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## **Solid Phase Coupling of Benzoic Acid to Wang Resin: A Comparison of Thermal Versus Microwave Heating.**

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**Abstract:** This presentation reports the possibility to carry out simple solid phase coupling reactions not only by conventional thermal heating but also by microwave dielectric heating. Thus coupling of benzoic acid to Wang resin occurs under microwave irradiation within 3 h in excellent yield (>99%) as compared to 72 h at room temperature. However, a further increase of reaction rates in this particular coupling reaction is not possible due to a side reaction that occurs at higher temperatures.

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### **Introduction**

Combinatorial chemistry has revolutionized drug discovery and many other branches of chemistry and related fields. Today there is an ever growing demand for large libraries of compounds that are being evaluated for their biological and other properties using high throughput screening (HTS) protocols. One of the cornerstones of combinatorial chemistry has been the development of solid-phase organic synthesis (SPOS) based on the original Merrifield method for peptide synthesis. Since reactions on polymer supports enable chemical reactions to be driven to completion, and allow simple purification of products, combinatorial chemistry has been primarily carried out by SPOS. However, solid-phase synthesis still exhibits several shortcomings due to the nature of heterogeneous reaction conditions. Nonlinear kinetic behavior, slow reactions, solvation problems, and degradation of the polymer support due to the long reaction times are some of the problems experienced in SPOS. Only very recently the first reports have emerged which demonstrate that microwave activation can be employed to speed up solid-phase reactions significantly [1] (for further details on microwave-enhanced chemistry, click [here](#)).

In this context we have carried out a thorough investigation of several microwave-enhanced solid-phase organic reactions. In contrast to earlier published experiments [1] we have used commercial microwave reactors from [Milestone MLS \(Ethos 1600 series\)](#), that allow temperature and pressure control inside the reaction vessel. This instrument features a built-in magnetic stirrer, direct temperature control of the reaction mixture with the aid of a shielded thermocouple, and software that enables online temperature/pressure control by regulation of microwave power output. The microwave reactor can either be fitted with standard glassware and a reflux condenser for operation at atmospheric pressure (Figure 1a), or can be equipped with a sealed PFA vessel for carrying out reactions at elevated pressure (Figure 1b).



