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An atom efficient and solvent-free synthesis of structurally diverse amides using microwaves

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Abstract—An array of structurally diverse amides was synthesized efficiently by combining (primary and secondary) amines and carboxylic acids in one-pot under solvent-free microwave (MW) conditions. In most cases, no racemization was observed with optically active inputs and chiral amides were obtained in high ee or de.

The relatively stable amide bond is not only common in natural-occurring materials (e.g., peptides and proteins) but is also found in many synthetic substances.[1,2] This makes the amide function important to synthetic chemists, especially in peptide[1] and lactam[2] syntheses, in which the formation of amide bonds is crucial. Many methods for the synthesis of carboxamides exist.[1] In general, amides are formed from activated carboxylic acids and amines. Carboxylic acids can either be activated separately, prior to the actual amide formation, or they can be activated in situ using coupling reagents.[3] Although good results are obtained with both approaches, they are time consuming and not atom efficient. To improve efficiency and reduce waste production mild methods to prepare amides directly from non-activated carboxylic acids and amines in the absence of coupling reagents and solvent are highly desired. In the last decade, microwaves (MWs) have been used to simplify and improve reaction conditions for many classic organic reactions. Reactions performed under MW-conditions proceed faster, more cleanly, and in much better yields than similar reactions under conventional conditions.[4–8] Single-mode MW-reactors, which are now used in many synthetic laboratories, have simplified the experimental set up of original MW-assisted reaction protocols and have enhanced the reproducibility considerably. As a result MW-reactors have developed into powerful synthetic tools.

The MW-assisted synthesis of amides has already been investigated.[9–11] However, in these studies a limited number of amines and carboxylic acids were combined to afford the corresponding amides. Only acids and amines with no additional functionality were used. Furthermore, for reactions with amines and carboxylic acids bearing an electron-withdrawing group, very low conversions were achieved even after long reaction times. In short, the chemical diversity covered in the amides generated was rather poor. Moreover, the compliance of MW-conditions with stereogenic information present in (one of) the inputs was not examined. Here, we wish to report on an improved protocol that considerably broadens the scope of direct MW-assisted amide synthesis.

We first decided to optimize the reaction conditions used in the previous studies[10] and chose the amide formation between aniline and benzoic acid as a test reaction (Table 1).

Loupy and co-workers obtained amide **1** in a 12% yield using a single-mode MW-reactor (150 °C, 120 min, 1.5 equiv aniline, in the absence of solvent).[10] Using closed vessels in the absence of solvent, we obtained **1** in 17% yield in only 10 min at 200 °C employing equimolar amounts of aniline and benzoic acid.[12] This finding encouraged us to explore further the influence of the

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Table 1. Optimization of the reaction temperature of MW-assisted amide formation

R^2	Compound	Reaction temperature (°C)	Reaction time (min)	Relative amount (acid/amine)	Yield[a] (%)
Ph	**1**	150	120	1/1.5	12[b]
Ph	**1**	200	10	1/1	17
Ph	**1**	250	10	1/1	44
Ph	**1**	300	10	1/1	51
Bn	**2**	150	30	1/1	10[b,c]
Bn	**2**	200	10	1/1	58
Bn	**2**	250	10	1/1	88

[a] Determined by ^{1}H NMR.
[b] The yield of the isolated product was determined by Loupy and co-workers.[10]
[c] Loupy and co-workers could improve this yield to 75% and 80% by using, respectively, 1.5 equiv excess of benzoic acid or benzylamine.[10]

reaction temperature on the direct MW-assisted amide formation. Thus, when the reaction temperature was increased to 250 or 300 °C,[13] while keeping the other reaction conditions the same, conversion to **1** improved significantly (44% and 51%, respectively). Such a dramatic improvement was also found when benzylamine and benzoic acid were allowed to react at increased reaction temperatures. Thus, heating at 150 °C for 30 min gave conversion to amide **2** in only 10% yield, whereas reaction for 10 min at 200 °C afforded **2** in 58% yield. Heating to 250 °C for 10 min even resulted in an 88% yield of **2**.

These initial studies showed that an increase in reaction temperature improves considerably the conversion of the direct MW-assisted amide formation. Next, the scope of the method was explored by applying a broad range of amines and carboxylic acids as inputs. First, the synthesis of amide **3** from 4-methoxycinnamic acid, which is less reactive towards amide formation then benzoic acid, and benzylamine, was studied. At 250 °C, 85% of amide **3** was found, which demonstrates that our method is well suited to prepare amides from acids of low reactivity (Fig. 1). Also a combination of bulky amines with carboxylic acids showed satisfying re-

