) and the resulting precipitate was filtered and washed with acidified water to give a crude product. The crude product was dissolved in aqueous NaOH (1 M, 20 mL) and extracted with CH_2Cl_2 (3×20 mL). The aqueous solution was acidified to $pH = 1$ and the resultant precipitate washed with acidified water to give the corresponding *trans*-cinnamic acid. For the alternate work-up required to afford the corresponding vinyl phenol, toluene (40 mL) was added to the cooled reaction mixture and the solvent volume reduced in vacuo at 30–40 °C. Additional toluene (20 mL) was then added and the solvent again removed in vacuo eliminating all traces of pyridine to afford the crude product. If the crude product obtained was the *trans*-cinnamic acid, then further purification was performed as for the standard work-up procedure. Otherwise, purification by column chromatography over silica gel (eluting with 2:1 hexane/ethyl acetate) gave the corresponding vinylphenol.
4. Knoevenagel, E. *Chem. Ber.* **1898**, *31*, 2585.
5. Cohen, L. A.; Jones, W. M. *J. Am. Chem. Soc.* **1960**, *82*, 1907–1911.
6. Hann, A. C. O.; Lapworth, A. *J. Chem. Soc.* **1904**, *85*, 46.
7. Tanaka, M.; Oota, O.; Hiramatsu, H.; Fujiwara, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2473.
8. Takemoto, M.; Achiwa, K. *Tetrahedron Lett.* **1999**, *40*, 6595–6598.
9. Dale, W. J.; Hennis, H. E. *J. Am. Chem. Soc.* **1958**, *80*, 3645–3649.
10. Bettach, N.; Le Bigot, Y.; Mouloungui, Z.; Delmas, M.; Gaset, A. *Synth. Commun.* **1992**, *22*, 513–518.
11. Fujiwara, H.; Yamazaki, H.; Ozawa, K. Eur. Pat. Appl., EP 128984 A1, 1984; *Chem. Abstr.* **1985**, *102*, 184819.
12. Tiedcke, C. Z. *Unters. Lebensm.* **1936**, *71*, 393.
13. Sinha, A. K.; Joshi, B.P.; Sharma, A. U.S. Pat. Appl., US 20040118673 A1, **2004**; *Chem. Abstr.* **2004**, *141*, 71343.