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New solid phase Knoevenagel catalyst

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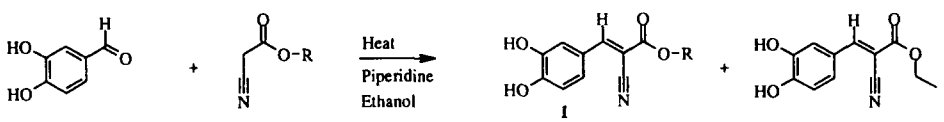
Abstract

A new solid phase Knoevenagel catalyst has been prepared and evaluated. The new resin based catalyst reduces by-product formation and has the advantage over conventional Knoevenagel catalysts of simple removal by filtration.

Keywords: aldehydes; catalysts; condensation; piperidine.

Knoevenagel condensation products of similar structure to caffeic acids **1**, have been shown to be active inhibitors of the 12- and 15-lipoxygenase pathway.[1] 12-Lipoxygenase inhibitors decrease tumour growth rate,[2] trigger apoptosis[3] and reduce cancer cell metastasis in vitro.[4] Inhibitors of 15-lipoxygenase are known to reduce tumour angiogenesis.[5] 12- And 15-lipoxygenase, therefore, offers a potential target for potential anti-cancer agents (Scheme 1).



R = Simple and functionalised alkyl groups

Scheme 1.

We have used automated parallel synthesis to prepare libraries of compounds in which the Knoevenagel condensation was the key step.[6] A range of benzaldehydes was heated at reflux for 2 h in ethanol, with a diverse set of active methylene substrates in the presence of catalytic piperidine. Most products were generally free of impurities after three washes with organic solvents. Some products, however, proved problematic in the removal of both piperidine and piperidine based by-products. Reactions performed in deoxygenated solvent under argon gave the same by-products. LC-MS analysis showed peaks consistent with a protonated piperidine. ^{1}H NMR showed peaks at 3.0 ppm and 1.65 ppm, consistent with a piperidine salt, compared with piperidine itself at 2.6 ppm and 1.4 ppm. Despite extensive efforts we were not able to determine the exact identity of this unwanted material. Other potential impurities including the aminal 2,6-$ClC_6H_3CH(NC_5H_{10})_2$, hemi-aminal 2,6-$ClC_6H_3CH(NC_5H_{19})OH$ and ether 2,6-$ClC_6H_3CH(NC_5H_{10})CH(CN)OC_2H_5$ were prepared, but the ^{1}H NMR spectra were inconsistent with

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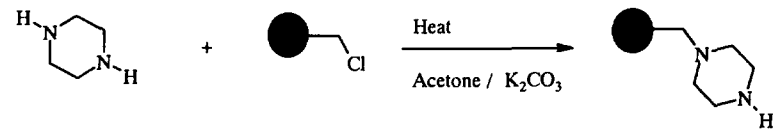
the observed ^{1}H NMR of the contaminating by-product. Analysis of the libraries by automated APCI mass spectrometry indicated a second problem. Caffeic acid analogues derived from certain aromatic aldehydes underwent significant amounts of transesterification with the alcoholic solvent.

A new solid phase catalyst was devised and prepared to overcome these limitations. Synthesis of the new catalyst involved the addition of an excess of piperazine **2** to Merrifield's solid phase resin (2% cross-linked, 200–400 mesh, 2.3 mmol Cl^{-1}/g) **3** under reflux in acetone in the presence of potassium carbonate, to give a resin-bound piperidine equivalent **4**† (Scheme 2).



2 **3** **4**

Scheme 2.

A pair of libraries of caffeic acid derivatives were then synthesised‡ in parallel using the new solid phase catalyst and piperidine for direct comparison of the two catalysts (Table 1). Aldehydes were chosen which had previously yielded impure products contaminated by transesterification and/or piperidine-

Table 1
Comparison of molar ratios of products to by-products using the new solid phase catalyst and piperidine

