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The effect of microwave irradiation on carbodiimide-mediated esterifications on solid support

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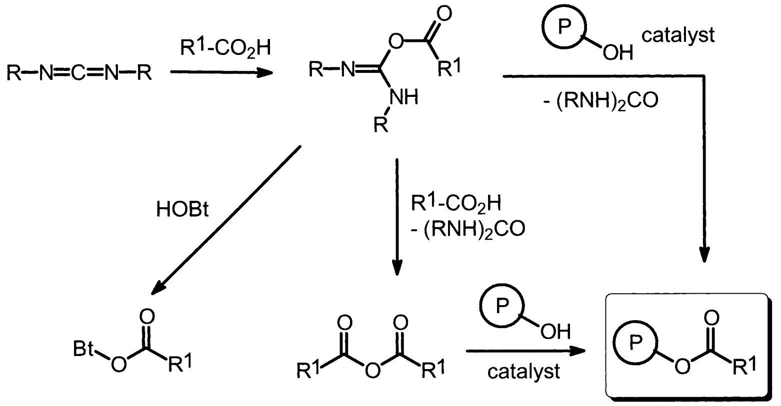
Abstract—The esterification of a polymer-supported alcohol (PS Wang resin) with benzoic acid was investigated using microwave irradiation. Activation of the carboxylic acid was carried out using diisopropylcarbodiimide, either via the *O*-acylisourea or symmetrical anhydride protocols. In the microwave-assisted solid-phase coupling using the *O*-acylisourea method the main product of the reaction was 1-benzoyl-1,3-diisopropylurea, formed by rearrangement of the thermolabile isourea intermediate. On the other hand, significant rate enhancements were observed for the coupling of benzoic anhydride to Wang resin using microwave flash heating in 1-methyl-2-pyrrolidone as solvent. Reaction times were reduced from 2 to 3 days using conventional conditions, to 10 min by microwave dielectric heating. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

One of the most common transformations in solid-phase organic synthesis involves the construction of an ester linkage between a solid-supported hydroxy or halogen functionality and a carboxylic acid derivative.[1–5] While different strategies to generate such an ester linkage on solid support are available, one especially convenient and straightforward method involves the direct esterification of a polymer-bound alcohol with a carboxylic acid using suitable coupling protocols.[1–5] Although many different reagent combinations, e.g. of the aminium or phosphonium type, have been reported in the recent literature, in particular in the context of attaching protected amino acids to polymer-bound alcohols (first residue attachment),[5] the activation of carboxylic acids by carbodiimides still constitutes the most frequently used method.[1–5]

Depending on the specific reaction conditions, such an activation proceeds either via an *O*-acylisourea (1 equiv. acid used), or via a symmetrical anhydride (2 equiv. acids) as reactive species (Scheme 1).[6–8] In the latter case, the carbodiimide is first treated with the carboxylic acid in a separate reaction vessel, *before* the polymer-bound alcohol is added to the preformed anhydride.[5] Alternatively, in situ activation of the carboxylic acid as, for example, a reactive benzotriazole ester (R^1CO_2Bt) is also possible employing 1-hydroxy-1*H*-benzotriazole (HOBt) as additive in the



Scheme 1.

Keywords: combinatorial chemistry; solid-phase synthesis; microwave-enhanced chemistry; *O*-acylisourea; anhydrides.

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one-pot sequence.[5] Although most of the transformations shown in Scheme 1 have been optimized to proceed under mild reaction conditions for a variety of carboxylic acids and polymer supports, long reaction times and non-quantitative loadings have nevertheless been known to create problems in these solid-phase esterification reactions.[1–5]