Figure 1a

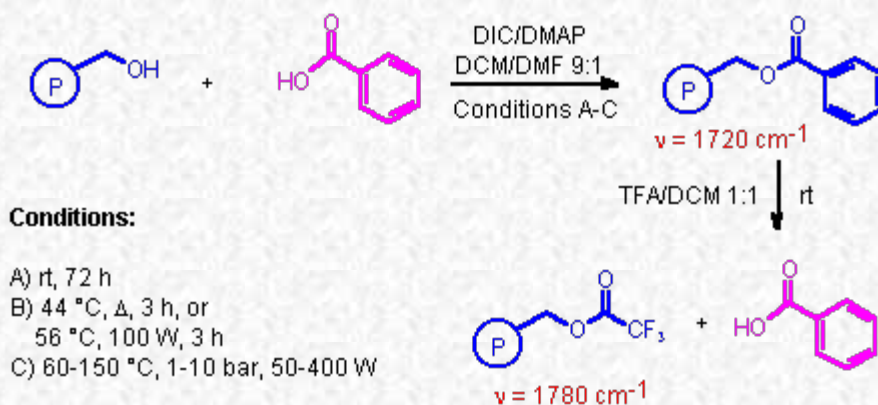


Figure 1b

**Figure 1.** ETHOS 1600 Microwave reactor with normal pressure (1a) and sealed vessel (1b) setup.

## Results and Discussion

One of the most common solid-phase reactions in combinatorial synthesis involves the coupling of an acid (*i.e.* an amino acid) to a Wang-type resin using diisopropylcarbodiimide (DIC) as coupling reagent [2]. The current work employs the conventional carbodiimide method for coupling aryl carboxylic acids to polystyrene resins [3]. As a solid support we have used standard polystyrene Wang resin (1.0 equiv. OH/g, 1 % DVB cross linked). The resin is swollen in the solvent mixture DCM/DMF 9:1 (10 ml) and treated with excess (3 equiv.) of DIC. Benzoic acid is added (5 equiv.) and after addition of a catalytic amount of DMAP the reaction mixture is being stirred under a variety of thermal/microwave conditions for several hours to permit complete coupling of the acid to the resin (see below). In all experiments the loading of the resin is estimated from FTIR measurements of the resin (KBr pellet) and also determined accurately by cleavage of the loaded resin with trifluoroacetic acid (TFA). Thus, the loaded polymer is treated with about 1 ml of the "cleavage cocktail" (TFA/DCM 1:1) per 100 mg of resin. The mixture is stirred for 30 min at room temperature and subsequently filtered by suction. After removal of the solvent pure benzoic acid was regenerated. The remaining resin is now carrying the trifluoroacetyl residue [4].



## Scheme 1

For comparison purposes this coupling reaction was carried out under a set of different conditions, involving a) standard coupling conditions at room temperature; b) thermal heating or microwave superheating at reflux temperature at atmospheric pressure (44 °C and 56 °C, respectively); and c) microwave superheating under sealed vessel conditions (50-400 W, 1-10 bar, 60-150 °C).

### A) Ester Coupling at Room Temperature:

The coupling reaction was conveniently monitored by FTIR-measurements as demonstrated in Figure 2, which shows the increasing intensity of the ester carbonyl absorption at 1720 cm<sup>-1</sup> going from 10 min to 180 min reaction time. By subsequent cleavage the exact yields were determined for reaction times of 18 h (66%), 48 h (87%), and 72 h (99%). Complete conversion for this model reaction at room temperature (25 °C) therefore requires ca. 3 days.

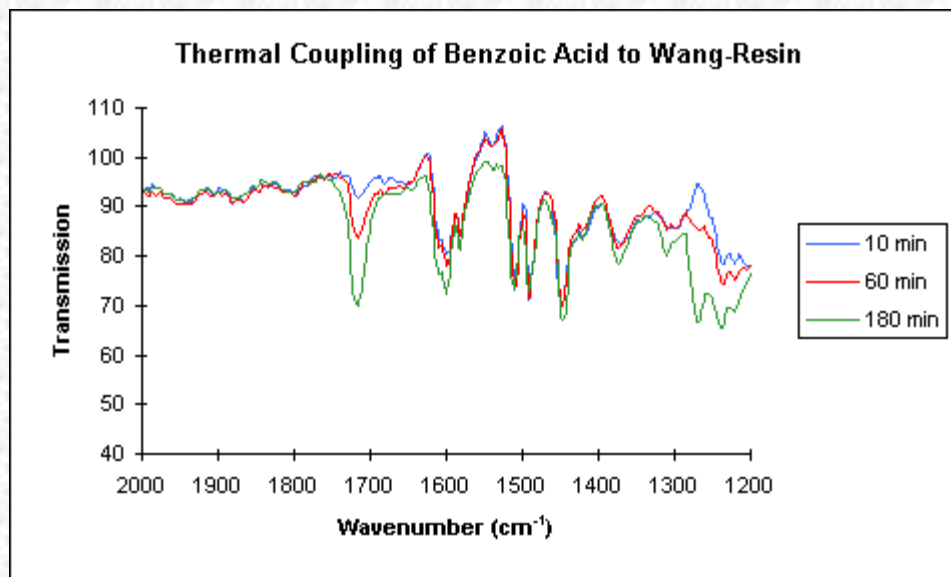
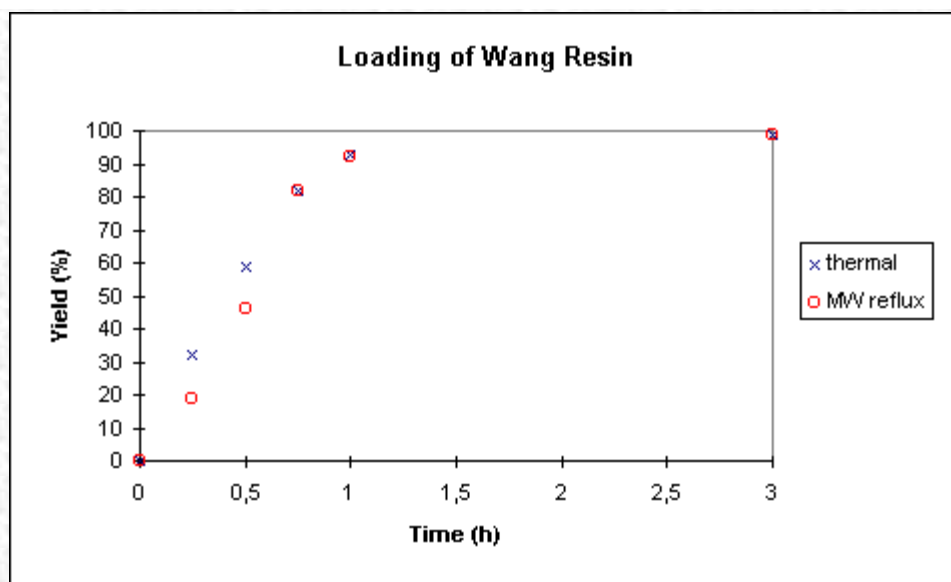


