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Solid phase sequential 1,3-dipolar cycloaddition–Pictet–Spengler reactions

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Abstract

Up to six bonds and two rings can be created, in five component processes (five points of diversity), by AgOAc catalysed imine cycloaddition to Wang resin acrylate followed by Pictet–Spengler and Pd(0) catalysed reactions.

Keywords: cycloaddition; Pictet–Spengler reaction; Pd catalysis; cascade reaction.

Solid-phase synthesis is now established as a powerful tool for the preparation of combinatorial libraries of small molecules for drug lead discovery.[1] The molecular diversity of these libraries is the key element in their usefulness and this is enhanced by incorporating a variety of chemistries and diverse building blocks. Our cascade imine→metalloazomethine ylide→cycloaddition chemistry[2] is ideal for solid phase chemistry and in this communication we report solid phase imine→metalloazomethine ylide→cycloaddition/Pictet–Spengler reactions.

The Wang resin acrylate **1** was treated with imines **2a**–**e** (15 mmol), AgOAc (1.5 mmol) and DBU (2 mmol) in methylene chloride (room temperature, 20 h) to afford resin bound cycloadducts **3a**–**e**. The beads were filtered and washed with methylene chloride and ether and deposited metallic silver was removed from the resin bound cycloadducts **3a**–**e** by treatment with NaCN in DMF/dioxane (Scheme 1). Two of the resin bound cycloadducts **3a** and **3d** were cleaved with NaCN:Et_3N in 3:1 v/v MeOH–THF at 50°C over 2 days. Cycloadduct **3a** afforded **4a** as a 2:1 mixture of *exo*- and *endo*-isomers in 54% yield whilst **3d** afforded **4b** as a 3:2 mixture of *exo*- and *endo*-isomers in 52% yield. In contrast the solution phase reactions gave only the *endo*-cycloadducts.[2] Recently two closely related solid phase cycloaddition reactions have been reported.[3,4] The formation of *endo exo*-cycloadduct mixtures in the

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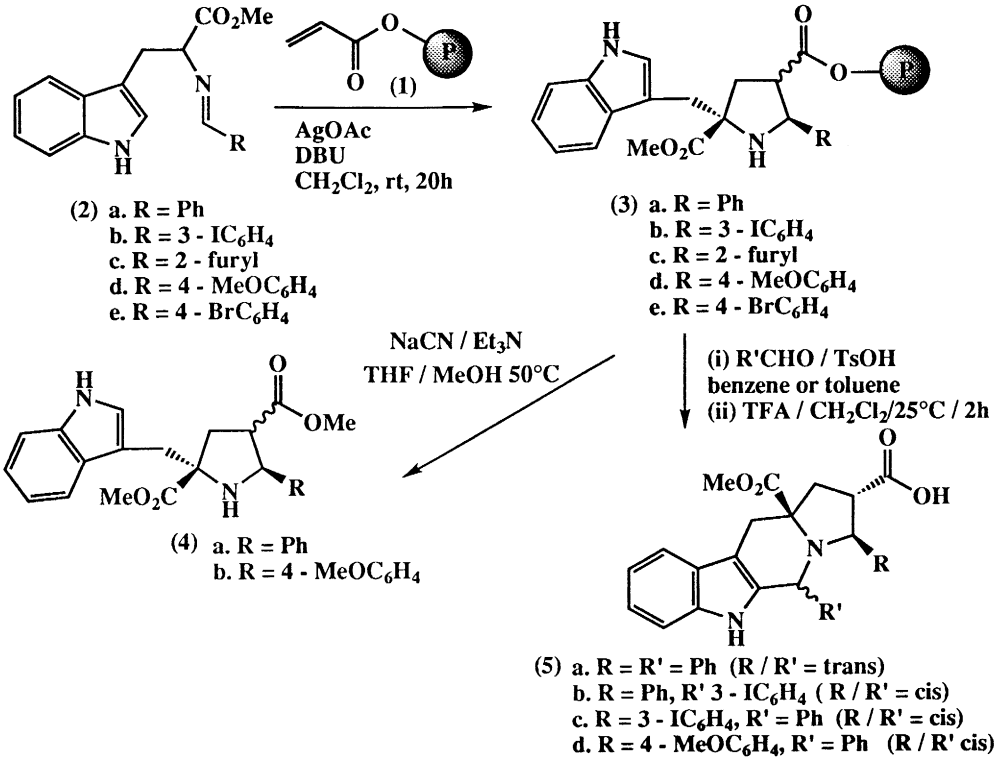
solid phase indicates that the combined steric effects of the resin and the bulky 3-indolylmethyl group conspire to make the *endo*- and *exo*-transition states nearly equal in energy.

