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Microwaves-assisted solvent-free synthesis of *N*-acetamides by amidation or aminolysis

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Abstract

The preparation of acetamides directly from amines and an acetyl donor under microwaves without any catalyst is described. The inexpensive, solvent free, and fast reaction conditions are the important features of this procedure.

Keywords: Acetamides; Solvent-free conditions; Microwave-assisted synthesis; Regiocontrol

The stable and polar amide functionality is an important unit among the organic molecules present in natural-occurring materials (e.g., peptides and proteins). It is also found in many synthetic substances as intermediates or as active pharmaceutical products or prodrugs.[1]

Due to its interest in organic synthesis, the preparation of amides from the corresponding amines is an important and well-known transformation. The most popular methods for the synthesis of carboxamides involve the conversion of carboxylic acid to a more reactive functional group or an in situ activation by using coupling reagents.[2] Although good results are obtained with both approaches, they need often expensive coupling reagents, which lead to the formation of by-products requiring further separations.

Over the last years, a large number of publications and reviews have clearly shown that many types of chemical transformations can be carried out successfully under microwaves (MW) conditions.[3] Most importantly, microwave processing frequently leads to dramatically reduced reaction times, higher yields, less formation of by-products, easier work-up matching with the goal of green chemistry, solvent-free organic transformations, atom economy, and selectivity of reactions. The application of microwave technology in the amide solvent-free synthesis is not frequently described in the literature.[4] In this Letter, we highlight that to improve efficiency and reduce waste production, the microwaves offer mild methods to prepare amides directly from non-activated carboxylic acids and amines in the absence of coupling reagents and solvents.

In a recent review bearing with the very complex thermal and non-thermal effects of microwave irradiation, De la Hoz emphasized that the microwave radiation is a very polarizing field and may stabilize polar transition states and intermediates.[4k] In the case of the solvent-free uncatalyzed amidations of acids, Loupy and Perreux has shown a microwave effect, attributed to the increase of polarity during the course of the reaction, due to the development of a dipole in the transition state.[4d]

In order to screen the uncatalyzed amidation under microwave-assisted solvent-free conditions of primary amines, we performed the reaction with 1.2 equiv of acetic acid, acetyl chloride or various esters as acyl donors in a Discover™ microwave synthesizer. Neat compounds were mixed in a sealed microwave reaction tube and irradiated under 25 W for few seconds to few minutes. The reactions were monitored by GC–MS analysis, and the purity of the desired products was evaluated by NMR spectroscopy.[5]

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In the case of primary amines **1**–**3**, all the tested acylating agents are very efficient for rapid amidation. The reactions were generally achieved within 3 min and the yields were excellent, typically higher than 84% and often quantitative.

With our goal in mind, we have chosen to carry our studies further with acetic acid, an acylating agent of choice, affording only water as a by-product. Most of the microwave-assisted amidations are performed at high temperature (150–300 °C).[4] In a preliminary study, we examined the temperature effect on the reaction of acetic acid and dodecylamine and we observed that whatever the wattage ($P = 2$–25 W) was, the amidation occurred as soon as the temperature (T) reached 80–90 °C (in less than 5 min). This is of interest for reactions involving thermically unstable compounds. Then, we checked the better conditions (P, T) to achieve the reaction (Fig. 1). The results from all these experiments show that the amidation reaction with dodecylamine **1** and a slight excess of acetic acid (1.2 equiv) can be performed under low wattage since the required temperature (90 °C) is rapidly reached. It should be noticed that after 30 min under 1 W, the temperature reached only 80 °C and no reaction occurred.

The reaction was quantitative in 5–15 min under 3–25 W, and required 2 h under 2 W. Table 2 shows the extension of these conditions to the quantitative acylation of aliphatic amines under low conditions of temperature and wattage. The reactions were performed with various primary amines **1**–**4** in the presence of 1.2 equiv of acetic acid at 90 °C under 2 W (MW) or by conventional heating in a thermostated oil bath (Δ: refluxing acetic acid, 115 °C) (Table 2). Wattage was automatically adjusted so as to maintain the desired temperature.

The reactions were performed on a 2 mmol scale. All the microwave-assisted amidation reactions studied proved to be 'directly scalable': about identical yields were obtained on a 2 mmol and 20 mmol scale without needing new development of the reactional conditions.[5] With microwave heating, the amidation was completed in 1 h (entries 1 and 8) or almost completed (entries 3, 4, and 5) in a shorter time compared to that of conventional heating.