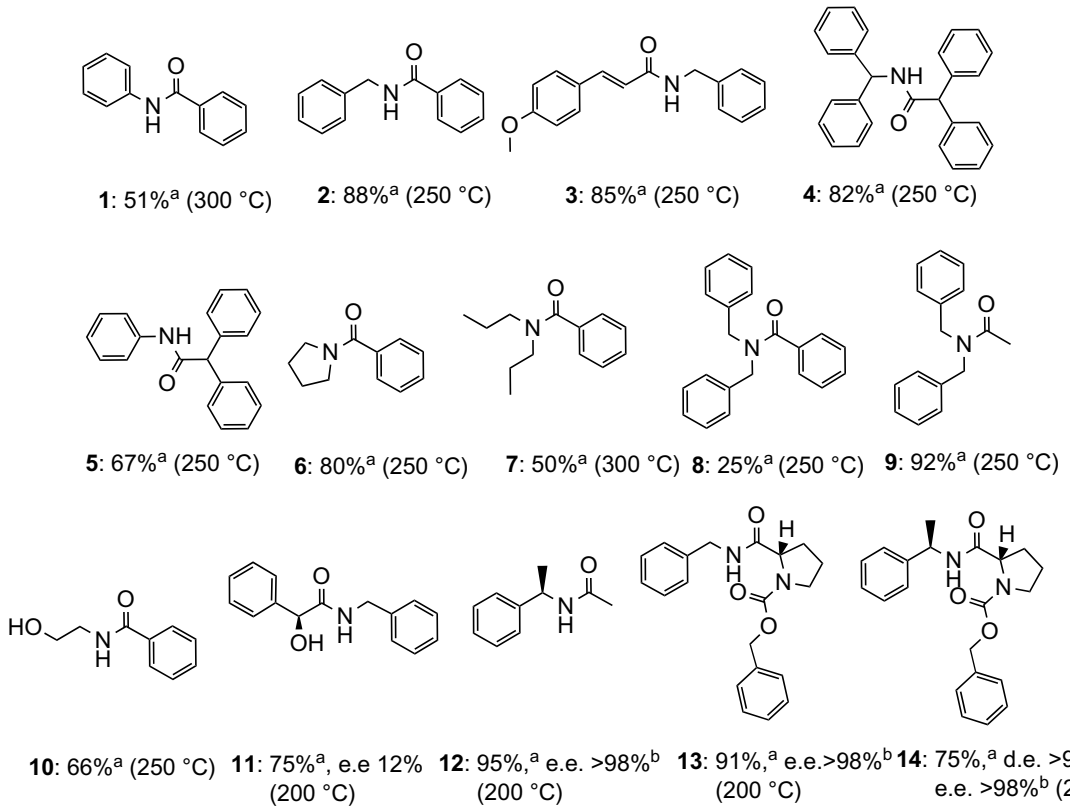

Figure 1. Amides **1**–**14** obtained after 10 min via MW-assisted reaction of the corresponding amines and carboxylic acids.[12] [a]Based on ^{1}H NMR. [b]Based on chiral HPLC or ^{13}C NMR.[23]

sults. When diphenylacetic acid was allowed to react with either benzhydrylamine or aniline, the expected amides **4** and **5** were obtained in 82% and 67% yields, respectively. Amide formation using the sterically demanding benzhydrylamine proved slightly more facile compared to amide formation using the less-reactive aniline. Next, the synthesis of tertiary amides was explored. Pyrrolidine was allowed to react with benzoic acid to give amide **6**[14] in 80% yield at 250 °C. For di-*n*-propylamine, a reaction at 250 °C gave only 10% of the corresponding amide **7**.[15] However, at 300 °C di-*n*-propylamine was converted to **7** in a 50% yield. On the other hand, using dibenzylamine this strategy was less successful. If dibenz- ylamine was allowed to react with benzoic acid at 250 °C, conversion to amide **8**[16] proceeded in only 25% yield. When the reaction temperature was increased to 300 °C, decarboxylated benzoic acid was obtained predominantly, instead of the expected amide **8**. However, reaction of dibenzylamine with acetic acid at 250 °C successfully gave amide **9**[17] in 92%. Next, ethanolamine was reacted with benzoic acid and amide **10** was successfully formed in 66% yield without the trace of any side product (Fig. 1).[18]

Encouraged by the range of substituents that were compatible with the direct MW-assisted amide formation described above, our attention was next focused on the synthesis of optically active amides. Although amide formation proceeds at relatively high temperatures, the reaction times are short and it was anticipated that stereogenic information in either the carboxylic acid or the amine input should be retained to produce the corresponding amides stereoselectively. As expected the reaction of L-mandelic acid with benzylamine gave the amide **11**[19] (75%) and no side products were detected. However, an almost racemic mixture of **11** was obtained. This is probably due to the fact that mandelic acid is very prone to racemization in the presence of base.[20] Also, optically active amines were considered as inputs for the MW-assisted amide formation. Thus (*R*)-α-methylbenzylamine was reacted with acetic acid and in this case amide **12**[21] was formed in 95% yield without racemization. As mandelic acid proved to be extremely sensitive to racemization, L-CBz-proline was considered instead as the asymmetric carboxylic acid input and indeed combination with benzylamine under the usual MW-conditions afforded amide **13**[22] (91%) with an ee of >98% after purification. Finally, two optically active inputs, L-CBz-proline with (*R*)-α-methylbenzylamine, were combined at 200 °C. Amide **14** (75%) was obtained in >98% ee and >95% de.