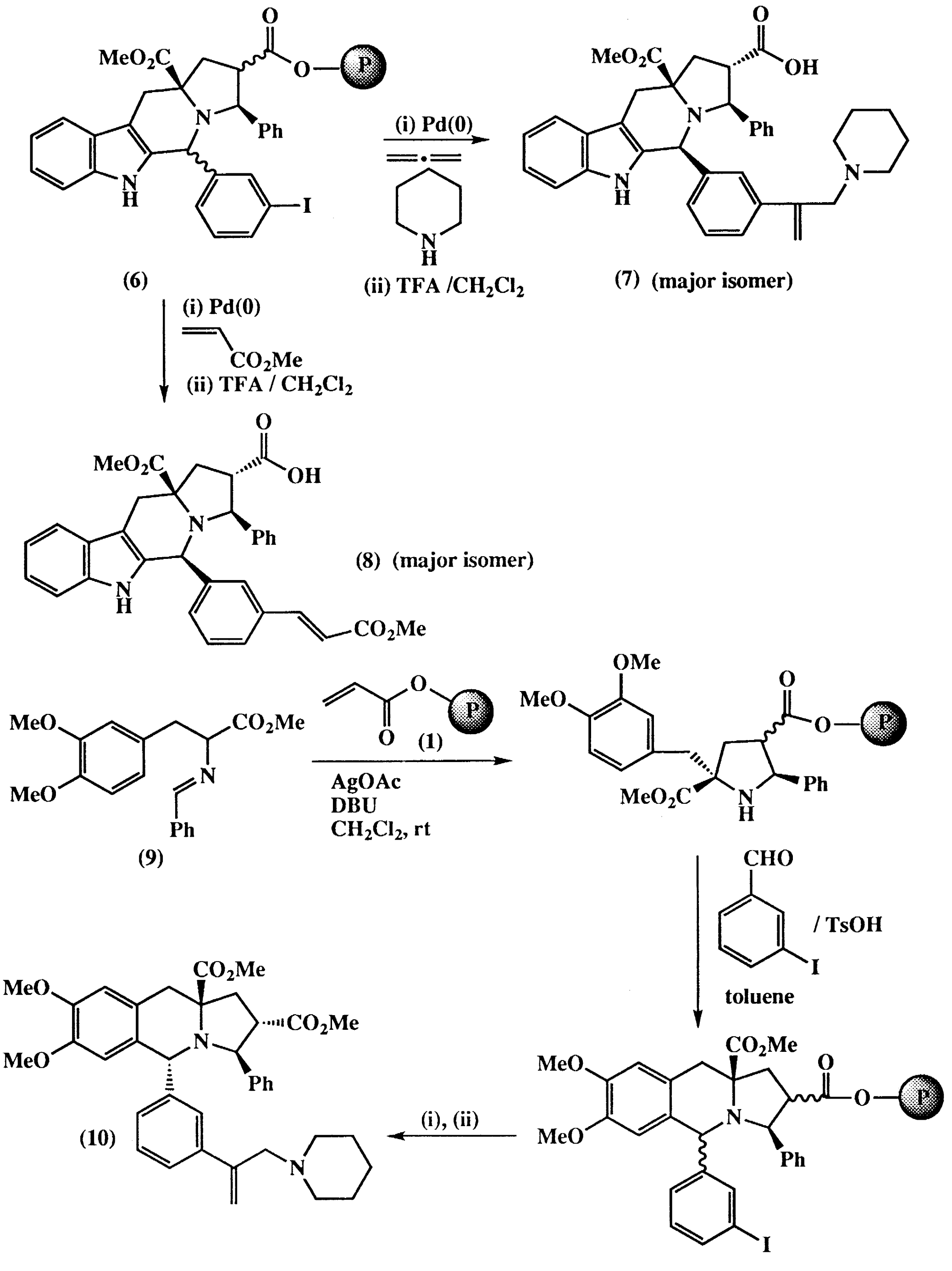


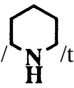
Scheme 1.

