High-Speed Couplings and Cleavages in Microwave-Heated, Solid-Phase Reactions at High Temperatures

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A rapid and efficient procedure of flash heating by microwave irradiation is described for the attachment of aromatic and aliphatic carboxylic acids to chloromethylated polystyrene resins via their cesium salts. Significant rate accelerations and higher loadings are observed when the microwave-assisted protocol is compared with the conventional thermal method. Reaction times are reduced from 12–48 h with conventional heating at 80 °C to 5–15 min with microwave flash heating at temperatures up to 200 °C. All transformations were carried out in a purpose-built microwave reactor with on-line temperature, pressure, and microwave power control. Kinetic comparison studies have shown that the observed rate enhancements can be attributed to the rapid direct heating of the solvent (NMP) by microwaves rather than to a specific nonthermal microwave effect. Furthermore, a microwave-assisted cleavage that allows acidolysis of the Merrifield linker with standard trifluoroacetic acid reagents has been developed.

Introduction

One of the cornerstones of combinatorial synthesis has been the development of solid-phase organic synthesis based on the original Merrifield method for peptide preparation.[1] Since transformations on insoluble polymer supports should enable chemical reactions to be driven to completion, and allow simple purification of products, combinatorial chemistry has been primarily carried out by solid-phase synthesis.[1] However, solid-phase synthesis still exhibits several shortcomings owing to the nature of the heterogeneous reaction conditions. Nonlinear kinetic behavior, slow reactions, solvation problems, and degradation of the polymer support owing to the long reaction times are some of the problems experienced in solid-phase organic synthesis.[2]

Parallel to the developments in combinatorial and solid-phase chemistry, microwave-enhanced synthesis has attracted a lot of attention in recent years. During the past decade a large number of reports have been published that advocate the advantages and the uses of microwave irradiation in organic synthesis.[3–5] Dramatic increases in rates, yields, and purities of products have frequently been observed with this nonconventional and energy-efficient heating method.[3]

It is therefore surprising, that the combination of solid-phase synthesis and microwave heating has so far received little attention. The few published examples include solid-phase peptide,[5a] and Suzuki coupling reactions,[5b] in addition to Knoevenagel-[5c] and Ugi-type condensation processes.[5d] Although in most of these cases significant rate enhancements were observed, the benefits associated with *microwave-assisted solid-phase synthesis* have not been rigorously established. For example, the temperature and pressure during the irradiation period were not determined in any of the published examples.[5] Therefore the reasons for the observed rate enhancements, and the possible involvement of the so-called nonthermal microwave effects,[3c] remain unclear.

Since reaction rate is generally recognized as an important factor in high-throughput solid-phase and combinatorial synthesis we now report on a detailed investigation of rate enhancements observed in solid-phase coupling protocols carried out using microwave irradiation. In order to be able to rationalize and interpret the observed phenomena we have employed state-of-the-art microwave reactor technology. The commercially available instrument used herein features a built-in magnetic stirrer, direct temperature control of the reaction mixture with the aid of fluoroptic probes and/or shielded thermocouples, and software that enables online temperature/pressure control by regulation of microwave power output (see Exp. Sect.).[6]

Results and Discussion

As a suitable model reaction for microwave-assisted solid-phase synthesis, we have chosen the alkylation of polystyrene-bound benzyl chlorides with carboxylate anions. Transformations between a range of support-bound alkyl halides (including support-bound benzyl chlorides, alkyl bromides, chlorotrityl chlorides, etc.) and carboxylate anions are quite common in solid-phase peptide and combinatorial synthesis.[1,7–9] Such alkylation reactions have not only been used for loading C-terminal amino acids onto a solid support,[7] but also employed to couple aromatic,[8] and aliphatic acids[9] onto resins. The obtained polymer-bound esters served as useful building blocks in a variety of solid-phase transformations.[7–9] The conventional thermal process typically involves treatment of chloromethylated