In recent years, the concept of speeding up resin-bound chemistry by microwave activation has created a lot of interest, both from the academic and industrial communities.[9–18] In a number of publications significant rate-accelerations and very high loadings for several solid-phase protocols including, e.g., peptide,[9] Suzuki,[10] Ugi,[11] and Knoevenagel reactions,[12] have been reported, with reaction times being reduced in some cases from hours to a few minutes.[9–17] Despite these initial reports, the benefits associated with this new technology have not been rigorously established, since in many cases domestic household microwave ovens have been employed that do not allow the monitoring of temperature or pressure profiles during the irradiation experiments. In a recent study using dedicated microwave reactors we have demonstrated that microwave flash heating, i.e. the very rapid heating of the reaction mixture, in combination with high reaction temperatures, may be responsible for the observed rate enhancements using this non-conventional heating method.[18] We now report on the effect of microwave irradiation on the ester coupling processes outlined in Scheme 1, specifically on the carbodiimide-mediated attachment of benzoic acid to Wang resin.

2. Results and discussion

As a suitable model reaction for the transformations shown in Scheme 1 we have chosen the diisopropylcarbodiimide (DIC)-mediated coupling of benzoic acid to Wang resin. As a solid-support standard polystyrene Wang resins (1% DVB cross linked) were employed. In the literature such DIC-promoted acid couplings have not only been described for loading N-protected amino acids to solid supports,[5] but also have been used to attach aromatic,[19] aliphatic,[20] and acrylic acids[21] onto resin. Therefore, a number of different experimental procedures are available for either the so-called *O*-acylisourea method, or the symmetrical anhydride protocol.[1–5,19–21] In general, when the reaction is conducted in one pot, i.e. by adding both DIC and the corresponding acid to the hydroxy functionalized resin in the presence of a suitable catalyst such as DMAP, an *O*-acylisourea derivative is implicated as an intermediate.[7] On the other hand, many procedures allow for the initial preparation and isolation of the corresponding symmetrical anhydride by treatment of DIC with 2 equiv. of acid, followed by addition of the anhydride to the hydroxy resin and DMAP.[5] Naturally, it is difficult to differentiate strictly between the isourea and anhydride reaction pathways if the one-pot method is chosen, in particular when non-equal amounts of carbodiimide and acid are employed, as is frequently the case. The choice of solvent in these processes is also critical. In most literature procedures, mixtures of dichloromethane (DCM) and dimethylformamide (DMF) are employed for the isourea coupling method, whereas DMF is the solvent of choice for the anhydride reaction, due to the apparently limited solubility of some of the anhydrides used in other solvents, particularly in DCM.[1–5,19–21]

For the present model studies involving benzoic acid we have generally employed a DCM/DMF 9:1 mixture for the isourea method, since this solvent combination is found most frequently in the literature. All anhydride reactions were carried out in 1-methyl-2-pyrrolidone (NMP) instead of the more commonly used DMF because of our previous encouraging experience with this solvent in microwave-assisted solid-phase synthesis (see below).[18] For an initial evaluation of both methods two series of kinetic experiments coupling benzoic acid to polystyrene Wang resin (2.3 mequiv. OH/g) were carried out. In the first series, the acid was coupled via the one-pot isourea method (3.5 equiv. DIC, 5 equiv. $PhCO_2H$) with the above-mentioned DCM/DMF solvent mixture and small amounts of DMAP as catalyst. These are essentially the conditions used, e.g., by Ley et al.[21] for closely related coupling protocols. Similarly, benzoic anhydride couplings (5 equiv.) were carried out in NMP in the presence of catalytic amounts of DMAP.[22] These experiments were conveniently conducted in a manual synthesizer in Teflon frits at room temperature (see Section 3). In all experiments the loading of the resins is estimated by on-bead FTIR analysis ($\nu_{C=O}=1720\ cm^{-1}$, KBr pellet, cf. Fig. 1)[23] and also determined accurately by cleavage of all the loaded resins with 50% trifluoroacetic acid (TFA) in DCM (Fig. 2). As can be seen from inspection of the data in Fig. 2, both coupling protocols provide rather similar results in terms of reaction rates. Under the relatively concentrated reaction conditions used here

