Carbon–carbon bond forming reactions with substrates absorbed non-covalently on a cellulose chromatography paper support

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Reactions and purifications, including carbon–carbon bond forming reactions, can be carried out on a cellulose support on which the substrates are non-covalently absorbed.

The chemical production of libraries and arrays where substrates are attached to a solid support have found widespread use in the last decade.[1] Variations on this theme where reagents, catalysts, or scavenger reagents are attached to a support have also become powerful and valuable tools.[2] Practically all of these techniques require the *covalent* attachment of the substrate or reagent to the support, irrespective of the nature of the support. Notable exceptions are elegant studies by Williams[3] and Field[4] where synthesis and purification (and in some cases biological screening) are carried out on TLC plates or on silica packed in a flash column.[4]

We have recently discovered that it is possible to carry out chemical transformations and produce arrays of compounds typically in 1–10 mg quantities, where the molecules are *only absorbed and not covalently bound* onto a support such as cellulose based chromatography paper.[5] This stands in contrast to previous reports where the substrates are covalently attached to derivatised cellulose.[6] We also demonstrated that it is possible to purify products non-covalently absorbed on the cellulose paper by washing with solvents which selectively remove impurities (such as excess reagent or unreacted starting material).

The cellulose paper (typically cut into 10 × 10 mm "tiles") can be regarded as an "immobilised solvent". Thus washing sequences that purify a crude reaction mixture dissolved in an organic solvent (such as washing out excess amine with dilute aqueous acid after an amide coupling), have been shown to be equally applicable to the washing of an "immobilised solvent"—in this case the cellulose. The advantages of the cellulose include its flexibility, simplicity of handling and processing large numbers of tiles, exceptionally low cost (100 × 1 cm^2 tiles cost 20 p), ease of "encoding" (simply by writing on the tile with a pencil or by cutting the tiles into different shapes) and ease of analysing the contents of a tile (by snipping off a small corner of the tile and placing the fragment in acetonitrile prior to LC-MS analysis). The potential of this technique appears considerable.[5]

Having previously described the conversion of amines into amides, sulfonamides and carbamates and demonstrated some simple deprotections,[5] we describe here carbon–carbon bond forming reactions. We also detail new washing procedures to effect purification on the tile and describe processing multiple substrates on the same tile with no inter-mixing of the products.

Ring closing metatheses have recently become a widespread and popular methodology for forming carbon–carbon double bonds.[7] An interesting recent development has been the use of metathesis catalysts in ionic liquids to aid product isolation and the removal of the catalyst.[8] Using a standard reaction,[8] we have demonstrated an olefin metathesis on a cellulose support (Scheme 1†).

Tosyl chloride (6 mg) (mp 67–69 °C) was loaded as a melt onto a 1 cm^2 tile of Whatman 17Chr chromatography paper followed by neat diallylamine. After 10 min, the tile was washed by vigorous shaking in dilute sodium bicarbonate solution (to remove unreacted tosyl chloride), water, dilute acid (to remove unreacted amine) and further water and then dried *in vacuo*.‡ After this purification the second reaction, the metathesis, was carried out. A catalytic (2.5 mol%) amount of the Grubbs[9] catalyst **3** was dissolved in the commercially available ionic liquid 1-butyl-3-imidazolium hexafluorophosphate **4** (60 μL) and then loaded onto the tile supporting the sulfonamide **2**. The tile was then sealed in a vial and left at room temperature for 3 d.§ After a single extraction by vigorous shaking in ether,¶ the pyrroline product **5** (1.1 mg) was obtained in 29% unoptimised yield in good purity by ^{1}H-NMR with no evidence for either the ionic liquid or contamination with the catalyst. As expected,[10] there was no indication of dissolution or degradation of the cellulose in the ionic liquid. (We have also found that Diels–Alder reactions mediated by Lewis acids in ionic liquids are feasible on a cellulose support. Further details will be reported elsewhere.)

We next explored a Wadsworth–Emmons reaction on the cellulose support. As cellulose is composed of polysaccharides derived from glucose, we planned to use sodium ethoxide as base for this reaction. If an equilibrium is set up between the ethoxide and alkoxides of the saccharide, in principle both may act as a base. Triethylphosphonoacetate was loaded onto a tile followed by an excess of benzaldehyde (10 equiv.) (Scheme 2†).

The sodium ethoxide in ethanol (*ca.* 7 equiv.) was then applied and the tile allowed to stand at room temperature in a sealed vial for 1 h. The tile was then washed sequentially by vigorous shaking with sodium bisulfite solution (to remove unreacted aldehyde), water, 8% sodium hydrogen carbonate solution, water and dried. Extraction of the product in the usual fashion gave a good yield (1.9 mg, 82%) of pure *E*-cinnamate as determined by ^{1}H-NMR.

