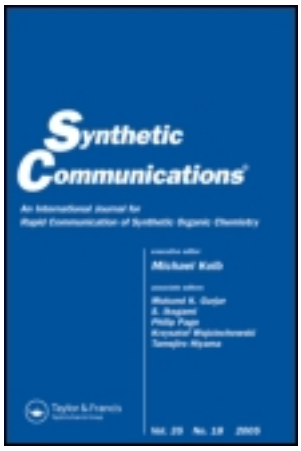

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

SYNTHESIS OF AMIDES FROM ESTERS AND AMINES UNDER MICROWAVE IRRADIATION

Fatima-Zohra Zradni [a], Jack Hamelin [b] & Aicha Derdour [a]

[a] Faculté des Sciences, Laboratoire de Synthèse Organique, Es-sénia, Oran Algerie, BP 1524

[b] Laboratoire de Synthèse et Electrosynthèse Organiques 3, Université de Rennes I et CNRS, UMR 6510, Avenue du Général Leclerc.F-35042, Rennes I, France

Version of record first published: 22 May 2009.

To cite this article: Fatima-Zohra Zradni , Jack Hamelin & Aicha Derdour (2002): SYNTHESIS OF AMIDES FROM ESTERS AND AMINES UNDER MICROWAVE IRRADIATION, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:22, 3525-3531

To link to this article: http://dx.doi.org/10.1081/SCC-120014792

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS
Vol. 32, No. 22, pp. 3525–3531, 2002

SYNTHESIS OF AMIDES FROM ESTERS AND AMINES UNDER MICROWAVE IRRADIATION

Fatima-Zohra Zradni,[1] Jack Hamelin,[2,*] and Aicha Derdour[1]

[1]Faculté des Sciences, Laboratoire de Synthèse Organique, BP 1524 Es-sénia, Oran Algerie
[2]Laboratoire de Synthèse et Electrosynthèse Organiques 3, Université de Rennes I et CNRS, UMR 6510, Avenue du Général Leclerc.F-35042 Rennes I, France

ABSTRACT

Formamide, primary and secondary amines react with esters in the presence of potassium *tert*-butoxide under microwave irradiation. Substituted amides are formed in yields (generally more than 70%) much higher than under conventional heating.

The amide bond is an important building unit naturally or synthetically occurring.[1,2] It is present as a key in many important natural products and man-made compounds.[2] For example, *N*-acylalkylenediamines[3] react with 4-amino-2-chloro-6,7-dimethoxyquinazolines to give a variety of antihypertensive agents.[4]

*Corresponding author. E-mail: jack.hamelin@univ-rennes1.fr

DOI: 10.1081/SCC-120014792
0039-7911 (Print); 1532-2432 (Online)

www.dekker.com

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

The synthesis of amides from carboxylic esters is a transformation of general synthetic interest which in many cases needs harsh conditions (temperature, reaction periods) or the use of strong catalysts.[5,6]

However, the enormous growth in the use of microwave irradiation this last decade in synthetic organic chemistry[7] inspired us to study this reaction. A recently described synthesis of *N*-acylalkylenediamines from the corresponding carboxylic esters and alkylene diamines which requires prolonged reaction times (3–16 h)[8] and also synthesis of *N*-arylamides,[9] prompt us to report our results under solvent-free conditions which proceed in a much shorter time (2–3 min).

For the synthesis of primary amides, the reactions were carried out using an ester (1 eq.), formamide (3 eq.) and solid potassium *tert*-butoxide (*t*-BuOK) (1 eq.) and the reaction mixture was submitted to microwave irradiation (MWI) in a focused microwave oven (Synthewave 402®).[10]

$$R^1CO_2R^2 + HCONH_3 \xrightarrow{MWI/t\text{-}BuOK} R^1CONH_2 + HCO_2R^2$$

R^1=Me, $C_6H_5CH_2$, $NCCH_2$, $C_6H_5CH{=}CH$, $H_3CCO_2CH_2$;

R^2=Me, Et

While the synthesis of secondary amides are realized from esters (1 eq.) and butylamine (1 eq.), tertiary amides result from esters (1 eq.) and secondary amines (1 eq.) with adjusted amounts of (*t*-BuOK) as shown in Table 2 for the following reactions.

$$R^1CO_2R^2 + BuNH_2 \xrightarrow{MWI/t\text{-}BuOK} R^1CONHBu$$

$$R^1CO_2R^2 + R^3R^4NH \xrightarrow{MWI/t\text{-}BuOK} R^1CONR^3R^4$$

Table 1. Solvent-Free Synthesis of Amides from Esters and Formamide Using Potassium *tert*-Butoxide