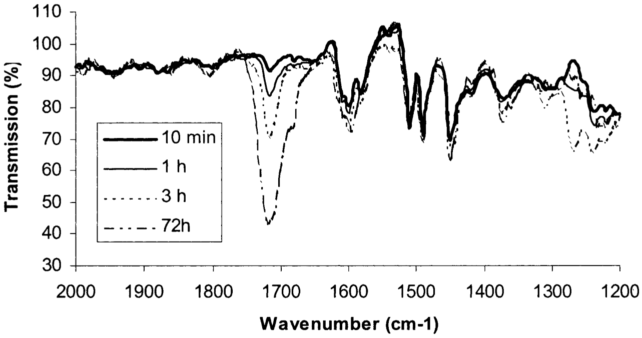


Figure 1. FTIR-monitoring of benzoic acid coupling to Wang resin ($\nu_{C=O}=1720\ cm^{-1}$, KBr pellet).

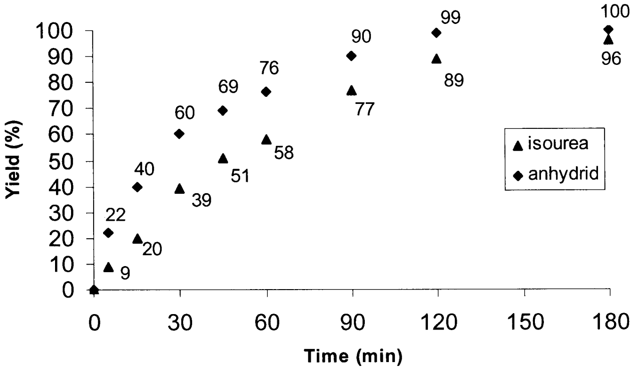


Figure 2. Kinetics of *O*-acylisourea versus symmetrical anhydride coupling (ACT PLS 4×6 synthesizer).

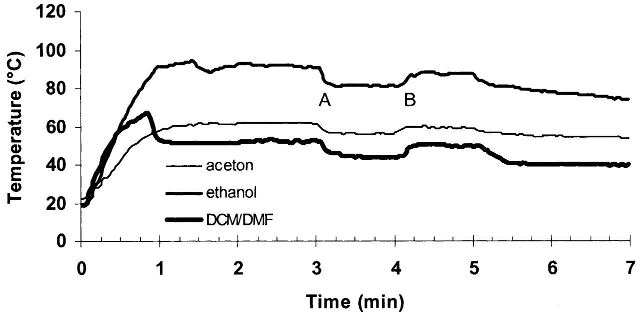


Figure 3. Heating profiles (superheating effects) for ethanol, acetone, and DCM/DMF 9:1. Sample volume 25 mL, 500 W output power (300 W for acetone), fluoroptic temperature measurement. Magnetic stirring on after 3 min (A), stirring off after 4 min (B), microwave power off after 5 min. Temperatures for ethanol: 89°C (superheating), 78°C (with stirring); for acetone: 62°C (superheating), 56°C (with stirring); for DCM/DMF 9:1: 51°C (superheating); 44°C (with stirring).

(0.46 mol/L of acid or anhydride, respectively) both procedures led to a more or less quantitative coupling in ca. 3 h, with a slight preference for the anhydride method. While a direct kinetic comparison between the two procedures is not feasible because of the different relative amounts of reagents and different solvents used, the above experiments nevertheless suggest that a priori both methods may be suitable for potential rate enhancements by microwave irradiation.

