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Palladium-catalysed arylation of poly(ethylene glycol) bound acrylate with aryl iodides in water: a liquid-phase synthesis of *trans*-cinnamic acids

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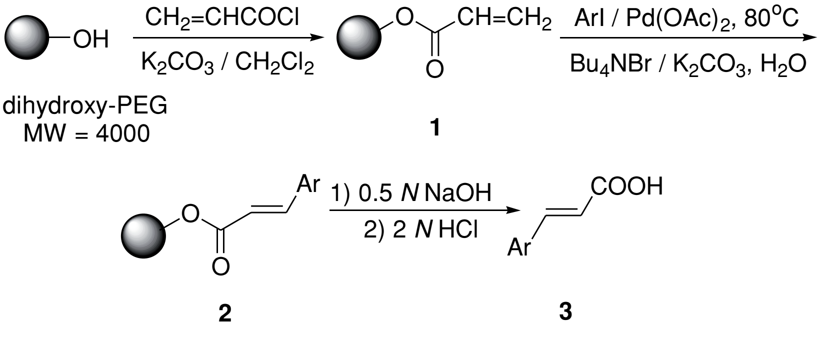
An efficient liquid-phase synthesis of *trans*-cinnamic acids with good yields and high purities on soluble polymer support has been developed by treatment of poly(ethylene glycol) bound acrylate with aryl iodides in the presence of catalytic amounts of palladium acetate and tetra-*n*-butylammonium bromide in water using potassium carbonate as a base, and subsequent cleavage from the PEG.

Keywords: poly(ethylene glycol), *trans*-cinnamic acids, palladium catalysis, liquid-phase synthesis

Solid-phase synthesis technique as a powerful tool has been applied successfully throughout the field of combinatorial chemistry.[1] However, the heterogeneous nature of this strategy might result in some problems, such as relatively low reactivity and selectivity, harsh reaction conditions and extended reaction time, as well as the difficulty for characterisation of the insoluble polymer-supported compounds. Therefore, development of liquid-phase synthesis using soluble polymers could provide an excellent opportunity to overcome the shortages of solid-phase approach to combinatorial library production and organic synthesis.[2] This has the advantages of liquid-phase reaction and easy separation/purification of the products in solid-phase synthesis. Moreover, the soluble polymer-bound species allow using routine analytical methods (^{1}H NMR, IR or TLC) to monitor the reaction process and to determine the structures of products attached to polymer support directly. Polyethylene glycol (PEG), as an inexpensive polymer, is an ideal support for liquid-phase combinatorial synthesis since it is soluble in many organic solvents, such as CH_2Cl_2, $CHCl_3$, THF, CH_3OH or H_2O at room temperature and can be precipitated from a solution by addition of diethyl ether, *tert*-butyl methyl ether, propan-2-ol or hexane.[3] *Trans*-cinnamic acids are important chemical substances and organic intermediates and usually prepared by Perkin reaction, but the yields and the stereoselectivity are moderate or poor.[4] The Heck reaction[5] is a very useful process for preparing disubstituted olefins which commonly exist in organic compounds. The reaction involves palladium catalysed carbon-carbon bond formation between an aryl halide and a vinyl functionality. The Heck reaction is generally very mild, and does not require strict anhydrous or inert atmosphere conditions which makes it easily amenable to automation. Recently, the Heck reaction has been applied to solid phase synthesis in an intramolecular[6] reaction for the synthesis of cinnamoyl derivatives and in an intramolecular macrocyclisation[7] reaction. However, to our knowledge, no palladium-catalysed arylation of PEG supported acrylate with aryl iodides, especially in pure water medium has been reported. Herein, we described a novel liquid-phase synthesis of *trans*-cinnamic acids on soluble PEG support (Scheme 1).

As shown in Scheme 1, esterification of commercially available difunctional PEG 4000 with acryloyl chloride in anhydrous dichloromethane in the presence of K_2CO_3 readily gave rise to the corresponding PEG bound acrylate **1**. The conversion of terminal hydroxyl groups on PEG was determined by ^{1}H NMR analysis to be quantitative. The loaded resin **1** showed complete disappearance of the hydroxyl OH stretch and the appearance of a C=O stretch at 1723 cm^{-1}. With the PEG-supported acrylate **1** in hand, we first switched our attention to its application in liquid-phase combinatorial synthesis of *trans*-cinnamic acids. When PEG-supported acrylate **1** reacted with iodobenzene in the presence of 2 mol% $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ and potassium carbonate in DMF/H_2O (90/10) mixture solvent at 40 °C[6b] for 8 h, followed by hydrolysis of resin **2a** using sodium hydroxide aqueous solution and subsequently acidified with hydrochloric acid solution, *trans*-cinnamic acid **3a** was obtained with a yield 30% and 27% based on loading of original PEG, respectively. Attempts to increase the yield of **3a** by replacing solvents such as DMF and THF, enhancing reaction temperature to 80°C or prolonging reaction time were unsuccessful. When *n*-Bu_4NBr was added in the above reaction, the yield of **3a** increased from 30 to 62%. Similarly, the 4-methylphenyl iodide was subjected to the same reaction conditions, but the yield of **3b** was not satisfactory. Here, the use of $Pd(OAc)_2$ instead of $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ produced a significant improvement, the 92% yield of **3a** was obtained. Interestingly, 95% yield of **3a** was obtained when pure water was used instead of DMF/H_2O mixture solvent at 80 °C reaction temperature (Table 1, Entry 1). The optimised



