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In Situ Observation of the Progress of a Large-Scale On-Bead Reaction

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We report the successful in situ monitoring of an on-bead synthesis (aldol-type condensation) using a fibreoptic probe and Raman spectroscopy.

Introduction -

Combinatorial chemistry and solid phase synthesis

Combinatorial chemistry is widely employed by the pharmaceutical industry as a new tool for drug discovery [1]. The solid phase approach plays a major role in this context [2]. Chemical development departments are seeking also to upscale solid-support multi-step syntheses, and therefore benefit from reduced processing time compared with solution phase chemistry [3]. A solution-based synthesis may not even exist for a target molecule stemming from a combinatorial library by the time the compound enters the early development phase.

Monitoring of Solid Phase Organic Synthesis

Monitoring is not as straight forward for chemical conversions of substrates linked to a solid as it is for solution phase reactions. Cleaving of substrate from bead samples and performing the usual TLC, GLC or HPLC analysis is one time-consuming possibility. Better is single-bead IR-spectroscopy, for which some tedious and time consuming bead preparations and adjustments are still necessary. Real online monitoring of the conversion would be highly beneficial, and to that end we employed Raman spectroscopy, in which an optical probe could be inserted into the reaction mixture (a slurry of beads) and the reaction followed by measuring Raman spectra at frequent time-intervals.

Claisen-Schmidt-condensation as a Model Reaction

The model reaction studied (Scheme 1) is the base catalysed aldol condensation of acetophenone with p-carboxybenzaldehyde, supported via the commercially available Rink-amide linker [4] to cross-linked polystyrene. This particular reaction is known to give rise to supportedchalcones which are building blocks for heterocyclic compound libraries [5].



Scheme 1

Results -

On-line Raman Spectroscopy of suspended, reacting beads

The rate of the reaction is highly dependent on the scale, the purity of the reagents and the composition of the solvent mixture. When scaling up, the termination of a particular batch cannot be simply predicted.

Measurement

Raman spectra were obtained at frequent intervals from the beads passing through the focal point of the probe while being stirred in the reaction mixture. To obtain a signal in the thick slurry, the focal point of the laser was set very close to the sapphire window.

Spectra

Fluorescence of a reaction component can often cause problems in Raman



Figure 1. a) Raman spectra (pre-processed), this peak predominantly shows formation of product. b) Spectral changes over time shown for the wavenumber of maximum signal (1608 cm⁻¹).

<u>Analysis</u>

A chemical model can be fitted to the spectral data e.g.

Reactant \rightarrow Product \rightarrow SideProduct

allowing the estimation of rate constants, and describing component distribution and absorptivities (Fig 2).



Figure 2. a) Component distribution. b) Component spectra (side product gives no signal at this wavenumber). c) An indication of the goodness of fit of model calculation (line) to measured data (points).

On-line Application

Knowing that Raman is an effective in situ method for following a) reactions on beads in general, and b) this reaction in particular, an on-line method could be applied. This method could, for example, detect the end of this reaction, i.e. the point at which product concentration starts to decrease, by following the first derivative of the peak at 1608 cm⁻¹.

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spectra. Fluorescence was also observed in this instance, but could be removed by reducing the window size (i.e. selection of a single peak) and offset correction. Reaction spectra are found in Figure 1.

Conclusions –

- Monitoring of the conversion on beads is possible.
- Analysis of the Raman spectra collected continuously during the reaction allows the determination of the optimal point to stop a . reaction with respect to formation of side-products and reaction time.

References

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