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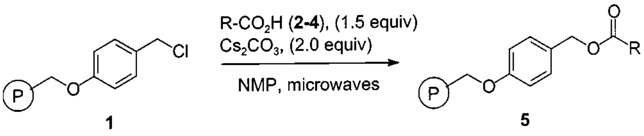
polystyrene (e.g. Merrifield resin) with 1.5−2.0 equiv. of the corresponding acid, 3.0 equiv. of Cs_2CO_3 and 0.5 equiv. of KI in DMF.[8] Since the reaction times for these alkylations have been reported to be rather long (16−48 h at 50−80 °C),[8] this transformation seemed to be a good starting point for the investigation of rate enhancements by microwave irradiation.

For the microwave-promoted solid-phase work described herein we have studied the coupling of a set of 33 substituted aromatic, heterocyclic, and alkyl carboxylates to the resin (see below), with the above-mentioned cesium salt method (**1** → **5**).[7−9] The following changes were made compared with the conventional thermal protocol: (i) the amount of acid (RCO_2H) and Cs_2CO_3 was reduced to 1.5 and 2.0 equiv., respectively, since we anticipated that owing to the beneficial effect of microwave irradiation high conversions could be obtained even with reduced proportions of excess reagents; (ii) the use of KI as additive was eliminated for similar reasons; (iii) in order to be able to readily determine the loading of the corresponding polymer-bound acids by direct cleavage we have used the commercially available polymer-bound 4-(benzyloxy)benzyl chloride **1** (Wang-type linker) as solid support (Scheme 1).



Scheme 1

Microwave Flash Heating − Choice of Solvent

For all solid-phase coupling reactions described herein we have used anhydrous 1-methyl-2-pyrrolidone (NMP) as solvent instead of the originally recommended DMF.[7−9] The main reason for this change is the increased thermal stability of NMP and its considerable higher boiling point (202−204 °C) compared with DMF (152−154 °C).[10] We anticipated that the high boiling point of NMP would make it unnecessary to carry out reactions in specialized sealed vessels under elevated pressure. Furthermore, polystyrene resins such as **1** typically show excellent swelling characteristics in NMP, even surpassing DMF.[11] Another important factor is the dielectric parameters of a given solvent in microwave-assisted chemistry, and they can be related to the ability of the solvent to absorb energy in a microwave cavity.[3e,12] Although to the best of our knowledge these parameters (i.e. the loss tangent) have not been determined for NMP,[3e] we anticipated that owing to the polar nature of NMP a sufficiently strong absorption of energy would take place. In order to test this hypothesis a variety of microwave irradiation experiments with NMP were conducted (Figure 1). These experiments were carried out at atmospheric pressure in standard Pyrex glassware with a reflux condenser fitted through the roof of the microwave cavity. The temperature of the stirred reaction mixture was monitored directly by a microwave-transparent fluoroptic probe inserted into the solution. As demonstrated in Figure 1, rapid heating of NMP occurs which is dependent on the selected maximum microwave output power. Importantly, with the purpose-built microwave reactor used, the maximum temperature reached by the system can be controlled by appropriate software settings. Using 700 W irradiation power the pre-selected maximum temperature of 200 °C is reached within ca. 40 s. For such rapid heating of organic solvents the term *microwave flash heating* has recently been introduced by Hallberg and co-workers.[4b,13] With NMP as solvent, it is crucial to monitor/control the maximum temperature in these experiments with the fluoroptic probe. While at 200 °C no boiling can be observed, intense boiling accompanied by partial decomposition of the solvent[10] was experienced at temperatures above 220 °C (uncontrolled heating) and/or during extended irradiation times (> 20 min).[14] It should be noted, however, that in these experiments superheating above the normal boiling range of 202−204 °C could very effectively be suppressed by stirring the reaction mixture with the aid of a Teflon coated stirring bar.[14]

