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Solvent-free synthesis of 4-aryl substituted 5-alkoxycarbonyl-6-methyl-3,4-dihydropyridones under microwave irradiation

Hortensia Rodríguez,[a] Margarita Suarez,[a] Rolando Pérez,[a] Alain Petit[b] and André Loupy[b,*]

[a]*Laboratorio de Síntesis Orgánica, Facultad de Química, Universidad de La Habana, 10400 Ciudad Habana, Cuba*
[b]*Laboratoire des Réactions Sélectives sur Supports, ICMMO, Université Paris-Sud, CNRS, UMR 8615, Bâtiment 410, 91405 Orsay Cedex, France*

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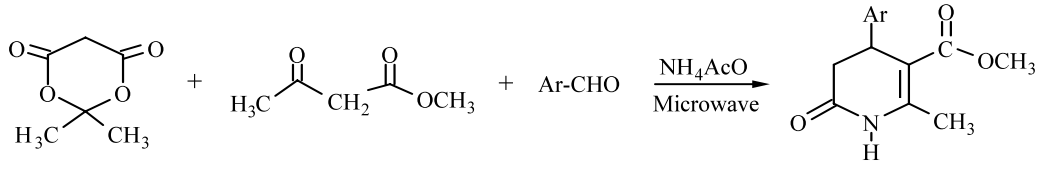
Abstract—4-Aryl substituted 5-alkoxycarbonyl-6-methyl-3,4-dihydropyridones have been prepared in one-pot condensation from Meldrum's acid, methyl acetoacetate and the appropriate benzaldehyde in the presence of ammonium acetate using microwave irradiation without solvent. This rapid method produced pure products in high yields (81–91%) due essentially to a specific non-thermal microwave effect (17–28%) by conventional heating under the same conditions.

Microwave activation as a non-conventional energy source has became an important method that can be used to carry out a wide range of reactions within short reaction times and with high yield and regioselectivity, essentially in the absence of solvents.[1–6] There has been growing interest in such methodology over the last 5 years, thus opening new horizons in the search of suitable drug candidates such as heterocyclic systems. Some studies have been published on syntheses using microwave irradiation of a wide variety of heterocycles as for example hexahydroquinoleines[7] and unsymmetrical 1,4-dihydropyridines,[7,8] imidazopyridines,[8] octahydroquinolines,[9] pyridopyrimidones,[10] dihydropyrimidines[11] and pyrazoloquinolines,[12] decahydroacridines[13] and dihydropyrimidinethiones.[14]

The research on the 1,4-dihydropyridines (1,4 DHP) systems is of current interest due to their exceptional properties as calcium antagonists.[15–17] Substitution on the 1,4 DHP ring has been widely studied[18] due to the important effects of some substituents on their biological activities.



1 **2** **3a-g** **4a-g**

4a Ar = C_6H_5 **4d** Ar = 2-Cl-C_6H_4
4b Ar = 3-NO_2-C_6H_4 **4e** Ar = 4-Cl-C_6H_4
4c Ar = 4-NO_2-C_6H_4 **4f** Ar = 4-CH_3OOC-C_6H_4
4g Ar = 2,4-di-NO_2-C_6H_4

Scheme 1.

Keywords: microwave irradiation; solvent-free synthesis; dihydropyridones.
* Corresponding author. Fax: +33 1 69 15 46 79; e-mail: aloupy@icmo.u-psud.fr

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In connection with our previous studies in the field of novel calcium channel blockers,[19,20] and in the use of non-conventional techniques in the synthesis of this class of compounds,[21] we describe here a facile one-pot condensation reaction of 4-aryl substituted 5-alkoxycarbonyl-6-methyl-3,4-dihydropyridones using microwave irradiation. These compounds are important key intermediates for the preparation of *o*-chloroformyl 1,4-DHPs by the Vilsmeier Haack reaction, substances that can be further transformed in a wide variety of pyridine fused heterocyclic systems.[19,22]

Equimolecular amounts of starting compounds **1**, **2** and **3a**–**g** (see Scheme 1) were placed in a microwave monomode reactor (Synthewave S402)[1] in a cylindrical Pyrex vessel. The mixtures were irradiated at controlled temperatures and for reaction times as indicated in Table 1. Continuous mechanical stirring provided a good homogeneity of materials. When the irradiation was stopped, the solids were treated with the adequate solvents and filtered to give the pure products **4a**–**g** in 81–91% yields.

