

# Rapid Generation of Polymer-Bound Enones by Microwave-Assisted Solid-Phase-Synthesis

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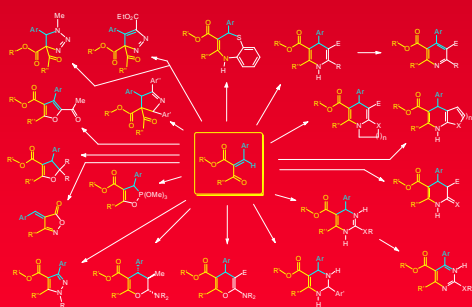


## 1 Enones as Precursors for Heterocycles

Enones are versatile intermediates for a number of synthesis of heterocycles. This is mainly due to their simple preparation via Knoevenagel condensation of commercially easily available  $\beta$ -keto esters and aldehydes with usually very high yields.

Enones are strong Michael acceptors and therefore most of the transformations proceed via a vinylogous addition of various nucleophiles (thiols, hydrazines, CH-acidic compounds) and subsequent ring closure (see scheme on the right side). This remarkable flexibility gives rise to lots of diverse molecules.

Apart from the synthetic aspects, several pharmacologically active compounds and lead structures including pyrazolones, benzothiazepines, (dihydro)pyridines and dihydropyrimidines can be made accessible.



## 2 Microwave Irradiation

### Advantages over conventional Heating

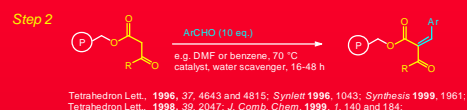
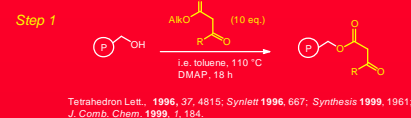
- rapid energy transfer
- use of vessel materials that have low thermal conductivity (PFA, PTFE ...)
- compatibility with flow-through reactors
- excellent temperature and pressure control in purpose-built appliances

### Disadvantages

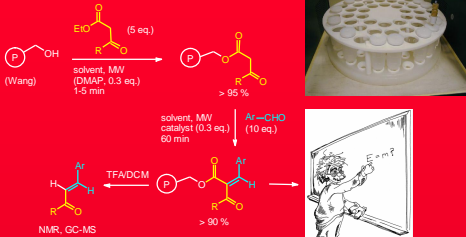
- useful only for thermal stable substances and therefore limited reactions (typically condensations, couplings, cycloadditions)
- high loss tangents of solvents necessary
- racemisation of enantiopure systems possible

## 3 Synthesis of Polymer-Bound Enones

### Conventional Protocol



### Microwave Protocol



### ETHOS multiPREP-50



"And I can't tell you when the journal comes out."

### Open Vessel



Reflux condenser

Thermocouple Temperature Measurement

<http://www.milestonesci.com/>

## 5 Library of Enones, On-Bead-FT-IR-Analysis



This graphic displays a comparison of polymer-bound acetoacetate and the corresponding enone after Knoevenagel condensation with benzaldehyde (both products bound to Wang resin 1.0mmol/g from Fluka). Acetoacetates usually present two characteristic carbonyl bands (1744 and 1721  $\text{cm}^{-1}$ ) whereas enones have only one band (1725  $\text{cm}^{-1}$ ) in that part of the spectrum guarded by further bands at 1700 and 1670  $\text{cm}^{-1}$ . It is obvious that this significant differences make it possible to study the progress of both transformations. Yields of each step can be further determined by measuring the weigh gain and in the case of the enone by cleavage.

## 6 Discussion

We have shown that two important reactions in solid-phase synthesis can be easily accelerated by the assistance of microwave irradiation. Acetoacetylations were performed in 1-5 minutes instead of 18 hours. Knoevenagel condensations were acceptably reduced from 1-3 days to one hour. The increased temperatures didn't reduce the purity of the final products.

## Acknowledgement

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