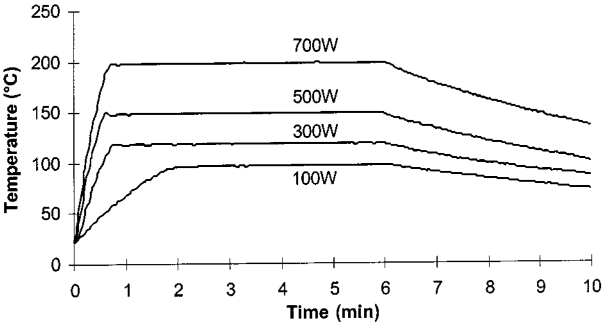


Figure 1. Microwave flash heating of NMP at different power levels

Microwave-Assisted High-Speed Solid-Phase Coupling

With identification of the optimum power/temperature profiles for NMP in hand, we carried out exploratory coupling reactions with the Wang-type resin **1** (1.1 mequiv. Cl/g) using benzoic acid (**2a**) (1.5 equiv.) and Cs_2CO_3 (2.0 equiv.) as reagents. The initial irradiation cycles at 700 W (200 °C maximum temperature) were 2, 3, 5, 10, 15, and 20 min. To our surprise, we found that after only 3 min of irradiation 97% loading, and after 5 min > 99% loading of the resin with benzoic acid was achieved.[15] Figure 2 illustrates a typical experiment with 5 min of irradiation time and demonstrates that once the maximum allowed temperature has been reached an average microwave output power of approximately 100 W suffices to keep the temperature at 200 °C. Importantly, even after 20 min at 200 °C the loading remained quantitative and shows the good thermal stability both of the polystyrene support and of the acid-sensitive linker under the reaction conditions.[16]

With this information in hand, we have studied the attachment of a wide variety of substituted aromatic (**2a−v**), heterocyclic (**3a−c**), and aliphatic carboxylic acids (**4a−h**)

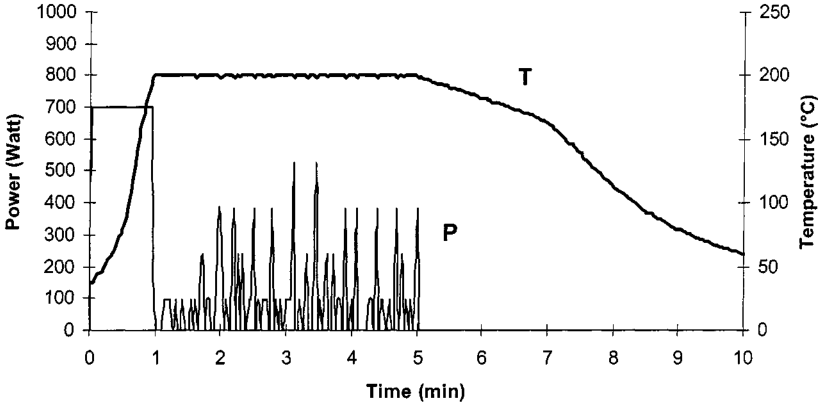


Figure 2. Temperature and power profiles for the coupling of benzoic acid to resin **1** in NMP (5 min irradiation, 200 °C, 700 W maximum power)