One- and two-dimensional NMR experiments confirmed the formation of the pyridone ring.[23] Their spectroscopic data were identical to those obtained from the products synthesized by following the method previously reported.[19,24,25]

All the reactions were followed by TLC and the experiments were replicated in order to ensure the reproducibility. The main results for the synthesis of compounds **4a**–**g** are indicated in Table 1.

In order to show the advantages of the microwave heating mode, Table 2 shows results for the synthesis of **4**, compared to classic methods. To check the possibility of intervention of specific non-purely thermal effects of microwaves, they are also compared to solvent-free reaction by classical heating (thermostated oil bath) in the same conditions as under microwaves (time, temperature, profiles of rise in temperature, vessels, …). The lower yields obtained with conventional heating mode, even after 2 h of reaction indicate once more that the effect of microwave irradiation is not purely thermal.

We could suggest that the improvement achieved with this method due to a strong specific MW effect is connected to the reaction mechanism and evolution of polarity during the course of the reaction.

The reaction consists in several successive steps (Scheme 2) with previous formation of two intermediates: the compound **5** resulting from Knoevenagel condensation of Meldrum acid **1** with benzaldehyde, the enamino compound **6** from β-ketoester and ammonia.

Table 1. Synthesis of **4a**–**g** under microwave irradiation

Compound	Reaction time (min)	Temperature (°C)[a]	m.p. (°C)	Yield (%)
4a	15	100	197–198 (lit.,[16] 197–198)	86
4b	10	100	205–206 (lit.,[16] 204–205)	82
4c	15	100	207–209	83
4d	10	130	199–200 (lit.,[16] 198–200)	91
4e	10	130	202–203	89
4f	15	130	186–187 (lit.,[16] 186–188)	81
4g	10	130	212–213	89

[a] The temperature was controlled throughout the reaction and evaluated by an infrared detector that indicated the surface temperature (cf. Fig. 1).

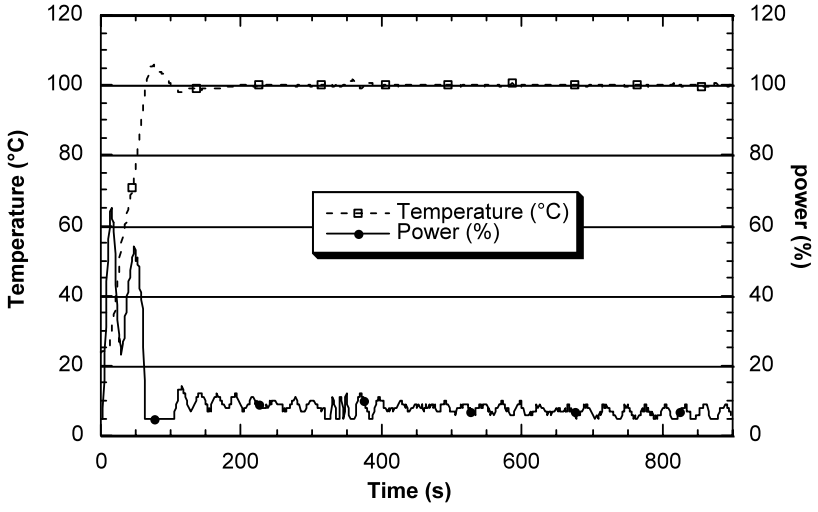
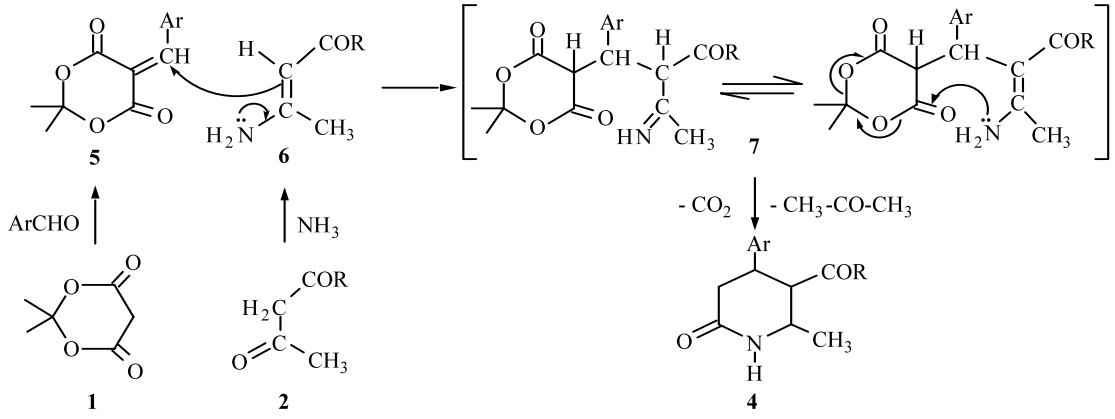