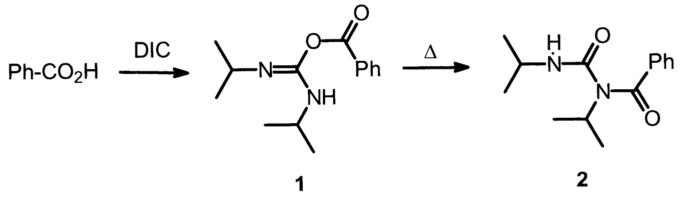
With this information in hand we have conducted a series of experiments at elevated temperature using both conventional and microwave dielectric heating under atmospheric and sealed vessel conditions. These irradiation experiments were either carried out at a fixed microwave output power (e.g. 100 W), or at a preselected maximum temperature. In the latter case, the software algorithm of the microwave reactor adjusts the output power so that the selected temperature profile is maintained. Because we wanted to observe and evaluate potential rate-enhancement effects more easily, we have chosen to use more dilute reaction conditions for all subsequent experiments. This was also necessitated by the microwave reactor and fluoroptic temperature measurement design, which would not allow such small volumes to be used as in the above synthesizer experiments (ca. 5 mL). Towards this end we have designed a new series of experiments for the isourea coupling protocol using Wang resin and the previously employed reagent and solvent mix (3.5 equiv. DIC, 5 equiv. $PhCO_2H$, DCM/DMF 9:1) in conventional glassware. Due to the now larger volume of solvent the effective concentration of benzoic acid was reduced to ca. 0.13 mol/L (see Section 3). The coupling reaction was conveniently monitored by FTIR-measurements (Fig. 1), which demonstrated the increasing intensity of the ester carbonyl absorption at 1720 cm^{-1}. By subsequent cleavage the exact yields were determined for reaction times of 18 h (66%), 48 h (87%), and 72 h (99%). Complete conversion under these conditions at room temperature (25°C) therefore requires ca. 2–3 days. A similar set of experiments was then conducted at elevated, i.e. reflux temperature. As one would expect the speed of this coupling process is significantly enhanced by performing the solid-phase process 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 (loadings after: 15 min=32%; 30 min=59%; 45 min=82%; 60 min 93%; 180 min 99%). Using the identical set of Pyrex glassware the same experiments were carried out in a microwave reactor having a reflux condenser fitted through the roof of the cavity (see Section 3). Here, a very similar conversion rate was observed at the identical temperature of 44°C. Although superheating of solvents at atmospheric pressure is a common phenomenon when dealing with microwave heating of organic solvents,[24,25] we have discovered that with the instrument and setup used in the experiments reported herein, magnetic stirring of the reaction mixture effectively eliminates this phenomenon as demonstrated for such common solvents, such as ethanol and acetone (Fig. 3). Therefore, the nearly identical conversion rates in the microwave-irradiation experiment as compared to the conventional heating are not surprising. A non-thermal microwave effect could evidently not have been observed.

Since we wanted to further decrease the reaction time by microwave activation we decided to repeat the above irradiation experiments in a closed vessel system under pressure. For this purpose the reaction mixture (identical to the experiments carried out under atmospheric pressure) was placed inside a Teflon-based sealed vessel specifically designed for microwave-irradiation experiments that allows on-line temperature and pressure monitoring (see Section 3).[18,26] This setup was initially irradiated at 100 W which led to a coupling in 73% yield after 15 min. Surprisingly, this seemed to be the maximum achievable conversion. Further increase of the irradiation power, leading to higher reaction temperatures, diminished the conversion rates, rather than increasing them (Table 1). Equally unsuccessful were attempts to change the reaction times (data not shown). Analysis of the reaction mixture after filtration from the resin indicated in all cases the formation of 1-benzoyl-1,3-diisopropylurea in substantial molar ratios. The reason for this unsatisfactory result is clearly the rearrangement of the DIC-activated acid (i.e. the *O*-acylisourea) under the relatively drastic reaction conditions used to the thermodynamically more stable *N*-acylurea (Scheme 2).[6–8]

Table 1. Effects of microwave power on the conversion in the *O*-acylisourea-mediated coupling of benzoic acid to Wang resin

Microwave power (W)	Temperature (°C)	Pressure (bar)	Conversion (%)
50	68	1.4	48
100	89	2.7	73
200	132	8.8	53
400	153	10.1	50

Sealed vessel conditions, 15 min reaction time, 3.5 equiv. DIC, 5 equiv. $PhCO_2H$, solvent: DCM/DMF 9:1; catalyst: DMAP. Yields given in % as determined after cleavage; see Section 3.



Scheme 2.