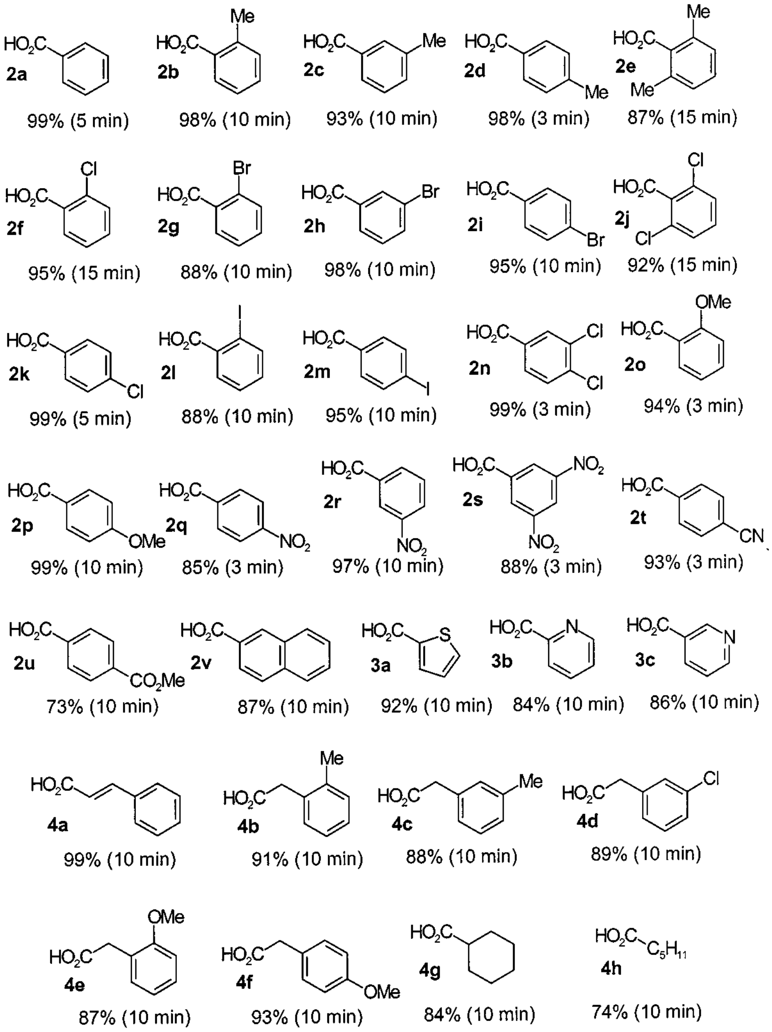


Figure 3. Loadings and reaction times (in parentheses) for the microwave-assisted coupling of carboxylic acids **2−4** to polymer-bound benzyl chloride **1**

to resin **1** using microwave flash heating (Figure 3). In most cases the conversion reached at least 85% after 3−15 min of irradiation time. While no attempt was made to optimize all examples shown in Figure 3, we have selected a number of sterically and/or electronically demanding substituted benzoic acids, and compared their coupling behavior under microwave activation with the conventional thermal protocols (Table 1). In order to be able to compare both methods in a balanced way, the microwave flash heating experiments were repeated under the conditions of the 80 °C thermal

Table 1. Thermal and microwave-promoted solid-phase coupling **1** → **5**

Entry[a]	Microwave irradiation[b] 3 min	5 min	10 min	15 min	Thermal comparison Method A[c]	Method B[d]
2a	97	> 99	> 99	> 99	> 99	–
2b	85	96	98	–	81	90
2e	61	68	78	87	82	82
2f	78	85	90	95	88	90
2h	86	93	98	–	86	90
2j	65	71	86	92	88	90
2p	70	93	99	–	71	98

[a] NMP as solvent, yields given in % as determined after cleavage (see Exp. sect.). – [b] Pulsed multimode cavity (Milestone MLS Ethos 1600 instrument, 2450 MHz, 700 W maximum power, 200 °C). – [c] 80 °C, 24 h, 1.5 equiv. of **2–4**, 2.0 equiv. of Cs_2CO_3. – [d] 80 °C, 48 h, 1.5 equiv. of **2–4**, 3.0 equiv. of Cs_2CO_3, 0.5 of equiv. KI.

runs (1.5 equiv. of RCO_2H, 2.0 equiv. of Cs_2CO_3, 24 h reaction time, method A). In addition, a comparison was made with the published thermal protocol by Frenette and Friesen[8a] using 1.5 equiv. of RCO_2H, 3.0 equiv. of Cs_2CO_3, and 0.5 equiv. of KI (reaction time 48 h) (method B).