Figure 1. Profile of rise in temperature for the MW assisted solvent-free synthesis of **4a**.

Table 2. Comparison between the conventional heating (Δ) and microwave irradiation (MW) for the synthesis of compounds **4a–g**

Compound	Method	Solvent	Reaction time (min)	Temperature (°C)[a,b]	Yield (%)
4a	Δ	EtOH	360	78	26[22]
	Δ	AcOH	600	118	59[16]
	MW	None	15	100	86
	Δ	None	120	100	20
4b	Δ	EtOH	360	78	24[22]
	Δ	AcOH	600	118	63[16]
	MW	None	10	100	82
	Δ	None	120	100	17
4c	Δ	EtOH	360	78	27[22]
	MW	None	15	100	83
	Δ	None	120	100	21
4d	Δ	AcOH	600	118	60[16]
	MW	None	10	130	91
	Δ	None	360	130	38
4e	MW	None	10	130	89
	Δ	None	360	130	25
4f	MW	None	10	130	89
	Δ	None	360	130	21
4g	Δ	AcOH	600	118	61[16]
	MW	None	15	130	78
	Δ	None	360	130	28

[a] Method Δ: The temperature was controlled using a glass thermometer inside the reaction mixture.
[b] Method MW: The temperature was controlled throughout the reaction and evaluated by an infrared detector that indicated the surface temperature after calibration with an optical fibre.



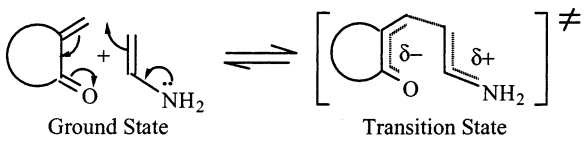
Scheme 2.

The greater acidity of Meldrum acid **1** ($pK_a = 9.97$) when compared to β-ketoester ($pK_a = 11.0$) can justify why we do not get 1,4-dihydropyridines.

Assuming that the rate-determining step of the overall reaction is the Michael-type addition of enamine **6** on ylidene compound **5**, one can expect a decrease in the energy of activation under microwaves due to a greater electrostatic stabilization of the transition state when compared to the ground state.[5] This can result from the increase in the polarity due to development of a dipole (Scheme 3).

In another way, and with the same arguments, the intramolecular nitrogen atom attack on the cyclic carbonyl group in intermediate **7** should be favoured too under MW activation as going through a dipolar transition state from a neutral ground state.

In summary, the MW-assisted procedure described here leads to high yields, in the absence of solvent, within very short reaction times and with simplified and safe work-up. It constitutes a noticeable improvement and involves 'green chemistry' techniques.



Scheme 3.

