SYNTHESIS OF DECAHYDROACRIDINES UNDER MICROWAVES USING AMMONIUM ACETATE SUPPORTED ON ALUMINA

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Abstract - Acridine derivatives have been synthesized under microwave irradiation under solvent-free conditions using ammonium acetate supported on neutral or basic alumina and catalytic *N,N*-dimethylformamide. The obtained results show high yields. The specific "non thermal" effect produced by microwave irradiation has been demonstrated.

INTRODUCTION

4-Aryl-1,4-dihydropyridines, also known as Hantzsch esters, have proved valuable as drugs for the treatment of cardiovascular disorders[1,2] and constitute an important class of calcium channel blockers.[3-6] The relationship between conformation and pharmacological effect in 1,4-dihydropyridines (1,4-DHPs) type compounds nifedipine-like has been reported.[7] Recent investigations carried out on rigid dihydropyridines have given information on the active conformation.[7] Thus, 4-aryl substituted 1,4-DHPs with calcium antagonist properties exist as a boat conformation in which the aryl substituent is in pseudoaxial position, orthogonal to the dihydropyridine plane.[8]

Previous reports described the synthesis of 1,4-DHPs fused to one[9] or two[10] cyclohexanone rings which present a positive ionotropic effect promoting (instead of blocking) the entry of calcium to the intracellular space (calcium agonist effect).[11]

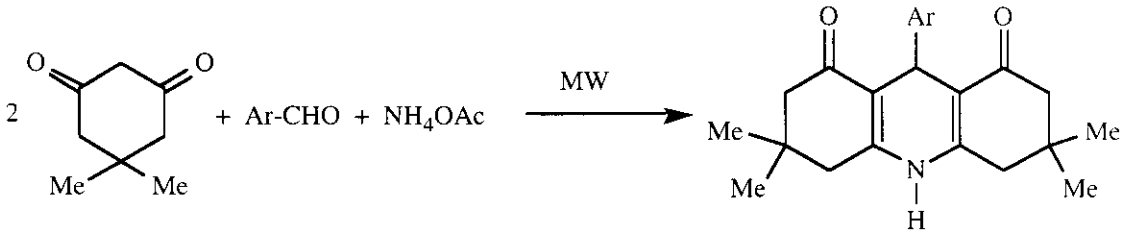
Recently, we have described the synthesis and conformational study of acridine derivatives related to 1,4-dihydropyridines.[12] Quantum chemical calculations were carried out on these molecules using the AM1 method with complete geometry optimization, suggesting that the 1,4-DHP moiety adopts a flattened boat conformation in which the carbon atoms of the two fused rings are almost in the same boat main plane. This conformation is analogous to that required for biological activity. In this case, the synthesis was carried out by the Hantzsch method. Thus, the reaction of two moles of dimedone (5,5-dimethyl-1,3-cyclohexanedione) with one mole of the corresponding aldehyde, in the presence of ammonium hydroxide.

yielded the 9-substituted 3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-diones (**I**) within 1–2 hours in 50–70% yield.

In this paper, we describe the solvent-free microwave assisted synthesis of decahydroacridine derivatives relative to 1,4-dihydropyridines showing advantages of this method compared to the reported traditional ones.[12] This study is motived by the successful synthesis in organic chemistry using microwave irradiation[13] and by our previous work concerning the preparation of different compounds of biological interest under these conditions.[14-16] The use of a domestic microwave oven coupled to supported reagents chemistry in dry media was shown to decrease reaction time and to increase seriously yields in these potential biologically active compounds.

RESULTS AND DISCUSSION

The syntheses of decahydroacridine derivatives using a solvent-free microwave assisted method were developed using a one pot reaction between two moles of dimedone with one mole of the choosen aromatic aldehyde using ammonium acetate (nitrogen donor) according to the Scheme 1.



Ia Ar = C_6H_5 **Ib** Ar = 4-$(CH_3)_2N$-C_6H_4 **Ic** Ar = 2-Cl-C_6H_4

Id Ar = 3-NO_2-C_6H_4 **Ie** Ar = 2-thienyl

Scheme 1

Taking into account our previous good results in the microwave preparation of hexahydroquinolines and unsymmetrical 1,4-dihydropyridines,[15] we obtained initially the acridine derivatives using ammonium acetate/neutral alumina and catalytic amounts of DMF, knowing its properties as an energy transfer medium allowing higher temperatures.[17] In Table 1, we report the main results obtained under these conditions.