As can be seen from the data presented in Figure 3 and Table 1 high loadings can be obtained very rapidly for most of the acids that were studied. Even sterically demanding acids such as 2,6-dimethylbenzoic acid (**2e**), 2,6-dichlorobenzoic acid (**2j**), or 2-iodobenzoic acid (**2l**) can be coupled successfully to the polymer support with a loading of approximately 90% after 10–15 min of irradiation time. Table 1 clearly demonstrates that for these demanding systems longer reaction times are required compared with the benzoic acid example (**2a**) where coupling is complete after only 3–5 min. Importantly, in all the examples given in Table 1 the loading accomplished after 10–15 min of microwave irradiation is actually higher than that achieved using either of the two conventional thermal protocols. Even with a higher excess of reagents, KI as additive, and 2 d of reaction time (method B) the thermal yields do not match the yields obtained under microwave activation. The benefits of the microwave protocol in terms of reaction rate and coupling efficiency are therefore apparent.

Involvement of Nonthermal Microwave Effects?

Apart from establishing the benefits of microwave-enhancement in solid-phase chemistry, we were also interested in the rationalization of the dramatic rate enhancements observed in both our current work, and in the earlier reports.[5] In general, the reasons for rate enhancements in microwave-assisted transformations in comparison with conventional heating are not fully understood, and some authors have postulated a specific "nonthermal microwave effect" for those effects that could not be rationalized as a simple consequence of superheated solvents and higher reaction temperatures.[17] We have therefore carried out a kinetic comparison of the thermal coupling of benzoic acid to resin **1** at 80 °C (method A), with the microwave-assisted coupling *at the identical temperature of 80 °C* and otherwise identical reaction parameters. Any significant differences in the reaction rates would provide a strong indication for a nonthermal microwave effect. As shown in Figure 4, the reaction rates for the two runs are quite similar. Only during the first hour does the microwave-heated process proceed somewhat faster, in particular in the very early stages of the experiment (59 versus 37% loading after 15 min). No explanation for these deviations can be given. However, these relatively small rate differences should not be attributed to nonthermal effects.[18] We attribute the dramatic acceleration of reaction rates in the above coupling processes mainly to the high temperatures that are rapidly attained by microwave flash heating (Figure 1). The dielectric properties[19] associated with the solvent NMP are therefore of critical importance. Although there may be other additional contributions such as the specific coupling of microwaves to the ionic species present in the reaction medium (i.e. Cs_2CO_3, RCO_2Cs),[3e] or an intramolecular rotation of polar functional groups (acting as "antennas") tethered on the polymer support,[3e] the strong coupling of NMP itself with microwaves is likely to be the predominant factor. In order to confirm this hypothesis we have also carried out coupling experiments with benzoic acid (**2a**) at 200 °C under standard thermal conditions. The loadings in these high-temperature thermal runs were comparable but somewhat lower than the microwave-promoted protocols (e.g. 86% at 3 min, and 95% at 10 min). However, such comparisons are troublesome since it is impossible to achieve similar high heating rates by thermal heating as compared with microwave flash heating (see Exp, Sect.). Note that superheating of solvent (suppressed by stirring and maximum temperature settings) cannot be responsible for the high reaction rates obtained with microwave irradiation.

Microwave-Assisted Coupling/Cleavage with the Merrifield Resin (6)

In order to investigate the effect of microwave irradiation on the cleavage of substrates from polymer supports, a number of the carboxylic acids shown in Figure 3 were also attached to the standard Merrifield resin (2.3 mequiv. Cl/g) by means of the microwave-promoted cesium salt protocol elaborated above (**6** → **7**). The loadings achieved at given irradiation times were virtually identical to those described above using Wang resin **1** (not shown). The difference in