One of the advantages of this cellulose supported technology is the ease with which the paper can be cut into different shapes. One example of this is described here where different substrates were

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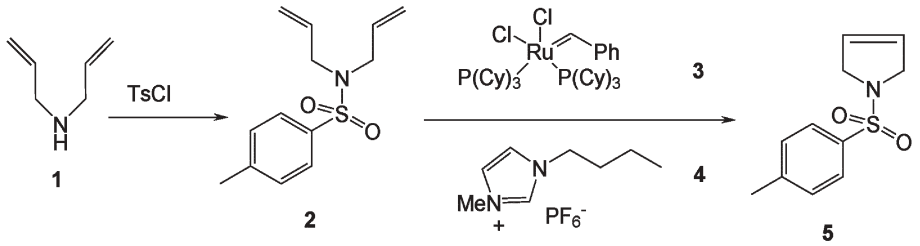
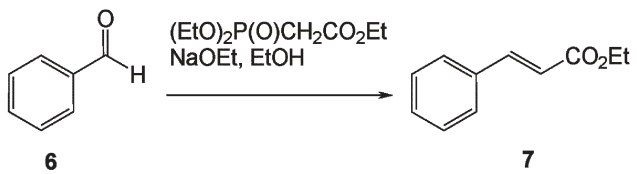


Scheme 1



Scheme 2

used on the same tile which had been cut into the shape of a "comb" (Fig. 1). This has advantages in streamlining the work-up procedures.

As an example, we carried out the Wadsworth–Emmons reaction above using three different benzaldehydes as substrates on the same tile (Scheme 3†).

Each "tooth" of the comb supported a different substrate—benzaldehyde on tooth A, tolualdehyde on tooth B and *para*-methoxybenzaldehyde on tooth C. In each case the reagents were applied to the centre of each tooth. There is no contamination between each tooth as the substrates and reagents remain confined to the tooth region with no or very little spread to the "backbone" of the comb. The multiple reactions and work-ups were carried out as before with the whole comb being washed to remove unreacted aldehyde and phosphonate by-products. Finally, before extraction of the products with ethyl acetate, the teeth were cut off (at the top of the tooth) and placed in separate vials. In this way, good yields

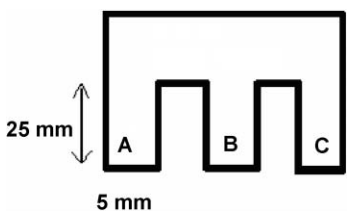
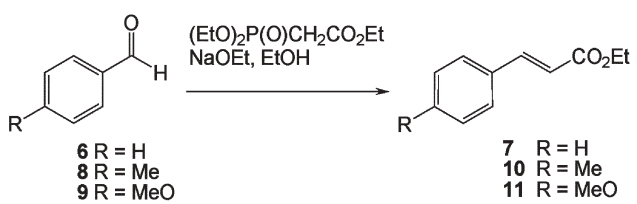


Fig. 1 Illustration and dimensions of the "comb". Each "tooth" of the comb (labelled A, B and C) supports a different reaction but the work up procedures can be carried out on the whole comb before cutting off each tooth and extracting the product.



Scheme 3

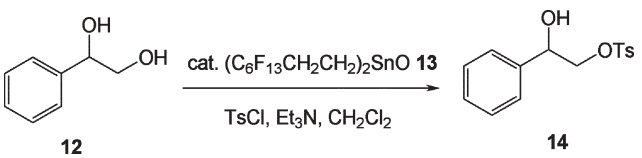
of *E*-ethyl cinnamate (1.8 mg, 78%), *E*-ethyl 4-methylcinnamate (1.5 mg, 60%) and *E*-ethyl 4-methoxycinnamate (2.3 mg, 85%) were obtained in high purity and with no cross-contamination as determined by ^{1}H-NMR.

Purification of the products for the Wadsworth–Emmons reactions involved washing the tiles or comb with aqueous sodium bisulfite and sodium hydrogen carbonate. There are other numerous potential washing procedures‖ for the selective removal of products, reagents or by-products aside from those described here and elsewhere.[5] One option is the use of "phase switching" methodologies where following its use in a reaction, a reagent is degraded allowing its removal by a washing procedure.[11] A further option is the use of fluorous reagents and/or solvents as described by Curran *et al.*[12] which would broaden the range of reactions that might be used with this technology. We illustrate here the use and removal of a fluorous tin reagent used in the selective monotosylation of phenyl-1,2-ethanediol **12** (Scheme 4).[13]

The fluorous tin oxide **13** was dissolved in perfluorohexanes and loaded onto a tile which was then dried. The substrate and other reagents were loaded in dichloromethane. Following reaction, the tile was dried and washed with dilute hydrochloric acid and perfluorohexanes prior to extraction of the product with dichloromethane. The product was not contaminated with any tin reagents as determined by ^{19}F-NMR. Alternatively the fluorous tin reagent could be selectively recovered in good yield by washing with perfluorohexanes.