Scheme 1

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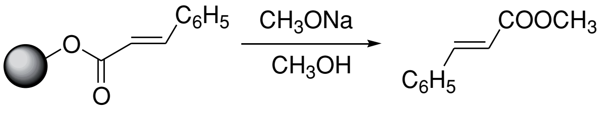
synthetic strategy was applied to the synthesis of **3b–3h**, and the results are summarised in Table 1. This protocol gave the crude products in good yields (80–86%) with excellent purity (>90% by HPLC analysis). However, it should be noted, the arylation reaction of aryl bromides with PEG bound acrylate **1** under similar conditions gave unsatisfactory results, e.g. the reaction of 4-bromobenzene with resin **1** give only 23% of *trans*-cinnamic acid. On the other hand, in some cases, a trace amount of the PEG residue might contaminate the final products **3**. This problem could be easily solved by passing the crude product through a pad of silica gel using acetone-methanol (1:1) as the eluent. The products were characterised by ^{1}H NMR, IR spectra and melting points, which were consistent with the literature data.

Table 1 Liquid-phase synthesis of *trans*-cinnamic acids

Entry	Ar	Product	Yield/%^{a}	Purity/%^{b}
1	C_6H_5	**3a**	83	95
2	4-$CH_3C_6H_4$	**3b**	86	96
3	4-$CH_3OC_6H_4$	**3c**	84	96
4	4-ClC_6H_4	**3d**	85	95
5	4-$NO_2C_6H_4$	**3e**	83	96
6	3-$NO_2C_6H_4$	**3f**	83	97
7	4-$CH_3OCOC_6H_4$	**3g**	80	96
8	4-HOC_6H_4	**3h**	81	94

^{a}Isolated yield based on loading of original HO-PEG-OH. ^{b}Purity determined by HPLC analysis of the crude products.

Finally, resin **2** cleaved with another method was further investigated as shown in Scheme 2. For example, treatment of the resin **2a** with 0.1 N MeONa in methanol at room temperature for 12 h afforded methyl cinnamate **4a** in 84% yield and 94% HPLC purity.[8] This methodology also could be used for preparation of the other corresponding cinnamic ester.



2a **4a**

Scheme 2

In summary, we have developed a novel liquid-phase methodology for the synthesis of substituted *trans*-cinnamic acids on soluble PEG support with satisfactory yields and high purity. The mild reaction conditions ensure the applicability of this procedure to combinatorial chemistry library synthesis.

Experimental

Melting points were uncorrected. ^{1}H NMR (400 MHz) spectra were recorded on a Bruker Avance (400 MHz) spectrometer, using $CDCl_3$ as the solvent and TMS as internal standard. FT-IR spectra were taken on a Perkin-Elmer SP One FT-IR spectrophotometer. Aryl iodides were obtained from commercial suppliers and used without further purification.

Preparation of poly(ethylene glycol) supported acrylate **1**: To a stirred solution of PEG (5.0 g, 2.5 mmol) in dichloromethane (20 ml) were added potassium carbonate (2.76 g, 20.0 mmol), and the mixture was cooled to 0 °C. Subsequently, acryloyl chloride (5.0 mmol) was added dropwise within 15 min. After the mixture was stirred for 1 h at 0 °C and 48 h at room temperature, the precipitate was removed by filtration and the polymer was precipitated by addition of diethyl ether (200 ml) to the filtrate. For completion of the precipitation, the suspension was left at 0 °C for another 30 min. The white precipitate was collected and washed several times with diethyl ether, and dried *in vacuo* to afford the PEG bound ester **1** as a white power**:** ^{1}H NMR δ 3.45–3.78 (m, PEG CH_2), 4.32 (t, *J* = 5.06 Hz, 2H, $CH_2OCOCH{=}CH_2$), 5.84 (dd, *J* = 10.3, 1.6 Hz, 1H), 6.16 (dd, *J* = 17.2, 10.3 Hz, 1H), 6.42 (dd, *J* = 17.2, 1.6 Hz, 1H).