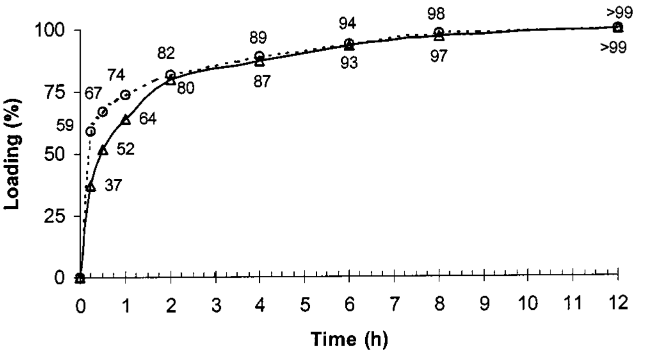
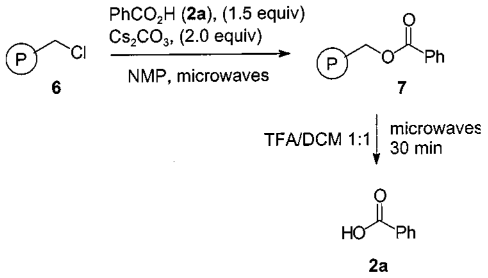


Figure 4. Kinetic comparison experiments between thermal and microwave-assisted loading of resin **1** with benzoic acid (80 °C); solid lines (triangles) represent thermal, and dashed lines (circles) represent microwave conditions

the initial Cl loadings of the resins (2.3 and 1.1 mequiv. Cl/g, respectively) apparently had no effect (Scheme 2).



Scheme 2

In general, acidolysis of the Merrifield linker requires acids with high ionizing power, such as hydrogen fluoride, trifluoromethanesulfonic acid, or hydrogen bromide/AcOH.[1] According to standard literature,[1] under conventional conditions cleavage does not take place with TFA and therefore, the selective deprotection of Boc-protected amino groups with TFA without cleavage of the product from the resin can be carried out.[1] With high-temperature microwave heating, such cleavage is possible under elevated pressure/temperature using sealed vessels. After some experimentation (Table 2) we have found that acidolysis of the Merrifield linker can be carried out effectively using the conventional TFA/DCM (1:1) mixture by exposure of the polymer-bound ester **7** together with the cleavage reagent to microwave irradiation at 500 W for 30 min. Although DCM does not couple effectively with microwaves (tan $\delta = 0.042$),[3e] the presence of the highly polar trifluoroacetic acid allows the mixture to absorb energy sufficiently from the microwave irradiation. Therefore, temperatures well above the normal boiling points can be reached (Table 2). Similar to the behavior of Wang resin **1** no degradation of the polymer support itself by microwave irradiation could be detected.

Table 2. Acidolysis of Merrifield linker by TFA/DCM under microwave irradiation

TFA/DCM	Temperature[a] [°C]	Pressure [bar]	Time [min]	Yield [%]
1:4	120	6.8	10	74
2:1	120	6.3	10	92
1:1	80	2.3	10	56
1:1	100	4.4	10	61
1:1	100	4.2	20	89
1:1	120	5.5	5	51
1:1	120	7.4	10	82
1:1	120	6.8	20	91
1:1	120	7.0	30	98

[a] Sealed teflon vessel, 500 W maximum microwave power output. Maximum temperature and power were preselected, the resulting pressure is dependent on these settings.

We also attempted to carry out the above cleavage process under classical heating conditions. At room temperature virtually no cleavage was detected after 2 h with TFA/DCM (1:1); however, 35% cleavage took place after the mixture had been refluxed (ca. 40 °C) for 2 h. In order to increase the cleavage rate in the above process, either the reaction time or the concentration of TFA had to be increased. In pure TFA, for example, 71% cleavage was obtained after 2 h at reflux temperature (ca. 72 °C). On the basis of these results, we therefore believe that the successful microwave-assisted cleavage protocol described above is a simple consequence of the high-temperature conditions, and does not involve any nonthermal effects.