Further applications of this technology that might be envisaged including derivation of the cellulose to provide a different environment for chemical reactions or alternative washing protocols. This is analogous to the derivation of resins or silica with, for example, long perfluorinated alkyl chains to provide a fluorous environment suitable for fluorous substrates.[12]

In summary, we have described carbon–carbon bond forming reactions where the substrates are absorbed non-covalently on a cellulose support. We have also demonstrated that multiple substrates can be processed on a suitably shaped comb without cross-contamination. Finally we have demonstrated the use and removal of a fluorous reagent in a cellulose environment. We hope these and previous[5] examples demonstrate the promise of this powerful but cheap technology which we have found exceptionally



Scheme 4

simple to use. In fact all the practical work described here and previously[5] was carried out by 16 year old school students.

Notes and references

† ***N*-Tosyl-3-pyrroline (5)**. Tosyl chloride (6 mg, 0.03 mmol) was melted and applied using a Gilson pipette onto the centre of a 1 cm^2 tile of Whatman 17Chr chromatography paper. Diallylamine (45 μL, 0.36 mmol) was added in a similar fashion. After standing in a sealed vial for 10 min, the tile was then vigorously shaken in 8% sodium hydrogencarbonate solution (5 mL) for 30 s, water (5 mL) for 1 min, 0.5 M hydrochloric acid (5 mL) for 1 min and finally water (5 mL) for 1 min. After drying *in vacuo*, a solution of Grubb's catalyst (benzylidene-bis(triphenylphosphine)ruthenium dichloride) (0.3 mg, 10 mol%, 0.003 mmol) in 1-butyl-3-methylimidazolium hexafluorophosphate) (60 μL) (requires warming to obtain a solution) was applied to the centre of the tile which was then allowed to stand in a sealed vial for 3 d at room temperature. The product was then extracted with diethyl ether (5 mL) for 10 min. The ether was evaporated under a stream of dry nitrogen followed by drying *in vacuo*, affording pure pyrroline **7** by ^{1}H-NMR (1.9 mg, 29%). ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.66 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H), 5.58 (s, 2H), 4.04 (s, 4H), 2.37 (s, 3H).

***E*-Ethyl cinnamate (7)** Using a Gilson pipette, triethylphosphonacetate (3.14 μL, 0.016 mmol) and benzaldehyde (13.4 μL, 0.16 mmol) were sequentially loaded onto the centre of a 1 cm^2 tile of Whatman 17Chr chromatography paper. Finally, sodium ethoxide in ethanol (21 wt%, 33.5 μL, 0.1 mmol) was added and the tile then sealed in a vial at room temperature for 1 h. The tile was then vigorously shaken in saturated sodium bisulfite solution (freshly prepared, 5 mL) for 5 min, then water (10 mL) for 10 min, 8% sodium hydrogencarbonate solution (5 mL) for 5 min and finally water (10 mL) for 10 min. The tile was then dried at high vacuum and finally extracted with boiling ethyl acetate (5 mL). Solvent removal by evaporation under a stream of dry nitrogen followed by drying *in vacuo* afforded pure cinnamate by ^{1}H-NMR (1.9 mg, 82%). ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.75 (d, J = 16 Hz, 1H), 7.57 (m, 2H), 7.43 (m, 3H), 6.50 (d, J = 16 Hz, 1H), 4.32 (quartet, J = 7 Hz, 2H), 1.41 (t, J = 7 Hz, 3H).

The "comb" array of cinnamates: *E*-ethyl cinnamate, *E*-ethyl 4-methylcinnamate, *E*-ethyl 4-methoxycinnamate. To each tooth of the comb, was added triethylphosphonoacetate (3.11 μL, 0.013 mmol). To tooth A was then added benzaldehyde (13.4 μL, 0.13 mmol), tooth B *p*-tolualdehyde (15.6 μL, 0.13 mmol) and tooth C *p*-methoxybenzaldehyde (16.1 μL, 0.13 mmol). To each tooth was then added sodium ethoxide (33.5 μL of a 21% solution in ethanol). The comb was then placed in an ethanol rich atmosphere for 30 min. The comb was then worked-up as before except the teeth were cut off at the top of the tooth before extraction of the product. The products obtained in good purity are *E*-ethyl cinnamate (1.8 mg, 78%), *E*-ethyl 4-methylcinnamate (1.5 mg, 60%) and *E*-ethyl 4-methoxycinnamate (2.3 mg, 85%).

‡ At this point the sulfonamide **2** (5.3 mg) can be isolated from the tile (by boiling in ethyl acetate for 3 min) in good purity as determined by ^{1}H-NMR.

§ In an attempt to increase the rate of the reaction, it was heated in a microwave; however the tile was pyrolised to an ash within seconds! It is known that microwaves heat ionic liquids with unusual efficiency.[14]

¶ For a good recovery of product from the tile multiple extractions with ether are required. From previous work, hot ethyl acetate is an effective extraction solvent, but in this case ether was preferred to avoid simultaneous extraction of ionic liquid.

‖ These include aqueous ethanolamine solutions to remove boronic acids, non-polar organic solvents such as hexane to remove highly lipophilic substances and aqueous fluoride solutions to remove tin reagents.

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