Entry	Starting Materials	Products	Time (min)	Yield[a] (%)
1	$CH_3CO_2C_2H_5$	CH_3CONH_2	2	80
2	$C_6H_5CH_2CO_2CH_3$	$C_6H_5CH_2CONH_2$	3	79
3	$NCCH_2CO_2CH_3$	$NCCH_2CONH_2$	2	72
4	$C_6H_5CH{=}CHCO_2CH_3$	$C_6H_5CH{=}CHCONH_2$	2	85
5	$CH_2(CO_2CH_3)_2$	$CH_3CO_2CH_2CONH_2$	3	43

[a]The yield refers to isolated products which exhibit physical and spectral properties (NMR spectra) in agreement with the assigned structures.

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

Table 2. Solvent-Free Synthesis of Secondary and Tertiary Amides from Esters and Amines During 3 min Under Irradiation

Entry	Starting Materials		Quantity of *t*-BuOK (eq.)	Irradiation Temp.[a] (°C)	Yield Under MW[b] (%)	Yield Under Δ[c] (%)
	Esters	Amines				
1	$CH_3CO_2C_2H_5$	$BuNH_2$ (**2a**)	1	95	70	25 (2 d)
2	$C_6H_5CH_2CO_2CH_3$	**2a**	0.5	105	97	36 (1 d)
3	$NCCH_2CO_2CH_3$	**2a**	1	83	60	17 (1 d)
4	$C_6H_5CH{=}CHCO_2CH_3$	**2a**	1	96	61	42 (1 d)
5	$CH_2(CO_2CH_3)_2$	**2a**	0.5	71	17	5 (2 d)
6	$CH_3CO_2C_2H_5$	$NH\text{-}(CH_2)_4$– (**3a**)	0.25	157	69	21 (1 d)
7	$C_6H_5CH_2CO_2CH_3$	**3a**	1	219	63	15 (3 h)
8	$NCCH_2CO_2CH_3$	**3a**	0.5	190	78	39 (8 h)
9	$C_6H_5CH{=}CHCO_2CH_3$	**3a**	0.25	198	69	9 (5 h)
10	$CH_2(CO_2CH_3)_2$	**3a**	0.25	95	52	5 (8 h)
11	$CH_3CO_2C_2H_5$	$NH\text{-}(CH_2)_5$– (**4a**)	0.5	129	74	30 (1 d)
12	$C_6H_5CH_2CO_2CH_3$	**4a**	0.5	204	70	25 (6 h)
13	$NCCH_2CO_2CH_3$	**4a**	0.25	140	75	12 (2 h)
14	$C_6H_5CH{=}CHCO_2CH_3$	**4a**	0.5	176	75	7 (5 h)
15	$CH_2(CO_2CH_3)_2$	**4a**	0.5	74	41	3 (6 h)

[a]The irradiation power is monitored for the desired temperature; [b]The yield refers to isolated products which exhibit physical and spectral properties (NMR spectra) in agreement with the assigned structures; [c]Reaction in an oil bath (Δ) previously set at the temperature of the microwave experiments. (d: days; h: hours).

We observe that the reaction yields are lower for dimethyl-malonate either with alicyclic or cyclic amines when compared to other esters (Entries 13–15). It is noteworthy that the reaction is also working for enolisable esters (which is not the case with the substrates used by Varma and Naicker[9]). The referee suggest that in the presence of a strong base, a ketene may be invoved in this case.

The structures of the amides were assigned on the basis of their ^{1}H NMR spectra and comparison with literature data.

We compared the results of the present synthesis using microwaves with classical heating during the same time. It is noteworthy that after 3 min in the same conditions, the yields under classical heating are nearly nul. In Table 2 we report in the last column the yields after a more longer time to allow the determination.

In conclusion, microwave irradiation accelerates considerably the process of condensation as compared with classical heating.

EXPERIMENTAL SECTION

NMR spectra were measured on a Bruker FT AM 200 spectrometer using $CDCl_3$ as solvent and TMS as internal standard.

General Procedure for the Preparation of Amides

Method A (MWI)

The typical procedure for the substituted amides synthesis is as follows: potassium *tert*-butoxide (1 eq., 5.10^{-3} mol or 0.5 or 0.25 eq.) was added to a premixed mixture of amines (1 eq.) and esters (1 eq.) in the (ø: 2.5 cm) reactor of a focused microwave oven (Synthewave 402)[10] and irradiated under stirring for the specified temperature and time (see Tables 1–2). On completion of the reaction, the mixture was extracted with CH_2Cl_2.