Apparently, at higher temperatures, such isourea derivatives preferably undergo rearrangement rather then the desired coupling to the corresponding polymer bound benzylic alcohol (Scheme 1), in particular in the presence of basic catalysts. The situation is further complicated however, by the fact that some of the isourea intermediate can also be expected to be converted into a symmetrical anhydride by the excess of acid present in the reaction medium (Scheme 1).[6–8] This makes the reaction system a rather complex one, not allowing for any detailed kinetic analysis of the individual reaction pathways.

In independent experiments involving DIC and benzoic acid in the DCM/DMF 9:1 solvent mixture (in the absence of polymer-bound alcohol) we have found that at elevated reaction temperatures however, the formation of *N*-acylurea **2** does not require the presence of DMAP. Even in the absence of the catalyst the formation of this product can be observed. It is formed, i.e. in 58% isolated yield within 60 min at 90°C (3 bar, 100 W, see Section 3).

Interestingly, we have discovered that by modifying the solvent mixture in the isourea coupling process, i.e. by elimination of DMF, this unwanted side reaction can be suppressed and a decent loading of the resin with benzoic acid can after all be achieved. Employing pure DCM as a solvent led to 84% loading after irradiation for 3 h under pressure, a mixture of DCM/THF 9:1 even provides 95% yield after only 1 h of irradiation at 89°C (Table 2). Using these solvent mixtures the formation of urea **2** could not be observed. Nevertheless, it is quite evident from the experiments described above that the one-pot *O*-acylisourea coupling protocol is probably not suited for any practical rate-enhancements by microwave irradiation, due to the inherent unfavorable effects of the higher temperatures on the thermally labile isourea **1**.

We have therefore focused our attention on the symmetrical anhydride procedure. As with the isourea protocols illustrated above, we have used considerably more dilute reaction conditions for the microwave runs than in the synthesizer experiments initially described in Fig. 2. In the event, Wang resin was treated with 5 equiv. of independently prepared $(PhCO)_2O$ in 12 mL of NMP (effective anhydride concentration ca. 0.13 mol/L). Similar to the experiments in the isourea-mediated coupling procedure a reaction time of 2–3 days was necessary to completely load the resin with benzoic anhydride at room temperature (loadings after 18 h, 76%, 48 h, 95%, 72 h, >99%). Since NMP (bp 202–204°C) was selected as solvent, all microwave irradiation experiments could be conveniently carried out in standard glassware inside the microwave cavity, making it unnecessary to carry out reactions in specialized sealed vessels under elevated pressure.[18] In contrast to the results obtained by the isourea method (Tables 1 and 2), here a significant increase in the reaction rates was observed (Table 3). Near quantitative loadings, for example, were achieved at 150°C within 20 min, or at 200°C using only 10 min of microwave irradiation. Considering the fact that these solid-phase couplings were carried out under relatively dilute—and therefore unfavorable conditions—it is reasonable to assume that even shorter reaction times can in principle be achieved using the more commonly employed higher reagent concentrations (Scheme 3).

In conclusion, we have demonstrated that microwave irradiation can be effectively employed to couple carboxylic acids to hydroxymethyl polystyrene resins, provided that the symmetrical anhydride protocol is used, and not the three-component *O*-acylisourea activation method. For the model

Table 2. Solvent effects on the conversion in the *O*-acylisourea-mediated coupling of benzoic acid to Wang resin

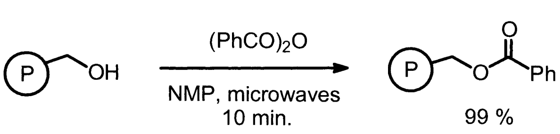
Reaction time (min)	Solvent:DCM	Solvent DCM/THF 9:1
15	29	53
30	57	77
45	68	89
60	73	95
180	84	n.d.

100 W microwave power (89°C, 2.9 bar), sealed vessel. Yields given in % as determined after cleavage; see Section 3.

Table 3. Effect of reaction temperature on the microwave-assisted esterification of Wang resin with benzoic anhydride

Temperature (°C)	Time (min)	Equiv. $(PhCO)_2O$	Conversion (%)
50	10	3	27
80	10	3	39
120	10	3	48
150	10	3	53
150	20	3	77
150	20	5	98
200	5	3	67
200	10	3	74
200	5	5	75
200	10	5	99

Solvent: NMP, atmospheric pressure. Yields given in % as determined after cleavage; see Section 3.