Differentially substituted polyamine moieties are found as either key pharmacophoric element or an important structural scaffold in a large number of biochemical targets across all the therapeutic areas.[6] Selective acetylation of the less hindered amino group in polyamines is often required. The quest for complete control over efficient and selective introduction of functionality is still a challenging problem. In the absence of inherent steric or electronic influences, conditions that are generally required for monoacetylation are either the use of excess diamine to avoid a statistical distribution of products (starting diamine, mono- and diacetylated products), or the reaction of one amine moiety by the use of structurally sophisticated selective acetylating agents which are not in accordance with the concept of atom economy.[7]

We expected that this process could provide practical and rapid preparative procedures for the selective acylation of polyamines. The previously described conditions (i.e., 2 W, 90 °C or 10 W, 130 °C) were applied to the amidation of *N*-cyclohexylpropylenediamine **9**, *N*-propylpropylenediamine **10**, and dibutylamine **11** with acetic acid, in order to study the competition between primary amine versus secondary amine, to evaluate the reactivity of secondary amines, and to optimize the conditions of acetylation (Table 3).

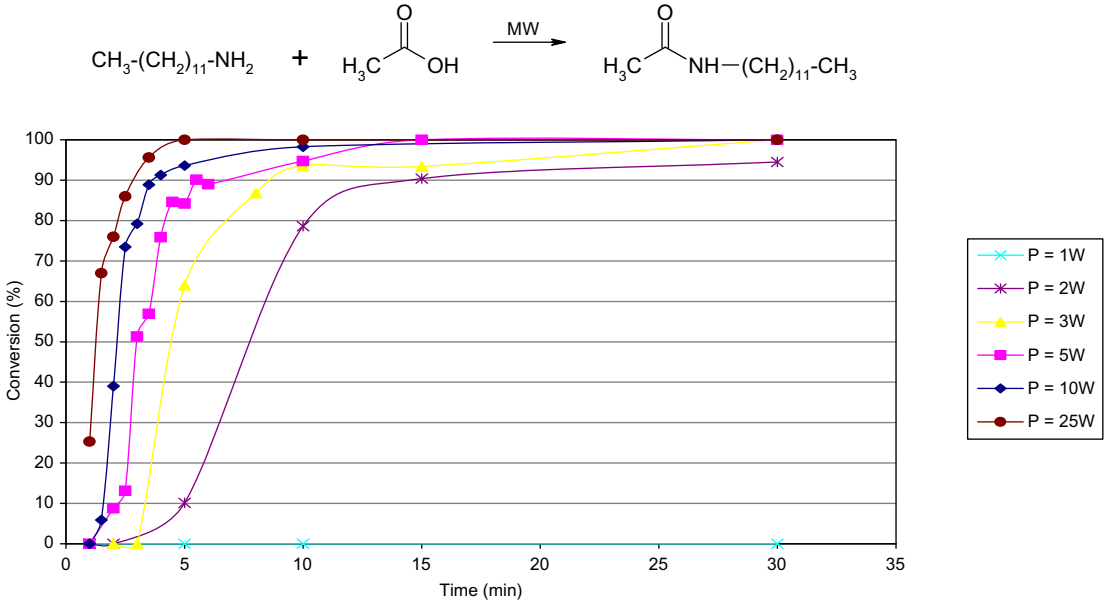
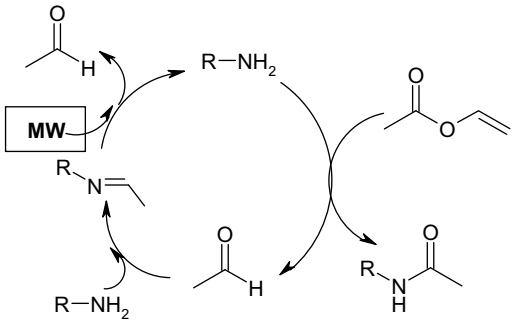


Fig. 1. Temperature effect on the acetamidation of dodecylamine **1** by acetic acid.