After filtration and evaporation of the solvent, the resulting mixture was analyzed by ^{1}H NMR.

Method B (Conventional)

Reactions are performed in the same conditions in the same vessel using an oil bath previously set at the temperature measured in the microwave oven. As this study was done only for the comparison,

the products were not isolated and the ratio were determinated by ^{1}H NMR.

Acetamide:[11] Yield : 80%; Solid, m.p.: 78–80°C, ^{1}H NMR (200 MHz, $CDCl_3$): δ : 1.6 (s, 2H, $N\underline{H}_2$); 2.0 (s, 3H,$C\underline{H}_3$).

Phenylacetamide:[12] Yield : 79%; Solid, m.p.: 154–157°C, ^{1}H NMR (200 MHz, $CDCl_3$): δ : 1.95 (s, 2H, $C\underline{H}_2$); 4.69 (s, 2H, $N\underline{H}_2$); 7.10 à 7.25 (m, 5H, phenyl).

Cyanoacetamide:[13] Yield : 71%; Solid, m.p.: 120–122°C, ^{1}H NMR (200 MHz, $CDCl_3$) : δ : 3.08 (s, 2H, $N\underline{H}_2$); 3.40 (s, 2H, $C\underline{H}_2$).

Cinnamamide:[14] Yield : 84%; Solid, m.p.: 140–148°C, ^{1}H NMR (200 MHz, $CDCl_3$) : δ : 3.49 (s, 2H, $N\underline{H}_2$); 6.45 à 7.65 (dd, $C\underline{H}=C\underline{H}$); 7.35 (m, 5H, phenyl).

Methylmalonamide:[15] Yield : 43%; Solid, m.p.: 216–217°C, ^{1}H NMR (200 MHz, $CDCl_3$) : δ : 3.76 (s, 2H,$N\underline{H}_2$); 3.50 (s, 3H, $C\underline{H}_3$); 1.67 (s, 2H, $C\underline{H}_2$).

***N*-Butyl-acetamide:**[16] Yield : 70%; Brown paste, b.p.: 229°C (lit), ^{1}H NMR (200 MHz, $CDCl_3$) : δ : 3.40 (t, 1H, $N\underline{H}$); 0.87 (t, 3H, $C\underline{H}_3$); 1.40 (m, 4H, $C\underline{H}_2$-$C\underline{H}_2$); 1.95 (s, 3H, $C\underline{H}_3$-CO).

***N*-Butyl-2-phenyl-acetamide:**[17] Yield : 97%; Solid, m.p.: 105°C (114°C lit.) ^{1}H NMR (200 MHz, $CDCl_3$) : δ : 7.3 (m, 5H, phenyl); 4.55 (s, 2H, -$C\underline{H}_2$-CO); 1.40 (m, 4H, $C\underline{H}_2$-$C\underline{H}_2$); 0.9 (t, 3H, $C\underline{H}_3$)

***N*-Butyl-2-cyano-acetamide:**[18] Yield : 60%; Solid, m.p. : 148–150°C, ^{1}H NMR (200 MHz, $CDCl_3$): δ : 3.90 (t, 1H, $N\underline{H}$-CH_2); 3.45 (s, 2H, -$C\underline{H}_2$-CO); 1.65 (q, 4H, $C\underline{H}_2$-$C\underline{H}_2$); 0.9 (t, 3H, $C\underline{H}_3$).

***N*-Butyl-cinnamic-amide:**[19] Yield : 61%; Solid, m.p.: 58–60°C, ^{1}H NMR (200 MHz, $CDCl_3$) : δ : 1.01 à 1.95 (δ Butyl); 3.80 (t, 1H, $\underline{NH}$-); 6.5 à 7.7 (dd, $C\underline{H}$=$C\underline{H}$); 7.35 (m, 5H, phenyl).

***N*,*N*-Dibutyl-malonamide:**[20] Yield : 17%; Liquid, b.p.: 46–48°C/ mmHg (lit.) ^{1}H NMR (200 MHz, $CDCl_3$) : δ : 0.77 à 1.85 (δ Butyl); 3.75 (t, 1H, $\underline{NH}$-); 3.95 (s, 2H, $C\underline{H}_2$); 4.02 (s, 3H, -$C\underline{H}_3$).

1-Acetyl-piperidine:[21] Yield : 74%; Solid, m.p. : 85–87°C, ^{1}H NMR (200 MHz, $CDCl_3$) : δ : 1.55 (m, 6H, $H_2H_3H_4$); 3.05 (t, 4H, H_1H_5); 3.45 (s, 3H, -$C\underline{H}_3$).