Scheme 3.

system investigated, reaction times could be reduced from days using conventional coupling conditions at room temperature to only minutes using microwave irradiation. As in our previously reported study on the concept of microwave-assisted solid-phase synthesis,[18] we believe that the reason for the observed rate enhancements is the direct and rapid 'in core' heating of the solvent by microwave energy, and not a specific (so-called non-thermal) microwave effect. The application of the microwave coupling reactions reported herein towards more complex systems (i.e. peptides couplings) is currently under investigation.

3. Experimental

^{1}H and ^{13}C NMR spectra were obtained on a Bruker AMX 360 instrument at 360 and 90 MHz, respectively. FTIR spectra of resins were recorded on a Mattson Instruments Unicam FTIR 7000 spectrophotometer using the KBr pellet method. Micro-analyses were obtained on a Fisons Mod. EA 1108 elemental analyzer.

3.1. Materials

The following polymer supports were used: Polystyrene Wang resin (1.0 mequiv. OH/g, 1% DVB, 200–400 mesh, Fluka 13611; 1.62 mequiv. OH/g, 1% DVB, 100–200 mesh, Novabiochem 01-64-0174; 2.3 mequiv. OH/g, 1% DVB, 100–200 mesh, Advanced Chemtech SA5110). Benzoic acid, DIC, DMAP, TFA, and anhydrous NMP were purchased from Aldrich and used as received.

3.2. Microwave irradiation experiments

Milestone MLS ETHOS 1600 Reactor: 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 cm× 35 cm×35 cm). For normal pressure operations standard glassware (25 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. Built-in magnetic stirring (Teflon-coated stirring bar) was used in both normal pressure and sealed vessel operation. During experiments, time, temperature, pressure, and power was monitored/controlled with the 'easyWAVE' software package (Ver. 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.

3.3. Benzoic acid coupling experiments (PLS 4×6 synthesizer, Advanced Chemtech

(A) *O*-Acylisourea-method. PS Wang resin (200 mg, 2.3 mequiv. OH/g) was placed in a Teflon frit and allowed to swell in dry NMP (2 mL) for 10 min. DIC (3.5 equiv., 1.61 mmol, 203 mg), benzoic acid (5 equiv., 2.3 mmol, 281 mg) dissolved in NMP (2 mL), and a catalytic amount of DMAP (0.1 equiv., 0.03 mmol, 4 mg) dissolved in NMP (1 mL) was added and the mixture was shaken at rt for the times specified in Fig. 2. After the respective reaction cycles were completed the resin was filtered, washed with DMF (2×), MeOH (3×), DCM (3×) and MeOH (3×), and dried by suction for approximately 20 min. For cleavage TFA/DCM 1:1 (3 mL) was added and the mixture was shaken for another 30 min at rt. The solution was filtered and washed with DCM (3 mL). Concentration to dryness furnished the recovered acid in the yields indicated in Fig. 2.

(B) Symmetrical anhydride method. The procedure was carried out in an analogous fashion as described above, using 5 equiv. benzoic anhydride (2.3 mmol, 520 mg) dissolved in NMP (2 mL) as reagent. Cleavage was carried out as described above.

3.4. Benzoic acid coupling experiments (Pyrex glassware)

(A) Room temperature conditions. PS Wang resin (250 mg, 1.0 mequiv. OH/g) was placed in a 25 mL two-necked flask and was allowed to swell in DCM/DMF 9:1 (10 mL) for 10 min. DIC (3.5 equiv., 0.875 mmol, 110 mg), benzoic acid (5 equiv., 1.25 mmol, 153 mg) in DCM/DMF (2 mL) and a catalytic amount of DMAP was added, and the mixture was allowed to stirr at rt for several hours (18, 48, or 72 h). After the reaction the resin was filtered, washed with MeOH (3×), DCM (3×), MeOH (3×) and dried overnight (40°C, 10 mbar, FTIR analysis see Fig. 1). For cleavage the resin was treated with TFA/DCM 1:1 (3 mL) for 30 min at rt. The solution was filtered and the resin washed with DCM (3 mL). Evaporation of the solvent yielded the recovered benzoic acid.