According to the results shown in Table 1, the synthesis was carried out in good yields within very short reaction times. All reactions were followed by TLC and yields were determined in isolated products or, in one case by GC (see Table, footnote b). Experiments were duplicated in order to ensure the reproducibility of the reactions. All reactions were carried out using the conventional heating mode (oil bath) at the same final temperature and reaction times as measured in the microwave experiments. No reaction occurred under these conditions.

Table 1 - Results obtained in microwave assisted synthesis of decahydroacridines (**Ia-e**) using NH_4OAc/neutral alumina and catalytic DMF (0.5 mL)

Compound	Method	Power	Reaction Time (min)	Final Temperature (°C)	Yield (%)[b]
Ia	A	660 W	5	100-110[a]	70[c]
	B	oil bath	5	110	—
Ib	A	660 W	6	100-110[a]	50[c]
	B	oil bath	6	110	—
Ic	A	660 W	6	100-110[a]	70
	B	oil bath	6	110	—
Id	A	660 W	6	100-110[a]	60
	B	oil bath	6	110	—
Ie	A	660 W	3	100-110[a]	50[d]
	B	oil bath	3	110	—

a) Final temperatures were measured by introducion of a glass thermometer into the reaction mixture and homogenizing it just after the reaction was stopped.

b) Reactions were followed by TLC and GC.Yields were determined for isolated products, except for compound (**Ie**), which was determined from the reaction mixture by GC analyses.

c) The traditional synthesis of these compounds was reported, they were obtained under ammonium hydroxide-ethanol refluxing conditions. Yields were respectively 70% for (**Ia**) within one hour and 50% in (**Ib**) within two hours.[12]

d) Longer exposure experiments gave decomposition products.

Developed studies allow us to optimize reaction conditions for the synthesis of (**Id**) which was examined using two types of alumina as mineral solid supports (neutral or basic). We also considered catalytic amounts of liquids (0.5 mL for 1.5 mmol of reactant impregnated onto 2 g of alumina) either polar (DMF) as energy transfer medium (allowing increase in temperature into the reaction mixture) or non-polar (toluene) to evaluate the specificity of addition of polar liquids.

As can be seen in Table 2, the best results were obtained with basic alumina and catalytic amount of DMF within 1 min of exposure to microwaves.

Table 2 - Synthesis of (**Id**) under microwave irradiation

Exp.	Support Alumina[a]	Reaction Time (min)	Transfer Medium	Final Temperature (°C)[b]	Yield (%)[c]
1	neutral	6	DMF (0.5 mL)	100	75 (70)
2	neutral	6	Toluene (0.5 mL)	90	62 (50)
3	neutral	6	–	85	58 (46)
4	basic	6	DMF (0.5 mL)	140	42 (28)
5	basic	6	Toluene (0.5 mL)	130	70 (64)
6	basic	6	–	110	65 (54)
7	basic	1	DMF (0.5 mL)	120	90 (81)
8	basic	1	Toluene (0.5 mL)	105	82 (72)
9	basic	1	–	90	78 (64)

a) The starting materials were dispersed into 2 g of alumina.

b) Final temperatures were measured by introduction of a glass thermometer into the reaction mixture and homogenizing it just after the reaction was stopped.

c) Yields were determined in the crude products by GC; yields in isolated pure products are given in brackets.

In order to show the advantages of the use of basic alumina/DMF under microwave heating mode, Table 3 shows the results obtained in the synthesis of acridines (**Ia-e**), compared to classical methods employing solvents under reflux. They are also compared to solvent-free reaction by classical heating (oil bath) under the same conditions as for microwaves.

Table 3 - Comparative results obtained for the synthesis of decahydroacridines (**Ia-e**) using conventional heating (A or B) and microwave irradiation (C, Power 660 W, basic alumina, DMF 0.5 mL)

Compound	Method	Solvent	Reaction Time (min)	Temperature ^{o}C	Yield[a] %
1a	A	EtOH	60	78	70[a]
	B	none	5	110	≤ 5[b]
	C	none	5	110	85[a]
Ib	A	EtOH	120	78	50[a]
	B	none	6	110	≤ 7[b]
	C	none	6	110	70[a]
Ic	A	EtOH	60	78	65[a]
	B	none	6	110	≤ 5[b]
	C	none	6	110	75[a]
Id	A	EtOH	60	78	95[a]
	B	none	4	110	≤ 5[b]
	C	none	4	110	60[a]
Ie	A	EtOH	120	78	40[a]
	B	none	3	110	—
	C	none	3	110	50[a]

a) Yield determined in isolated product
b) Yield determined by GC.