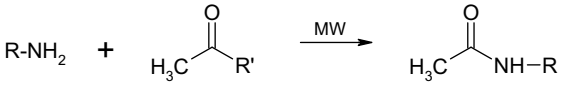
The results showed that, in all cases, the reactions proceeded cleanly, and the less hindered acetylated products *N*-[3-(cyclohexylamino)propyl]-acetamide **12** and *N*-[3-(propylamino) propyl]-acetamide **13** were selectively formed in high yields. These results confirm the interest of our method in regard to the monofunctionalization methods described previously requiring complex acylating agents for the same discrimination.[7]

We then decided to find better conditions to perform the acetylation of secondary amines in order to check the selectivity of their monoacetylation. Under the conditions described by Orru and co-workers,[4h] a low selectivity between primary amine versus secondary amine (respectively 85:15) was observed for diamine **9** (entry 1, i.e., 200 W, 1 h, 200 °C), compared to total discrimination that we obtained in 1 h at 130 °C under 10 W. The acetylation of the secondary *N*,*N*-dibutylamine **11** required 2 h at 130 °C under 10 W to give 96% of the expected acetamide **14**. These results were confirmed in the case of piperazine



Scheme 1. Microwave-assisted stoichiometric acetamidation of amines by vinyl acetate.

Table 1
Microwave-assisted acetylation of primary amines

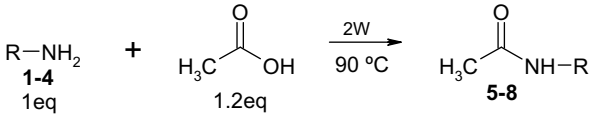


R=alkyl, benzyl
R'=Cl, OH, Oalkyl

	AcCl[a]		AcOH[b]		AcOCH=CH$_2$[c]		AcOMe[c]		AcO*t*Bu[c]		AcOEt[c]	
	Time (s)	Yield (%)	Time (s)	Yield (%)	Time (s)	Yield (%)	Time (s)	Yield (%)	Time (s)	Yield (%)	Time (s)	Yield (%)
Dodecylamine **1**	180	100	30	100	10	100	15	93	60	97	150	87
Benzylamine **2**	120	99	30	100	10	100	15	96	60	84	150	72
Cyclohexylamine **3**	1800	100	60	100	15	100	30	91	120	37	150	22

[a] 100 °C, 25 W.
[b] 150 °C, 100 W.
[c] 200 °C, 200 W.

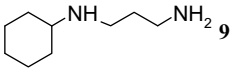
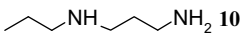
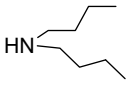
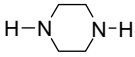
Table 2
Microwave-assisted amidation of primary amine under mild conditions



Entry	R	Scale (mmol)	Reaction time (h)		Ratio[a] amine/product (%)	
					MW	Δ
1	**1** CH_3–$(CH_2)_{11}$-	2	1	**1/5**	0/100	87/13
2		20	2		15/85	
3		20	6		4/96	47/53
4	**2** Benzyl-	2	1	**2/6**	11/89	69/31
5		20	5		10/90	22/78
6	**3** Cyclohexyl-	2	1	**3/7**	93/7	
7		2	1		0/100[b]	
8	**4** CH_2=CH–CH_2-	2	1	**4/8**	0/100[c]	78/22[c]

[a] Ratio was determined by GC–MS spectroscopy and confirmed by ^{1}H NMR.[5]
[b] 10 W, 130 °C, 1 h.
[c] Ratio was determined only by NMR spectroscopy because of the volatility of the allylamine.

Table 3
Selective acetylation of primary amines versus secondary amines

Entry	Amine (2 mmol)	Conditions	Starting material		Mono	Di	By-products
1	 **9**	2 W, 90 °C, 1 h	31	**12**	69	0	
		Δ: 115 °C, 1 h	94		6	0	
		10 W, 130 °C, 1 h	0		100	0	
		200 W, 200 °C, 1 h	0		85	15[a]	
2	 **10**	2 W, 90 °C, 1 h	43	**13**	45	0	13
		Δ: 115 °C, 1 h	100		0	0	
		5 W, 110 °C, 1 h	8		72.5	3	16.5
		10 W, 130 °C, 1 h	0		78	15.5	6.5
3	 **11**	2 W, 90 °C, 1 h	93	**14**	7		
		Δ[b]: 130 °C, 1 h	100		0		
		10 W, 130 °C, 1 h	38		62		
		10 W, 130 °C, 2 h	4		96		
		Δ[b]: 130 °C, 2 h	100		0		
4	 **15**[c]	10 W, 130 °C, 1 h[d]	0	**16**	57	43	
		200 W, 200 °C, 1 h	0		27	73	

[a] Conditions described by Orru and co-workers.[4h]
[b] In sealed tube.
[c] Ratio amine **15**/AcOH:1/2.
[d] Because acetic acid did not mix well with piperazine even at 130 °C in a sealed tube, the reaction was not performed under classical heating.