(B) Thermal reflux conditions. The procedure was carried out in an analogous fashion as described above, by heating the DCM/DMF mixture in a conventional oil bath to reflux (44°C). Work-up etc. was performed as described under (A).

(C) Microwave heating conditions (atmospheric pressure). The procedure was carried out in an analogous fashion as described above, by heating the DCM/DMF mixture in the cavity of the ETHOS microwave oven at 100 W with magnetic stirring (T=44°C). Work-up etc. was performed as described under (A).

(D) Microwave heating conditions (sealed vessel). Polystyrene Wang resin (250 mg, 1.0 mequiv. OH/g) was placed in a 100 mL PFA sealed reactor vessel and allowed to swell in DCM or DCM/THF 9:1 (10 mL) (see Table 2) for 10 min. DIC (3.5 equiv., 0.875 mmol, 110 mg), benzoic acid (5 equiv., 1.25 mmol, 153 mg) dissolved in solvent (2 mL) and a catalytic amount of DMAP was added and the mixture was subsequently irradiated in the microwave cavity at 100 W, leading to a temperature of ca. 90°C and a pressure of ca. 3.0 bar independent of the solvent used. After cooling the mixture to rt using an ice bath, the resin was filtered, washed with MeOH (3×), DCM (3×), MeOH (3×) and dried overnight (40°C, 10 mbar). Cleavage is carried out in the same way as described above.

3.4.1. 1-Benzoyl-1,3-diisopropylurea (2). 3.5 equiv. DIC and a catalytic amount of DMAP was added to a solution of 5 equiv. of benzoic acid in DCM/DMF 9:1 (10 mL). The mixture was transferred into a 100 mL PFA sealed reactor vessel and irradiated at 100 W for 60 min (3.0 bar, 90°C). After cooling to rt the solvent was evaporated and the remainder purified by flash chromatography, using petroleum ether/ethyl acetate 1:1 as an eluent. After evaporation of the solvent *N*-acylurea **2** was isolated in 58% yield as a white powder, mp 114°C; IR (KBr): 3300, 2970, 1687, and 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 and 1.45 (2d, J=7.0 Hz, $CH(CH_3)_2$, 2×6H), 3.80 and 4.35 (2m, J=7.0 Hz, $CH(CH_3)_2$, 2×1H), 6.65 (brs, N*H*, 1H), 8.32–8.50 (m, ArH, 5H); ^{13}C NMR ($CDCl_3$): δ 20.9, 22.3, 42.7, 50.4, 126.4, 128.7, 130.6, 137.3, 154.2, 172.5 ppm; calcd for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.27. Found: C 67.61; H, 8.17; N, 10.88.

3.5. Benzoic anhydride coupling experiments (Pyrex glassware)

(A) At room temperature. To a solution of benzoic acid (10 equiv. relative to resin loading, 3.24 mmol, 396 mg) in NMP (10 mL) DIC (5 equiv. relative to resin loading, 1.62 mmol, 204 mg) was added. The flask was fitted with a $CaCl_2$-tube and the mixture was cooled down to 0°C with an ice bath. The formation of benzoic anhydride was monitored during the reaction by TLC. After 30 min, when no more starting material was detected, the ice bath was removed and PS Wang resin (200 mg, 1.62 mequiv., OH/g), preswollen in NMP (2 mL) was added. Under slight stirring the mixture was allowed to react at room temperature for several hours (18, 48, and 72 h). The resin was filtered and washed with MeOH (3×), DCM (3×) and MeOH (3×) and dried overnight (40°C, 10 mbar). For cleavage the resin was treated with 50% TFA in DCM (3 mL) for 30 min at rt. The solution is filtered and washed with 3 mL DCM. Concentration to dryness furnished the recovered acid in the yields indicated in the text.