Conclusion

In conclusion, we have demonstrated that microwave flash heating allows rapid and efficient attachment of carboxylic acids to chloromethylated polystyrene supports. Loadings of > 90% are typically achieved in less than 10 min by microwave irradiation while the conventional thermal protocols (80 °C) require reaction times of 12−48 h. With NMP as solvent, the microwave flash heating can safely be performed at atmospheric pressure and eliminates the need for specialized pressure vessels. We believe that the reason for the dramatic rate enhancement is the direct rapid "in core" heating of the solvent by microwave energy, and not a specific ("nonthermal") microwave effect. It is very likely that this is also the case for the earlier published examples.[5] Although similar high conversion rates for solid-phase processes can, in principle, be achieved also by conventional thermal heating at high temperatures, the flexibility and convenience offered by microwave heating clearly makes the thermal process a less attractive alternative. In this context we wish to stress the significance of using dedicated microwave reactors specifically designed for synthetic operations. Measurement and temperature/pressure/power control is of critical importance in the reproducibility of such processes. We are currently exploring the scope and potential of microwave-assisted solid-phase synthesis by extending the protocols described herein to other solid-phase transformations.

Experimental Section

Materials: The following polymer supports were used: Wang-type resin **1** (1.10 mequiv. Cl/g, 1% crosslinked with DVB, 200−400 mesh, Fluka 02377), Merrifield resin **6** (2.30 mequiv. Cl/g, 2% crosslinked with DVB, 200−400 mesh, Aldrich 44,911−3). Carboxylic acids **2−4**, Cs_2CO_3, KI, TFA, and anhydrous 1-methyl-2-pyrrolidone were purchased from Aldrich.

Microwave Irradiation Experiments

Milestone MLS ETHOS 1600 Reactor:[20] The multimode microwave reactor has a twin magnetron (2 × 800 W, 2455 MHz) with a maximum delivered power of 1000 W in 10-W increments (pulsed irradiation). A rotating microwave diffuser ensures homogeneous microwave distribution throughout the plasma-coated PTFE cavity (35 × 35 × 35 cm). For normal-pressure operations standard glassware (25- or 50-mL two-necked Pyrex round-bottomed flask) with a water-cooled reflux condenser fitted on top of the cavity was used. For experiments carried out in sealed vessels a 100-mL PFA reaction vessel, contained in a single high-pressure HPR1000 rotor block segment, was employed. A built-in magnetic stirrer (Teflon-coated stirring bar) was used in both the normal-pressure and the sealed-vessel operations. In the experiments time, temperature, pressure, and power were monitored/controlled with the "easyWAVE" software package (Vers. 3.2.). Temperature was monitored with the aid of a fluoroptic probe (ATC-FO) and/or with a shielded thermocouple (ATC-300) inserted directly into the corresponding reaction container. For experiments in sealed vessels a pressure sensor (APC-55) was additionally employed.

Microwave Flash-Heating of NMP: Anhydrous NMP (20 mL) was placed in a two-necked 100-mL round-bottomed Pyrex flask (fitted with a reflux condenser and the fluoroptic probe), and irradiation with magnetic stirring inside the cavity of the ETHOS 1600 microwave reactor was carried out with the maximum power levels indicated in Figure 1. Irradiation was continued for a total of 6 min.

Microwave-Assisted Coupling of Acids 2−4 to Polymer-Bound 4-(Benzyloxy)benzyl Chloride Resin 1: Chloromethylpolystyrene resin **1** (200 mg, 1.10 mequiv. Cl/g) was placed in a 25-mL two-necked flask and allowed to swell in dry NMP (10.00 mL) for a period of 10 min. After the addition of the corresponding acid (**2−4**) (0.33 mmol, 1.50 equiv.), dissolved in NMP (2.00 mL), and solid Cs_2CO_3 (0.44 mmol, 143 mg, 2.00 equiv.), the mixture was irradiated for 3−15 min (Figure 3) at 700 W and 200 °C. Following a cool-off period of 2 min, the flask was immersed in a water bath for another 3 min which led to a drop in temperature to ca. 60 °C (cf. Figure 2). The resin was filtered, washed with water (4 ×), DCM (3 ×), and methanol (3 ×), and dried (40 °C, 10 mbar, 14 h. The accurate loading of the individual resins **5** was established by standard TFA cleavage and weight determination of the recovered acids: Resin **5** (ca. 210−240 mg) was stirred with TFA/DCM (1:1) (3 mL) for 30 min. After filtration and washing with DCM, the solution was concentrated to dryness to yield the pure acids **2−4**. The identity and purity (> 98%) of the recovered acids was established by comparison with the authentic samples (m.p., IR, NMR).