15 for which, in the presence of 2 equiv of acetic acid, an emitted power of 10 W was required for a total conversion but no selectivity was observed. The results depicted in Table 3 show the unreactivity of the secondary amines **9**–**11** under classical thermal conditions and thus confirm the influence of the microwave irradiation.

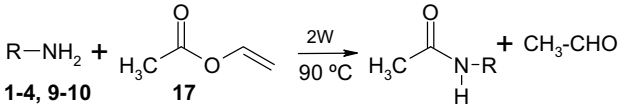
From the preliminary results given in Table 1, it clearly appeared that vinyl acetate **17** was also of interest as an acyl donor. We decided to explore its potentiality in selective monoacetylation of polyamines (Table 4).

When the reaction was performed at room temperature without any microwave activation, a rapid transfer of acyl was observed in a few seconds but a twofold excess of amine was required. These results show that the amine reacts by two different pathways. The reaction of the primary amine with vinyl acetate leads in a first step to the formation of the acetamide together with the formation of acetaldehyde as the by-product which reacts in situ with the excess amine to give the corresponding imine. On the other hand, under microwave activation, the hydrolysis of the intermediate imine (probably favored by a polar transition state) undergoes rapidly and allows a stoichiometric reaction. Thus, the starting amine re-formed by the imine hydrolysis can react again with the unreacted vinyl acetate to lead to the formation of the acetamide and so on until the overall consumption of the vinyl acetate (Scheme 1).

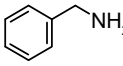
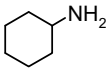
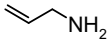
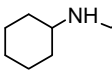
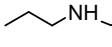
The analysis of the results depicted in Tables 2–4 shows a similar reactivity of the amines studied with either acetic acid or vinyl acetate (2 W, 90 °C) except for the two cyclohexylamines **3** and **9** for which more drastic conditions were required to achieve the acetylation with acetic acid (Table 2, entries 6, 7 and Table 3, entry 1). No explanation can be given to account of this discrepancy.

In conclusion, all the tests carried out under microwave activation show higher product yields, milder reaction conditions, and shorter reaction times accompanied by a cleaner reaction profile compared to those obtained under

Table 4
Vinyl acetate: a green reagent for quantitative selective monofunctionalization of amines



1-4, 9-10 **17** **5-8, 12-13**
1eq 1.2eq

Entry	Amine/conditions	Starting material	Product
	CH_3–$(CH_2)_{11}$–NH_2 **1**		**5**
1	2 mmol (1 h)	0	100
2	20 mmol (1 h)	0	100
	 **2**		**6**
3	2 mmol (1 h)	0	100
4	20 mmol (1 h)	0	100
	 **3**		**7**
5	2 mmol	0	100
	 **4**		**8**
6	2 mmol	0	100
	 **9**		**12**
7	2 mmol	0	100
	 **10**		**13**
8	2 mmol	0	84:16[a]

[a] Ratio of acetylation of primary amine versus secondary respectively determined by GC–MS spectrometry.

thermal conditions. However, at this stage we have not investigated further to conclude to a specific microwave effect which is still a controversial topic. Concerning the selectivity, the monoacetylation of polyamines, obtained under these conditions, is broadly equivalent to those described in the literature with more sophisticated reagents and shows still the interest of the use of the microwaves in organic synthesis.

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5. *Typical procedure*: In a capped 10 mL MW-vessel, the carboxylic acid (or the carboxylic acid derivative) (2.4 mmol, 1.2 equiv) and the amine (2 mmol) were mixed. The tube was positioned in the irradiation cavity and the mixture was heated with stirring under microwave irradiation to 90 °C with 2 W of power and held for about 1 h (reactions on a 2 mmol scale realized in sealed CEM 10 mL microwave reaction vials and reactions carried out on a 20 mmol scale in the open-vessel were all performed with a CEM Discover® single mode microwave reactor equipped with a 300 W power source). After completion, upon cooling to ambient temperature, the conversion was directly determined by GC–MS analyses (Agilent 6890 N Gas Chromatograph equipped with a column HP-5MS (30 m × 250 μm × 0.25 μm). The mass spectra resulting from ionization by electronic impact (EI-LRMS) were acquired on an Agilent 5973 Network MSD). A consecutive work up was simply performed by dissolving the reaction mixture in dichloromethane and then concentrated under vacuum in order to eliminate either the acetic acid or the vinyl acetate in excess. The purity of the final products was controlled by ^{1}H NMR. Characterization data were consistent with that of previously described products.[8]
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