In all the studied cases, using the microwave heating mode in solvent-free conditions, the obtained results show good yields within very short reactions times (3–6 min). This one pot reaction is faster in a microwave environment than under conventional heating mode, affording good yields in the desired products.

EXPERIMENTAL

Starting materials came from commercial sources. Uncorrected melting points were determined on an Electrothermal 9100 apparatus. Reactions were carried out in a Sanyo microwave oven equipped with a turnable plate, which allows the selection of output powers up to 800 Watts.

TLC analyses were run on 60 F_{254} silicagel chromatoplates from Merck in mixtures of n-hexane:methyl acetate 20:15 as eluent. GC analyses were performed on a Shimadzu apparatus fitted with flame ionization detector and OV-101 column (1 m x 3 mm) on chromosorb W-HP. The temperature was programmed from

80 to 300°C at 6°C/min (injector temperature 300°C). DMF and all solvents used for chromatographic analyses were HPLC grade from BDH. The supports used were neutral and basic alumina grades for column chromatography from Merck. IR spectra were recorded on a Philips Analytical PU9600 FTIR spectrophotometer. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker AC (250- ^{1}H; 62.0-^{13}C) F using TMS as the internal standard and DMSO-d_6 as the solvent. Microanalyses were performed on a Carlo Erba equipment.

General procedure to obtain acridine derivatives: 1.5 mmol of dimedone (210 mg) and 0.75 mmol of aldehyde were smoothly mixed with 2 g of neutral or basic alumina impregnated with ammonium acetate (from an aqueous solution of 1.5 mmol in 10 mL of water , and subsequent removal of water under reduced pressure) using a Teflon rod (to avoid any damage to the support particles). Then, 0.5 mL of DMF (or toluene) was previously added to the mixture which was then placed into a Pyrex-glass open vessel and irradiated for times and at tepmeratures as indicated in the Tables inside a domestic microwave oven. When the irradiation was stopped, the final temperature was measured by introducing a glass thermometer into the reaction mixture and homogenizing it in order to obtain a temperature value representative of the whole mass. Reaction products were extracted by using the adequate solvents until neither reactant nor products are detected in the support.

3,3,6,6-Tetramethyl-1,8-dioxo-9-phenyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine (Ia).
mp 190-192°C (EtOH). ^{1}H-NMR (DMSO-d_6) δ, ppm: 9.30 (s, 1H, NH), 6.99-7.21 (m, 5H, phenyl), 4.82 (s, 1H, CH), 2.29-2.49 (m, 8H, CH_2), 1.10 (s, 6H, CH_3), 1.01 (s, 6H, CH_3); ^{13}C-NMR (DMSO-d_6) δ, ppm: 187.3 (C1, C8), 149.3 (C4a, C10a), 141.0, 127.9, 126.5, 125.4 (phenyl), 114.5 (C8a, C9a), 50.2 (C2, C7), 46.6 (C4, C5), 32.6 (C9), 31.3 (C3, C6), 29.1, 27.8 (4 CH_3). IR (KBr), 3460 (NH), 1720 (C=O), 1640 (C=C) cm^{-1}. *Anal.* Calcd for $C_{23}H_{27}NO_2$: C, 79.08; H, 7.73; N, 4.01; Found: C, 79.29; H, 7.85; N, 4.16.