(B) Microwave flash heating. PS Wang resin (200 mg, 1.62 mequiv. OH/g) was placed in a 25 mL two-necked flask and allowed to swell in dry NMP (10 mL) for 10 min. Next, 3 or 5 equiv. benzoic anhydride (0.97 mmol, 220 mg; or 1.62 mmol, 366 mg, respectively), dissolved in NMP (2 mL) and a catalytic amount of DMAP was added and the mixture was irradiated in the microwave cavity at 700 W with preselected temperatures between 50 and 200°C (Table 3). After cooling to rt using a water bath, the resin was filtered, washed with MeOH (3×), DCM (3×), MeOH (3×) and dried over night (40°C, 10 mbar). Cleavage was carried out as described above.

Acknowledgements

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References

1. Zaragoza Dörwald, F. *Organic Synthesis on Solid Phase*; Wiley/VCH: Weinheim, 2000.
2. *Solid-Phase Organic Synthesis*; Burgess, K., Ed.; Wiley/Interscience: New York, 2000.
3. Obrecht, D.; Villalgordo, J. M. *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound-Libraries*; Pergamon: Oxford, 1998.
4. Bunin, B. A. *The Combinatorial Index*; Academic: San Diego, 1998.
5. *Fmoc Solid Phase Peptide Synthesis*; Chan, W. C., White, P. D., Eds.; Oxford University: Oxford, 2000.
6. Slebioda, M. *Tetrahedron* **1995**, *51*, 7829–7834.
7. Mathias, L. J. *Synthesis* **1979**, 561–576.
8. Kurzer, F.; Douraghi-Zadeh, K. *Chem. Rev.* **1967**, *67*, 107–143.
9. Yu, H.-M.; Chen, S.-T.; Wang, K.-T. *J. Org. Chem.* **1992**, *57*, 4781–4784.
10. Larhed, M.; Lindeberg, G.; Hallberg, A. *Tetrahedron Lett.* **1996**, *37*, 8219–8222.
11. Hoel, A. M. L.; Nielsen, J. *Tetrahedron Lett.* **1999**, *40*, 3941–3944.
12. Kuster, G.; Scheeren, H. W. *Tetrahedron Lett.* **2000**, *41*, 515–519.
13. Yu, A.-M.; Zhang, Z.-P.; Yang, H.-Z.; Thang, C.-Y.; Liu, Z. *Synth. Commun.* **1999**, *29*, 1595–1599.
14. Chandrasekhar, S.; Padmaja, M. B.; Raza, A. *Synlett* **1999**, 1597–1599.
15. Combs, A. P.; Saubern, S.; Rafalski, M.; Lam, P. Y. S. *Tetrahedron Lett.* **1999**, *40*, 1623–1626.
16. Alterman, M.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 7984–7989.
17. Scharn, D.; Wenschuh, H.; Reineke, U.; Schneider-Mergener, J.; Germeroth, L. *J. Combust. Chem.* **2000**, *2*, 361–369.
18. Stadler, A.; Kappe, C. O.; Eur *J. Org. Chem.* **2001**, 919–925.
19. Kiselyov, A. S.; Armstrong, R. W. *Tetrahedron Lett.* **1997**, *35*, 6163–6166.
20. Li, W.; Yan, B. *J. Org. Chem.* **1998**, *63*, 4092–4097.
21. Ley, S. V.; Mynett, D. M.; Koot, W.-J. *Synlett* **1995**, 1017–1020.
22. Ref. 5, p. 46.
23. Yan, B. *Acc. Chem. Res.* **1998**, *31*, 621–630.
24. Baghurst, D. R.; Mingos, D. M. P. *J. Chem. Soc., Chem. Commun.* **1992**, 674–677.
25. Saillard, R.; Poux, M.; Berlan, J.; Audhuy-Peaudecerf, M. *Tetrahedron* **1995**, *51*, 4033–4042.
26. Stadler, A.; Kappe, C. O. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1363–1368.