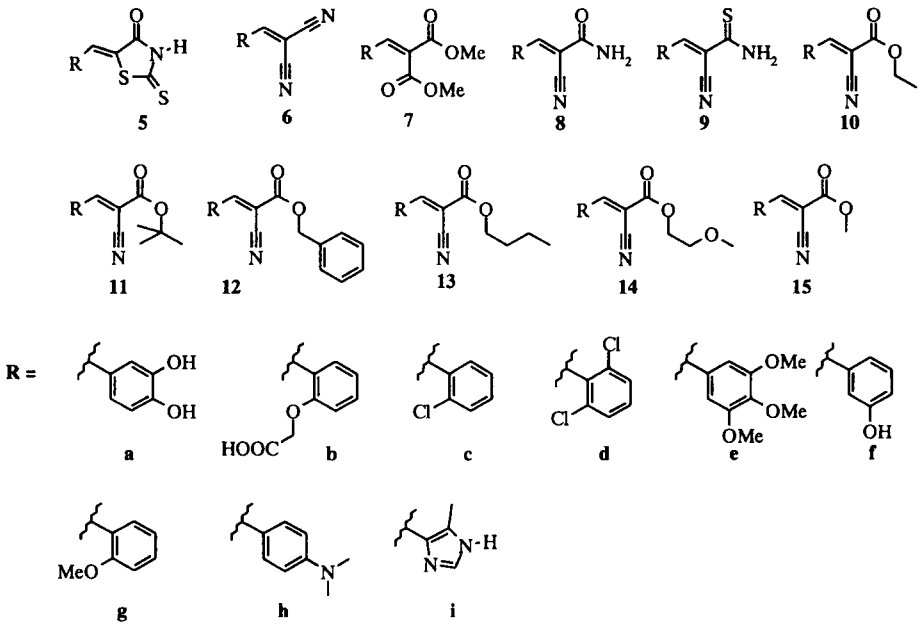
Compound	SOLID CATALYST Product/By-Product/ Transesterified Product	% Yield Pure Product	PIPERIDINE CATALYST Product/By-Product/ Transesterified Product	Proton Coupled ^{13}C-Data* C=O PPM/Hz	CN PPM/Hz
5a	1 / 0 / NA	96	1 / 0.21 / NA	177.0 / 5.4	NA
6a	1 / 0 / NA	87	1 / 0.09 / NA	NA	115.5,114.5 /8.4,14.2
7a	1 / 0 / 0	65	1 / 0.24 / 0	167.4,164.4 / 12.3,3.8	NA
8a	1 / 0 / NA	79	1 / 0.12 / NA	163.8 / 6.2	117.6 / 14.1
9a	1 / 0 / NA	100	1 / 0.21 / NA	161.2 / 2.4	117.3 / 13.9
10a	1 / 0 / NA	96	1 / 0.12 / NA	163.0 / 3.4	116.6 / 13.0
10b	1 / 0 / NA	79	1 / 0.39 / NA	162.3 / 3.8	116.0 / 14.1
10c	1 / 0 / NA	91	1 / 0.04 / NA	161.3 / 3.5	114.9 / 13.8
11a	1 / 0 / 0	88	1 / 0.25 / 0	161.9 / 6.8	116.2 / 13.7
11d	1 / 0 / 0	89	1 / 0.25 / 0.12	159.0 / 6.3	113.6 / 13.9
12e	1 / 0 / 0	96	1 / 0.24 / 1.68	162.6 / 3.3	116.2 / 13.8
13f	1 / 0 / 0	93	1 / 0.16 / 0	162.1 / 3.3	115.7 / 14.0
13g	1 / 0 / 0	96	1 / 0.04 / 0.42	162.2 / 3.2	115.7 / 14.0
12a	1 / 0 / 0.18		1 / 0.65 / 0.93		
12d	1 / 0 / 3.67		1 / 0.43 / 4.28		
12f	1 / 0 / 0.39		1 / 0.65 / 3.55		
12h	1 / 0 / 0.31		0 / 0.04 / 1		
12i	1 / 0 / 0.08		1 / 0.18 / 1.96		
14d	1 / 0 / 15.89		1 / 0.69 / 27.70		
15d	1 / 0 / 2.91		0 / 0.03 / 1		

*^{13}C-NMR produced on Bruker AC250 machine operating at sweep frequency 62.9MHz, solvent d_6-DMSO, spectrum referenced to DMSO at 39.7 ppm.

† Elemental analysis of the new catalyst gave a nitrogen content of 4.2% indicating a loading of 1.5 mmol piperazine/g.

‡ Aldehyde (1 mmol) and active methylene (1 mmol) were dissolved in ethanol (10 ml). Piperidine (1 drop) or the solid phase catalyst (50 mg) was added and the reaction mixture was refluxed for 2 h. Solid phase catalyst was removed by filtration and excess ethanol was removed under vacuum.

Table 2
Components used to synthesise libraries for comparison of catalysts



derived by-products. As can be seen from Table 2 this new catalyst eliminates the piperidine-derived by-product and reduces transesterification. The materials obtained were analysed by ^{1}H NMR and mass spectrometry. ^{1}H NMR and ^{13}C NMR confirm that all compounds were produced as single isomers. Previous workers[7] starting from an X-ray crystal structure have established that the coupling constant of the olefinic proton *trans* to the nitrile carbon or ester carbonyl carbon is in the range 13–14 Hz and that the corresponding *cis* coupling constant is in the range 3–8 Hz. The coupling constants reported in the present paper confirm the stereochemistry of the Knoevenagel products as those described in Table 2.

The new catalyst is easily removed from the reaction mixture compared with piperidine, catalyst derived impurities are eliminated and transesterification is minimised. Although transesterification could be avoided by the use of non-alcoholic solvents, the solid catalyst gives the freedom to use alcohols when the solubility profile of substrates makes it necessary.

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