References

1. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213–1234.
2. Varma, R. S. *Green Chem.* **1999**, 43–55.
3. Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J.-L.; Petit, A. *Tetrahedron* **1999**, *55*, 10870–10951.
4. Rodríguez, H.; Pérez, R.; Suárez, M.; Lam, A.; Cabrales, N.; Loupy, A. *Heterocycles* **2001**, *55*, 291–301.
5. (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223; (b) Arrieta, A.; Lecea, B.; Cossio, F. P. *J. Org. Chem.* **1998**, *63*, 5869–5874.
6. Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
7. Suárez, M.; Loupy, A.; Pérez, E.; Morán, L.; Gerona, G.; Morales, A.; Autié, M. *Heterocycl. Commun.* **1996**, *2*, 275–280.
8. Alajarin, R.; Jordan, P.; Vaquero, J.; Alvarez-Builla, J. *Synthesis* **1995**, 389–391.
9. Tu, S.; Wei, Q.; Ma, H.; Shi, D.; Gao, Y.; Cui, G. *Synth. Commun.* **2001**, *31*, 2657–2661.
10. Quiroga, J.; Cisneros, C.; Insuasty, B.; Abonia, R.; Nogueras, M.; Sanchez, A. *Tetrahedron Lett.* **2001**, *42*, 5625–5627.
11. Stadler, A.; Kappe, C. O. *J. Chem. Soc., Perkin Trans. 2* **2000**, *27*, 1363–1368.
12. Paul, S.; Gupta, M.; Gupta, R.; Loupy, A. *Tetrahedron Lett.* **2001**, *42*, 3827–3829.
13. Suarez, M.; Loupy, A.; Salfran, E.; Moran, L.; Rolando, E. *Heterocycles* **1999**, *51*, 21–27.
14. Kidwai, M.; Saxena, S.; Mohan, R.; Venkataramanan, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1845–1846.
15. Bossert, F.; Vater, W. *Med. Res. Rev.* **1989**, *9*, 291–324.
16. Martín-Leon, N.; Seoane, C. *Quim. Ind.* **1990**, *36*, 115–127.
17. Janis, R. A.; Triggle, D. J. *J. Med. Chem.* **1983**, *26*, 775–785.
18. Kuthan, J.; Kurfurst, A. *Ind. Eng. Chem. Prod. Res. Dev.* **1982**, *21*, 191–261.
19. Verdecia, Y.; Suárez, M.; Morales, A.; Rodríguez, E.; Ochoa, E.; González, L.; Martín, N.; Quinteiro, M.; Seoane, C.; Soto, J. L. *J. Chem. Soc., Perkin Trans. 1* **1996**, 947–951.
20. Ochoa, E.; Suárez, M.; Verdecia, Y.; Pita, B.; Martín, N.; Quinteiro, M.; Seoane, C.; Soto, J. L.; Duque, J.; Pomes, R. *Tetrahedron* **1998**, *54*, 12409–12420.
21. Rodríguez, H.; Reyes, O.; Suárez, M.; Garay, H.; Pérez, R.; Cruz, L.; Verdecia, Y.; Martín, N.; Seaone, C. *Tetrahedron Lett.* **2002**, *43*, 439–441.
22. Suárez, M.; Ochoa, E.; Pita, B.; Espinosa, R.; González, L.; Martín, N.; Quinteiro, M.; Seoane, C.; Soto, J. L. *J. Heterocycl. Chem.* **1997**, *34*, 931–935.
23. Data for compound **4e**: ^{1}H NMR (DMSO-d_6): δ 9.98 (1H, brs, NH), 7.36–7.05 (4H, m, Ph), 4.67 (1H, dd, H-4, $J=8.3$ Hz, $J=1.9$ Hz), 3.58 (3H, s, OCH_3), 2.90 (1H, dd, H-3, $J=16.5$ Hz, $J=8.3$ Hz), 2.69 (1H, dd, H-3′, $J=16.5$ Hz, $J=1.9$ Hz), 2.37 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6): δ 171.5 (C2), 169.0 (COO), 146.3 (C6), 139.1, 133.0, 129.2, 128.4, 127.5, 124.0 (aryl), 106.7 (C5), 49.2 (OCH_3), 38.4 (C3), 35.1 (C4), 18.7 (CH_3). Anal. calcd for $C_{14}H_{14}ClNO_3$ (279.72): C, 60.11; H, 5.04; N, 5.01. Found: C, 60.29; H, 5.15; N, 5.19.
24. Morales, A.; Ochoa, E.; Suárez, M.; Verdecia, Y.; González, L.; Martín, N.; Quinteiro, M.; Seoane, C.; Soto, J. L. *J. Heterocycl. Chem.* **1996**, *33*, 103–107.
25. Svétlik, J.; Goljer, I.; Turecek, F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1315–1318.