1-Phenyl-acetyl-piperidine:[22] Yield : 70%; Solid, m.p. : 52–54°C/ 16 mmHg (lit.) ^{1}H NMR (200 MHz, $CDCl_3$) : δ : 1.60 (m, 6H, $H_2H_3H_4$); 3.20 (t, 4H, H_1H_5); 3.9 (s, 2H, -$C\underline{H}_2$); 7.25 (m, 5H, phenyl).

1-Cyanoacetyl-piperidine:[23] Yield : 75%; Solid, m.p.: 88–90°C, ^{1}H NMR (200 MHz, $CDCl_3$) : δ : 1.60 (m, 6H, $H_2H_3H_4$); 3.20 (t, 4H, H_1H_5); 3.50 (s, 2H, -$C\underline{H}_2$).

3-Phenyl-1-piperidine-1-yl-propenone:[24] Yield: 75%; Solid, m.p.: 45–47°C, ^{1}H NMR (200 MHz, $CDCl_3$) : δ: 1.55 (m, 6H, $H_2H_3H_4$); 3.05 (t, 4H, H_1H_5); 6.45 à 7.6 (dd, $C\underline{H}$=$C\underline{H}$); 7.35 (m, 5H, phenyl).

3-Oxo-3-piperidin-1-yl-propionicacid-methyl-ester:[25] Yield : 41%; Liquid, b.p.: 75–76°C (lit.) ^{1}H NMR (200 MHz, $CDCl_3$) : δ : 1.55 (m, 6H, $H_2H_3H_4$); 3.05 (t, 4H, H_1H_5); 3.7 (s, 2H, -C$\underline{H}_2$); 3.9 (s, 3H, -C$\underline{H}_3$).

***N*-Acetyl-pyrrolidine:**[26] Yield : 69%; Liquid, b.p. : 53–54°C (lit.) ^{1}H NMR (200 MHz, $CDCl_3$): δ: 1.9 (m, 4H, H_2H_3); 3.5 (t, 4H, H_1H_4); 3.75 (s, 3H, -C$\underline{H}_3$).

1-Phenylacetyl-pyrrolidine:[27] Yield : 63%; Liquid, b.p.: 47–50°C (lit.) ^{1}H NMR (200 MHz, $CDCl_3$) : δ: 1.85 (m, 4H, H_2H_3); 3.45 (t, 4H, H_1H_4); 3.99 (s, 2H, -C$\underline{H}_2$); 7.4 (m, 5H, phenyl).

1-(Cyanoacetyl)-pyrrolidine:[28] Yield : 78%; Solid, m.p. : 35–37°C, ^{1}H NMR (200 MHz, $CDCl_3$) : δ: 1.95 (m, 4H, H_2H_3); 3.45 (t, 4H, H_1H_4); 3.80 (s, 2H, -C$\underline{H}_2$).

1-Cinnamoyl-pyrrolidine:[29] Yield : 68%; Solid, m.p. : 47–49°C, ^{1}H NMR (200 MHz, $CDCl_3$) : δ: 1.85 (m, 4H, H_2H_3); 3.3 (t, 4H, H_1H_4); 6.5 à 7.7 (dd, -C$\underline{H}$ = C$\underline{H}$-); 7.5 (m, 5H, phenyl).

3-Oxo-3-pyrrolidin-1-yl-propionicacid-methyl-ester:[30] Yield : 51%; Liquid, b.p.: 65–67°C (lit.) ^{1}H NMR (200 MHz, $CDCl_3$) : δ: 1.85 (m, 4H, H_2H_3); 3.25 (t, 4H, H_1H_4); 3.75 (s, 2H, -C$\underline{H}_2$); 3.95 (s, 3H, -C$\underline{H}_3$).