The MW-assisted solvent-free synthesis of amides by direct assembly of amines and carboxylic acids is a versatile method for the efficient synthesis of diverse arrays of amides. A set of structurally different amines and carboxylic acids were combined under optimized conditions to obtain a total of 14 structurally different amides. Furthermore, the direct MW-assisted amide formation is compatible with optically active inputs. Both optically active amines and some carboxylic acids were found to react smoothly and without racemization to give the desired optically active amides, which makes this method potentially a powerful tool for asymmetric peptide synthesis.

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12. *General reaction protocol*: In a capped 10 mL MW-vessel, the carboxylic acid (2 mmol for **1**–**12**, 1 mmol for **13** and **14**) and the amine (2 mmol for **1**–**12**, 1 mmol for **13** and **14**) were mixed. The mixture was heated at 200, 250 or 300 °C for at least 10 min (the ramp time was set at 5 min (average effective ramp time = 1 min), hold time was 10 min). The power was set at 200 W and the pressure was set at 17 bar (average effective pressure = 5 bar). After completion the conversion was directly determined from the ^{1}H NMR spectrum and a consecutive work up was performed by dissolving the crude mixture in DCM (10 mL) and washing the DCM layer with 1 M NaOH (2 × 5 mL) and 2 M HCl (2 × 5 mL). Next, the organic phase was dried ($MgSO_4$) and evaporated. The analytical data of amides **1**–**2**[10] and **6**–**13**[14–22] were identical to those reported previously. New amides **3**, **4**, **5** and **14** were purified and characterized by ^{1}H NMR, ^{13}C NMR and HRMS. The ee's and de of the chiral amides **11**–**14** were determined with chiral HPLC by comparing them with their racemic counterparts.
N-Benzyl-4-methoxycinnamic amide (**3**): Yield: 279 mg (52%); ^{1}H NMR ($CDCl_3$): δ 7.58 (d, 1H, J = 15.6 Hz), 7.38 (d, 2H, J = 8.7 Hz), 7.34–7.22 (5H, m), 6.82 (d, 2H, J = 8.8 Hz), 6.29 (d, 1H, J = 15.6 Hz), 6.19 (br s, 1H), 4.51 (d, 2H, J = 5.8 Hz), 3.77 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 166.1, 160.7, 140.7, 138.2, 129.2, 128.5, 127.7, 127.3, 117.9, 114.0, 55.2, 43.6. HRMS (EI) calculated for $C_{17}H_{17}NO_2$ (M^+) 267.1259. Found: 267.1263.
N-Benzhydryl-2,2-diphenyl-acetamide (**4**): After the general protocol the product was precipitated from ethyl acetate. This yielded 521 mg of **4** (69%). ^{1}H NMR ($CDCl_3$): δ 7.32–7.21 (m, 16H), 6.10–7.05 (m, 4H), 6.27 (br s, 2H), 4.96 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 170.7, 141.2, 139.1, 128.7,

128.6, 128.5, 129.3, 127.2, 58.9, 56.9. HRMS (EI) calculated for $C_{27}H_{23}NO$ (M^+) 377.1780. Found: 377.1766.
2,2-N-Triphenyl-acetamide (**5**): Yield: 247 mg (43%). ^1H NMR ($CDCl_3$): δ 7.46–7.22 (m, 14H), 7.10–7.03 (m, 2H), 5.06 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 169.9, 138.9, 137.5, 128.8, 128.8, 127.3, 124.4, 119.6, 59.9. HRMS (EI) calculated for $C_{20}H_{17}NO$ (M^+)287.1310. Found: 287.1298.
(R,S)-2-(1-Phenyl-ethylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (**14**): Yield: 214 mg (33%); ^1H NMR ($CDCl_3$): δ 7.45–05 (m, 10H), 6.13 (br s, 1H), 5.22–4.91 (m, 3H), 4.33 (br s, 1H), 3.60–3.32 (m, 2H), 2.50–1.70 (m, 4H), 1.53–1.35 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 128.0, 127.1, 125.9, 77.1, 67.3, 60.8, 48.7, 47.7, 24.1, 21.9; HRMS (EI) calculated for $C_{21}H_{24}N_2O_3$ (M^+) 352.1787. Found: 352.1762. $[\alpha]_D^{20}$ 40 (*c* 0.1, EtOH). Enantiomeric excess (ee) >98% (based on chiral HPLC[23]). Diastereomeric excess (de): >95% (based on ^{13}C NMR).
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