3,3,6,6-Tetramethyl-9-(4-*N,N'*-dimethylaminophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridine (Ib).
mp 264-266°C (EtOH). ^{1}H-NMR (DMSO-d_6) δ, ppm: 9.21 (s, 1H, NH), 6.50 (d, 2H, phenyl, J 8.1 Hz), 6.97 (d, 2H, phenyl, J 8.1 Hz) , 4.69 (s, 1H, CH), 2.80 (s, 6H, CH_3), 2.10-2.5 0 (m, 8H, CH_2), 1.01(s, 6H, CH_3), 0.88 (s, 6H, CH_3). ^{13}C-NMR (DMSO-d_6) δ, ppm: 194.5 (C1, C8), 148.6 (C4a, C10a), 148.8, 135.7, 128.1, 112.0 (phenyl), 111.9 (C8a, C9a), 50.3 (C2, C7), 40.3 (C4, C5), 40.1 [$(CH_3)_2N$], 32.1 (C9), 31.5 (C3, C6), 29.2, 26.5 (4 CH_3). IR (KBr), 3440 (NH), 1720 (C=O), 1645 (C=C) cm^{-1}. *Anal.* Calcd for $C_{25}H_{32}N_2O_2$: C, 76.50; H, 8.28; N, 7.14; Found: C, 76.97; H, 7.98; N, 7.28.

9-(2-Chlorophenyl)-3,3,6,6-Tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridine (Ic).
mp 222-224°C (EtOH). ^{1}H-NMR (DMSO-d_6) δ, ppm: 9.39 (s, 1H, NH), 6.90-7.30 (m, 4H, phenyl), 5.08 (s, 1H, CH), 2.00-2.40 (m, 8H, CH_2), 1.01 (s, 6H, CH_3), 0.90 (s, 6H, CH_3); ^{13}C-NMR (DMSO-d_6)

δ, ppm: 194.1 (C1, C8), 149.6 (C4a, C10a), 144.0, 140.0, 130.9, 128.4, 126.9, 125.6 (phenyl), 110.6 (C8a, C9a), 50.1 (C2, C7), 40.2 (C4, C5), 32.1 (C9), 31.8 (C3, C6), 29.0, 26.2 (4 CH_3). IR (KBr), 3440 (NH), 1720 (C=O), 1645 (C=C) cm^{-1}. *Anal.* Calcd for $C_{23}H_{26}NO_2Cl$: C, 71.96; H, 6.83; N, 3.65: Found: C, 72.06; H, 7.00; N, 3.71.

3,3,6,6-Tetramethyl-9-(3-nitrophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridine (Id).

mp 285-286°C. ^{1}H -NMR (DMSO-d_6) δ, ppm: 9.46 (s, 1H, NH), 7.49-7.96 (m, 4H, phenyl), 4.91 (s, 1H, CH), 1.98-2.48 (m, 8H, CH_2), 1.00 (s, 6H, CH_3), 0.85 (s, 6H, CH_3); ^{13}C-NMR (DMSO-d_6) δ, ppm: 194.4 (C1, C8), 150.0 (C4a, C10a), 149.2, 147.3, 134.4, 129.2, 122.0, 120.7 (phenyl), 110.5 (C8a, C9a), 50.0 (C2, C7), 39.1 (C4, C5), 33.5 (C9), 32.2 (C3, C6), 29.0, 26.3 (4 CH_3); IR (KBr): 3340 (NH), 1720 (C=O), 1640 (C=C), 1540, 1350 (NO_2). IR (KBr), 3440 (NH), 1730 (C=O), 1645 (C=C) cm^{-1}. *Anal.* Calcd. for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10; Found: C, 70.27; H, 6.84; N, 7.25.

3,3,6,6-Tetramethyl-1,8-dioxo-9-(2-thienyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridine (Ie).

mp 278-279°C (EtOH). ^{1}H-NMR ($CDCl_3$) δ, ppm: 8.36 (s, 1H, NH), 6.61-7.26 (m, 3H, thiophenyl), 5.62 (s, 1H, CH), 2.25-2.50 (m, 8H, CH_2), 1.20 (s, 6H, CH_3), 1.09 (s, 6H, CH_3). ^{13}C-NMR (DMSO-d_6) δ, ppm: 189.9 (C1, C8), 145.0 (C4a, C10a), 139.7, 126.3, 124.5, 123.4 (thiophenyl), 115.9 (C8a, C9a), 52.2 (C2, C7), 46.2 (C4, C5), 31.1 (C9), 30.3 (C3, C6), 28.5, 26.7 (4 CH_3). IR (KBr), 3440 (NH), 1720 (C=O), 1645 (C=C) cm^{-1}. *Anal.* Calcd for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09; N, 3.94: Found: C, 71.12; H, 7.42; N, 3.52.

ACKNOWLEDGEMENT

To *Proyectos CITMA* (Cuba) for its financial support and Alejandro Alemán for the GC determinations.

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Received, 26th June, 1998