REFERENCES

1. North, M. Contemp. Org. Synth. **1994**, I, 475.
2. Beckwith, A.L.J. In *The Chemistry of Amides: Synthesis of Amides*; Zabicky, J., Ed.; Interscience: New York, 1970; p 96.
3. (a) Koo, J.; Avakian, S.; Martin, G.J. J. Am. Chem. Soc. **1995**, *77*, 5373; (b) Dessai, M.; Watthey, J.W.H.; Zuckerman, M. Org. Prep. Proced. Int. **1976**, *8*, 85; (c) Butora, C.; Blaha, L.; Rajsner, M.; Helfert, I. Collect. Czech. Chem. Commun. **1992**, *57*, 1967; (d) Boschi, D.; Stilo, A.D.; Fruttero, R.; Medana, C.; Sorba, G.; Gasco, A. Arch, Pharm. (Weinheim Ger) **1994**, *327*, 661; (e) Novelli, F.; Sparatore, F. Farmaco. **1996**, *51*, 551.
4. (a) Althuis, T.H.; Hess, H.J. J. Med .Chem. **1977**, *20*, 146; (b) Manoury, P.M.; Binet, J.L.; Dumas, A.P.; Lefevre-Borg, F. Cavero; Hardstone, J.D.; Lewis, B.N.; Plamer, M.J. J. Med. Chem. **1987**, *30*, 49.
5. Marsh, J. *Advanced Organic Chemistry*, 3rd Ed.; J .Wiley & Sons: New York, 1985; 375.
6. Basha, A.; Lipton, M.; Weinreb, S.M. Tetrahedron Lett. **1977**, 4171.
7. For recent review on Microwave assisted reactions, see: (a) Abramovitch, R.A. Org. Prep. Proced. Int. **1991**, *23*, 683; (b) Caddick, S. Tetrahedron **1995**, *51*, 10403; (c) Galema, S.A. Chem. Soc. Rev. **1997**, *26*, 233; (d) Loupy, A.; Petit, A.; Hamelin, J.;

Texier-Boullet, F.; Jacquault, P.; Mathé, D. Synthesis **1998**, 1213; (e) Varma, R.S. Green Chemistry **1999**, 43.
8. Chou, W.C.; Tan, C.W.; Chen, S.F.; Ku, H. J. Org. Chem. **1998**, *63*, 10015.
9. Varma, R.S.; Naicker, K.P. Tetrahedron Lett. **1999**, *40*, 6177.
10. We used a focused microwave oven: Synthewave 402®. This oven is fitted with an open reactor vessel and a stirring device. R. Commarmot, R. Diderot, J.F. Gardais, Rhone-Poulenc/Prolabo, Patent Number 84/03496. Octobre 27th **1986**. The temperature is measured by an IR captor, Prolabo, Patent Number 62241D. 14669 FR. Decembre 23rd **1991**.
11. Charles, L.P.; Nunez, O. J. Am. Chem. Soc. **1987**, *109*, 522.
12. Arndt, F.; Eistert, B. Chem. Ber. **1935**, *68*, 200.
13. Mahajan, J.R.; Ferreira, G.A.L.; Araujo, H.C.; Nunes, B.J. Synthesis **1976**, 112.
14. Levin, J.I.; Turos, Ed.; Weinreb, S.M. Synth. Commun. **1982**, 989.
15. Paraskewas, S. Synthesis **1974**, 574.
16. Heyns, K.; Von Bebenburg, W. Chem. Ber. **1953**, *86*, 278.
17. Glasoe, P.K.; Scott, L.D.; Audrieth, L.F. J. Am. Chem. Soc. **1941**, *63*, 2965.
18. Shukla, J.S.; Bhatia, P. J. Indian. Chem. Soc. **1978**, *55*, 281.
19. Parfenov, E.A.; Smirnov, L.D. Chem. Heterocycl. Compd. **1991**, *27*, 799.
20. Kisenyi, J.M.; Willey, G.R.; Drew, M.G.B. J. Chem. Soc. Dalton. Trans. **1985**, 1073.
21. Marvel, C.S.; De Radzitzky, P.; Brader, J.J. J. Am. Chem. Soc. **1955**, *77*, 5997.
22. Chou, W.C.; Chou, M.C.; Lu, Y.L.; Chen, S.F. Tetrahedron Lett. **1999**, *40*, 3419.
23. Werner, A.; Guareschi, A. Chem. Ber. **1892**, 326.
24. Pollard, A.; Mattson, D. J. Am. Chem. Soc. **1956**, *78*, 4089.
25. Palasz, P.D.; Utley, J.H.P. J. Chem. Soc. Perkin Trans. 2 **1984**, *4*, 807.
26. Dendrinos, K.; Jeong, J.; Huang, W.; Kalivretenos, A.G. Chem. Commun. **1998**, *4*, 499.
27. Cossy, J.; Pale-Grosdemange, C. Tetrahedron Lett. **1989**, *30*, 2771.
28. Gazit, A.; Osherov, N.; Posner, I.; Yaish, P. J. Med. Chem. **1991**, *34*, 1896.
29. Gasanov, R.G.; Videnska, S.O.; Ilinskaya, L.V. Russ. Chem. Bull. **1994**, *43*, 1688.
30. Box, V.G.S.; Marinovic, N.; Yiannikouros, G.P. Heterocycles **1991**, *32*, 245.

Received in the UK August 6, 2001

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016