Figure 2. FTIR Monitoring of Benzoic Acid Coupling to Wang Resin.

### B) Ester Coupling at Reflux Temperature (Thermal Versus Microwave Heating):

As one would expect the speed of this coupling process is significantly enhanced by performing the solid phase coupling at reflux temperature, *i.e.* 44 °C for the DCM/DMF 9:1 mixture. Here, a complete loading of the resin was achievable within 3 h (Figure 3).

Superheating of solvents at atmospheric pressure is a common phenomenon when dealing with microwave heating of polar organic solvents [5]. The origin of this superheating effect has been rationalized in terms of an "inverted heat transfer" effect (from the irradiated medium towards the exterior) preventing the onset of nucleate boiling [5]. For the particular DCM/DMF 9:1 mixture (including reagents) the reflux temperature at 100 W was determined to be 56 °C (setup as shown in Figure 1a). As can be seen in Figure 3, no further improvement of yield can be achieved by switching from conventional to microwave heating. On the contrary, it appears that early on in the experiment the conversion rates are lower in the microwave run than under thermal conditions. At the present time no explanation for this phenomenon can be given.



**Figure 3.** Loading of Wang Resin under Thermal (44 °C) and Microwave (56 °C) Conditions (1 atm)

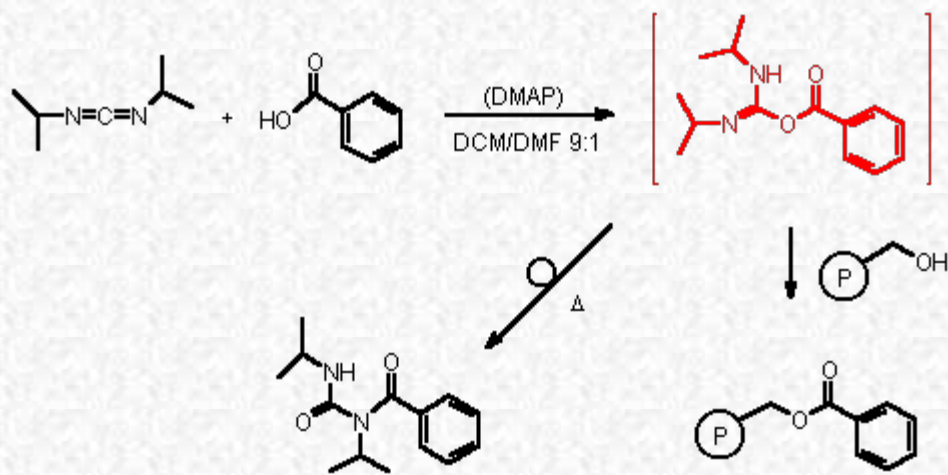
### C) Ester Coupling under Microwave Superheating and Sealed Vessel Conditions:

Since we wanted to further decrease the reaction time by microwave activation we decided to repeat the above microwave experiments in a closed vessel system under pressure. For this purpose the reaction mixture was placed inside the setup shown in Figure 1b and initially irradiated at 100 W. This method leads to coupling in 73% yield after 15 min, which unfortunately seemed to be the maximum achievable conversion. Further increase of the reaction time diminished the yield to 59 % after 30 min and 44% after 60 min. Similarly, an increase in microwave input power (200 W, 400 W) resulting in higher temperatures and pressure also had a negative effect on the loading (Table 1). While it is tempting to assume that at higher temperatures some cleavage of the material from the resin has occurred, independent studies have confirmed that the resin used is quite stable in its free (OH) and loaded form (O<sub>2</sub>CPh), and no cleavage from the loaded resin occurs under resubjection to the reaction conditions.

**Table 1.** Dependence of Benzoic Acid Loading on Microwave Output Power (DCM/DMF 9:1)

MW-Power [W]	Time (min)	T [°C]	Pressure [bar]	Loading (%)
50	15	68	1.5	48
100	15	89	2.7	73
200	15	132	8.8	53
400	15	153	10.1	50

The reason for this unsatisfactory result is most probably the rearrangement of the DIC-activated acid (i.e. the isourea) under the reaction conditions to the thermodynamically more stable *N*-acylurea (Scheme 2) [6]. Apparently, at higher temperatures, such isourea derivatives preferably undergo rearrangement rather than coupling to the corresponding polymer bound benzylic alcohol.



**Scheme 2**

In subsequent studies we have found that the formation of the *N*-acylurea does not require the presence of DMAP. Even in the absence of DMAP the formation of this product can be observed as shown by independent studies. It is formed in 58% yield within 60 min at 100 °C (3 bar, 100 W), having a mp of 114 °C.

We have found however, that by modifying the solvent mixture for the coupling reaction this unwanted side reaction can be suppressed and a decent loading of the resin with benzoic acid can after all be achieved. Pure DCM as a solvent leads to 84% yield after irradiation for 3 h under pressure, a mixture of DCM/THF 9:1 even provides 95% yield after only 1 h of irradiation under pressure (Table 2).

**Table 2.** Comparison of Coupling Efficiencies (in %) in Thermal and Microwave Heated Experiments

Time (h)	CONV	MW I	MW II	MW III
0.25	32 %	19 %	29 %	53 %
0.50	59 %	46 %	57 %	77 %
0.75	82 %	82 %	68 %	89 %
1.00	93 %	92 %	73 %	95 %
3.00	99 %	99 %	84%	

CONV: DCM/DMF 9:1, thermal reflux, 44 °C.

MW I: DCM/DMF 9:1, microwave superheating, 56 °C, 1 atm.

MW II: DCM, microwave superheating, 89 °C, 3 bar.

MW III: DCM/THF 9:1, microwave superheating, 89 °C, 3 bar.

## Conclusions

In summation it is shown that microwave irradiation does reduce the time required for complete loading of Wang resin with benzoic acid as compared to room temperature conditions. Coupling of benzoic acid to Wang resin at thermal reflux leads to identical conversion rates and yields as microwave induced reflux at atmospheric pressure. At higher temperatures the thermodynamically favored rearrangement of the isourea intermediate becomes the preferred reaction pathway, therefore yields are decreasing significantly. These results clearly demonstrate that care must be taken in the application and interpretation of microwave assisted solid phase chemistry.

## Acknowledgments

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## References and Notes

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