General procedure for the preparation of trans-cinnamic acids **3a–3h**: A mixture of PEG-bound ester **1** (1.0 mmol), aryl iodides (1.5 mmol), Pd $(OAc)_2$ (0.02 equiv.), *n*-Bu_4NBr (0.1 mmol), K_2CO_3 (1.5 mmol) in neat water (8 ml) was stirred vigorously under nitrogen atmosphere at 80 °C for 8 h. After accomplishment of the reaction, the reaction mixture was cooled and the diethyl ether (50 ml) was added to allow the precipitation of PEG-bound product **2**, which was collected by filtration and washed with diethyl ether for three times. The obtained product **2** was dissolved in 2 ml of 0.5 N NaOH aqueous solution and stirred at room temperature overnight. Then the solution was acidified to pH 2–3 using 2 N HCl and the final product was precipitated. After filtration, the collected solids were redissolved in small amount of methanol/acetone (1/1) mixed solvent and the solution was allowed to pass through a short silica gel column with methanol/acetone (1/1) as the eluent. The combined filtrate was evaporated under reduced pressure to give the product **3a–3h**.

(E)-Cinnamic acid (**3a**)[9]: M.p. 131–132 °C (lit.133 °C); ^{1}H NMR: δ = 7.57 (d, *J* = 15.8 Hz, 1H), 7.12–6.88 (m, 3 H), 6.80–6.55 (m, 2 H), 6.32 (d, *J* = 15.8 Hz, 1H), 5.81 (br s, 1H); IR (KBr): ν = 3030, 2910, 1690, 1625, 1500, 1420, 760, 699 cm^{-1}.

(E)-4-Methylcinnamic acid (**3b**)[10]: M.p. 199–200 °C (lit.198–199 °C); ^{1}H NMR: δ = 7.56 (d, *J* = 16.0 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 6.24 (d, *J* = 16.0 Hz, 1H), 2.35 (s, 3H); IR (KBr): ν = 3033, 2925, 1688, 1631, 1600, 1495, 1376, 824 cm^{-1}.

(E)-4-Methoxylcinnamic acid (**3c**)[9]: M.p. 171–172 °C (lit.172 °C); ^{1}H NMR: δ = 7.67 (d, *J* = 16.0 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.26 (d, *J* = 16.0 Hz, 1H), 3.78 (s, 3H); IR (KBr): ν = 3032, 2924, 1682, 1630, 1600, 1500, 1378, 1250, 1171, 828 cm^{-1}.

(E)-4-Chlorocinnamic acid (**3d**)[10]: M.p. 248–249 °C (lit.249–250 °C);^{1}H NMR: δ = 7.78 (d, *J* = 15.9 Hz, 1H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 6.26 (d, *J* = 15.9 Hz, 1H); IR (KBr): ν = 3032, 2931, 1686, 1634, 1587, 1495, 950, 832 cm^{-1}.

(E)-4-Nitrocinnamic acid (**3e**)[10]: M.p. 286–287 °C (lit.288 °C); ^{1}H NMR: δ = 7.80 (d, *J* = 16.0 Hz, 1H), 8.21 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 6.53 (d, *J* = 16.0 Hz, 1H); IR (KBr): ν = 3030, 2950, 1685, 1632, 1600, 1541, 1423, 1341, 840 cm^{-1}.

(E)-3-Nitrocinnamic acid (**3f**)[11]: M.p. 196–197 °C (lit.197 °C); ^{1}H NMR: δ = 8.35 (s, 1H), 8.21–7.8 (m, 2H), 7.75 (d, *J* = 15.9 Hz, 1H), 7.45–7.55 (m, 1H), 6.52 (d, *J* = 15.9 Hz, 1H); IR (KBr): ν = 3030, 2948, 1686, 1633, 1600, 1542, 1424, 1340, 956, 842 cm^{-1}.

(E)-4-(Methoxycarbonyl)cinnamic acid (**3g**)[12]: M.p. 240–241 °C (lit.241–242 °C); ^{1}H NMR: δ = 7.55 (d, *J* = 15.8 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.36 (d, *J* = 15.8 Hz, 1H), 3.89 (s, 3H); IR (KBr): ν = 3032, 2910, 1712, 1685, 1630, 1600, 1100, 848, 772 cm^{-1}.

(E)-4-Hydroxycinnamic acid (**3h**) [9]: M.p. 206–207 °C (lit.206 °C); ^{1}H NMR: δ = 7.45 (d, *J* = 15.9 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 6.74 (d, *J* = 8.3 Hz, 2H), 6.22 (d, *J* = 15.9 Hz, 1H), 3.57 (br s, 1H); IR (KBr): ν = 3400, 29125, 1712, 1685, 1630, 1600, 1100, 848, 772 cm^{-1}.

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