Solid phase Pictet–Spengler reactions were carried out on the cycloadducts **3a**, **3b** and **3d** using various aldehydes in the presence of 10 mol% TsOH in benzene (80°C) or toluene (110°C). Resin bound Pictet–Spengler products were then cleaved from the resin with 1:1 v/v TFA:methylene chloride at room temperature over 2 h to afford **5a**–**d** in 33–46% yield. In all cases **5** comprises a mixture of four isomers of which one was major and the stereochemistry of the major isomers are shown in **5a**–**d** (Scheme 1). The major products **5b**–**d** were found to be those in which the CO_2Me and R^1 groups bear a *cis*-relationship to each other whilst **5a** was the *trans*-isomer. Alternatively the Pictet–Spengler products were cleaved from the resin by transesterification ($NaCN/Et_3N$ in MeOH/THF) to afford the corresponding methyl esters: e.g. of **5c** in 61% yield. Recently solid phase Pictet–Spengler reactions have been reported using more complicated linkers.[5–8]

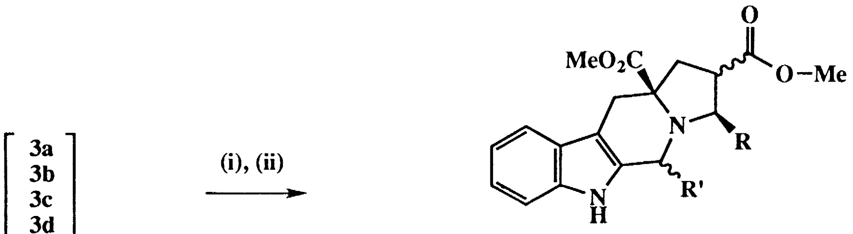
We further enhanced the diversity of **6b** using palladium catalysed procedures. Thus **6b** was treated with $Pd(OAc)_2$ 10 mol%, PPh_3 20 mol%, K_2CO_3 (2 mol equiv.) and piperidine (2 mol equiv.) in toluene at 90°C in the presence of allene (1 atm) to afford **7** (42%), after cleaving from the resin using TFA in methylene chloride. Similarly **6b** was treated with the same catalyst system but in the presence of methyl acrylate to afford **8** in 36% yield after cleaving from the resin using TFA in methylene chloride.

Next we briefly studied one example of the benzaldimine of DOPA dimethyl ether methyl ester **9** in the 1,3-dipolar cycloaddition/Pictet–Spengler-palladium catalysed allenylation sequence (Scheme 2). This sequence afforded a mixture of four isomers from which the major isomer **10** was isolated in 41% overall yield. Incorporation of the Pd catalysed sequence provides an overall process with up to five points of diversity.



Scheme 2. (i) Pd(0)/=·=/  /toluene/90°C. (ii) NaCN/Et$_3$N/THF/MeOH/50°C

Finally we have generated a small library using split-mix methodology. Thus each of the five resin bound cycloadducts **3a**–**e**, which comprised mixtures of two isomers, were mixed and split into five parts. Pictet–Spengler reactions were carried out with five different aldehydes separately in the presence of 10 mol% TsOH in benzene (80°C). Each library comprised, as expected, a mixture of 20 compounds since the Pictet–Spengler reactions also give two isomers (Scheme 3). The libraries **11** were cleaved from the resin by transesterification and their integrity established by MS.[9]



(11) **a. R' = Ph**
b. R' = 2 -furyl
c. R' = 4 - MeOC_6H_4
d. R' = 4 - BrC_6H_4
e. R' = 4 - ClC_6H_4

Scheme 3. (i) R′CHO/TsOH/C_6H_6/80°C. (ii) NaCN/Et_3N/MeOH/THF/50°C

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9. The samples were dissolved in MeOH and injected directly into a Micromass Platform II spectrometer (APCI mode) using a 4:1 v/v MeOH:H_2O mobile phase. For all libraries **11a**–**e** the expected molecular ions (MH^+) were detected unambiguously.