Thermal Coupling of Acids 2 to Polymer-Bound 4-(Benzyloxy)benzyl Chloride Resin 1 (Table 1)

Method A: Chloromethylpolystyrene resin **1** (200 mg, 1.10 mequiv. Cl/g) was placed in a 25-mL flask and allowed to swell in dry NMP (10 mL) for a period of 10 min. After the addition of the corresponding acid (**2**) (0.33 mmol, 1.50 equiv.), dissolved in NMP (2.00 mL), and solid Cs_2CO_3 (0.44 mmol, 143 mg, 2.00 equiv.), the mixture was stirred at 80 °C for 24 h. After cooling to room temp. the resin was filtered, washed with water (4 ×), DCM (3 ×), and methanol (3 ×), and dried (40 °C, 10 mbar, 14 h). Cleavage as described above led to the recovered aromatic acids **2** and reflected the loading of the resin (Table 1).

Method B: The procedure was carried out in an analogous fashion as described in method A with 3.00 equiv. of Cs_2CO_3 and 0.50 equiv. of KI as additives, and the reaction time was extended to 48 h.

Microwave-Assisted Coupling of Benzoic Acid (2) to Merrifield Resin (6): Merrifield resin **1** (200 mg, 2.30 mequiv. Cl/g) was placed in a 25-mL two-necked flask and allowed to swell in dry NMP (10.00 mL) for a period of 10 min. After the addition of benzoic acid (**2a**) (0.69 mmol, 84 mg, 1.50 equiv.), dissolved in NMP (2.00 mL), and solid Cs_2CO_3 (0.92 mmol, 300 mg, 2.00 equiv.), the mixture was irradiated for 5 min at 700 W and 200 °C. Workup as described above for the Wang-type resin produced the loaded support **7** (239 mg, ca. 100% loading).

Microwave-Assisted Cleavage of Polymer-Bound Ester (7): Resin **7** (239 mg) and TFA/DCM (10.00 mL, for ratios see Table 2) were placed inside a 100-mL PFA sealed reactor vessel and irradiated with stirring for 5−30 min at 500 W with a maximum preselected temperature of 80−120 °C (Table 2). After cooling the pressure container in an ice-bath for 20 min, the system was vented, the solution filtered and washed with DCM. Concentration to dryness furnished the recovered benzoic acid **2a** in the yields indicated in Table 2.

Microwave Versus Thermal Heating Experiments: Resin **1** (200 mg, 1.10 mequiv. Cl/g) was placed in a 25-mL two-necked flask and allowed to swell in dry NMP (10.00 mL) for a period of 10 min. After the addition of solid Cs_2CO_3 (0.44 mmol, 143 mg, 2.00 equiv.), the mixture was preheated to 80 °C either in the ETHOS 1600 reactor by microwave irradiation (fluoroptic probe) or in an oil bath by conventional heating (inner thermometer). After equilibration of temperature had occurred, a solution of benzoic acid (**2a**) (0.33 mmol, 40 mg, 1.50 equiv.), dissolved in NMP (2.00 mL), was added. Microwave irradiation or thermal heating was continued with magnetic stirring at 80 °C for 15 min. Workup and standard cleavage as described above furnished the recovered benzoic acids in the yields of 59 and 37%, respectively, reflecting the loading of the resin after 15 min. An identical series of experiments was performed with reaction times of 0.5, 1, 2, 4, 6, 8, and 12 h (Figure 4). Additionally, two thermal runs at 200 °C were performed according to the method described herein. The loadings after 3 min and 10 min were 86 and 95%, respectively. Note that it took 10−15 min to preheat the solvent to 200 °C by thermal heating.

Acknowledgments

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