AN EFFICIENT PROCEDURE TO OBTAIN HEXAHYDROQUINOLEINES AND UNSYMMETRICAL 1,4-DIHYDROPYRIDINES USING SOLID INORGANIC SUPPORTS AND MICROWAVE ACTIVATION

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Abstract : Satisfactory yields have been obtained in a one pot synthesis of hexahydroquinoleines and unsymmetrical 1,4-dihydropyridines using acidic or basic alumina respectively using catalytic DMF under microwave activation. Results were compared with those obtained following the classical method. The advantages obtained by the use of microwave irradiation were demonstrated.

Introduction :

The research on 1,4-dihydropyridines (1,4-DHP) systems is of current interest due to their exceptional activities as calcium antagonists (1). Substitution on the 1,4-DHP ring has been widely studied (2) because of the dramatic effect that some substituents induce on their biological properties. As a fact, cyclohexanone ring fused to 1,4-DHP moiety resulted in a striking effect on the entry of calcium ions into the intracellular space (calcium agonist effect) (3).

Recent works have been devoted to the study of unsymmetrically substituted 1,4-DHP such as nimodipine (4) or amlodipine (5). Pharmacological studies showed quantitative differences in both enantiomers and consequently a great effort has been directed towards a symmetric synthesis of 1,4-DHP (6).

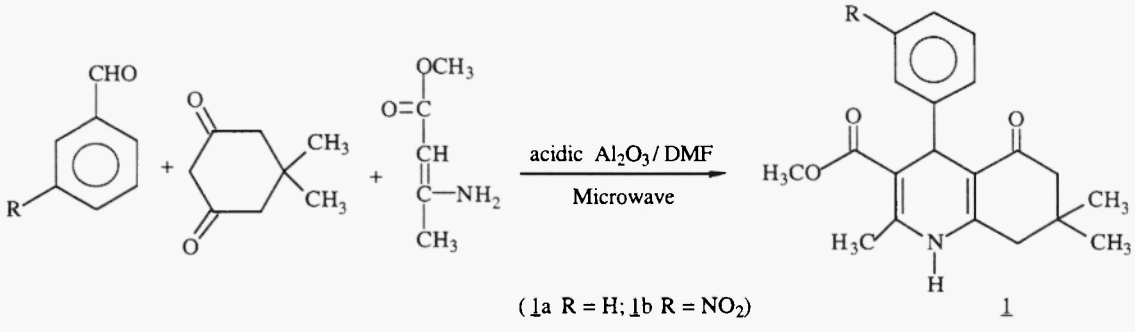
As the conventional synthesis of 1,4-DHP has been carried out most commonly by the Hantzsch method (7) or by using a modification involving enamine condensation (8), leads to moderate yields and tedious purification procedures, it seems to be necessary to find new more efficient and easy methods.

Microwave irradiation to synthesize several class of organic compounds has been successfully applied in recent years (9).The coupling of microwave heating mode with the use of mineral solid supports such as alumina, silica and clays (10) have been allowed the synthesis of several organic compounds with higher selectivity, yield and purity compared to traditional methods. Such approaches to obtain symmetrical 1,4-DHP have been reported (11).

We would like to describe an efficient procedure to obtain two hexahydroquinoleine analogues of 1,4-DHP and one unsymmetrically substituted 1,4-DHP using a "one pot" reaction of an aldehyde, a 1,3-dicarbonyl compound and methyl β-aminocrotonate on mineral solid supports under microwave irradiation. Short reaction times together with easy work up (without any further purification procedure) were the main advantages observed. All compounds reported here have been previously obtained using conventional methods (12). Reported synthesis of the unsymmetrical 1,4-DHP was carried out in more than one step, requiring first the preparation of the corresponding Knoevenagel derivative by condensation of the aldehyde with the 1,3-dicarbonyl compound (13).

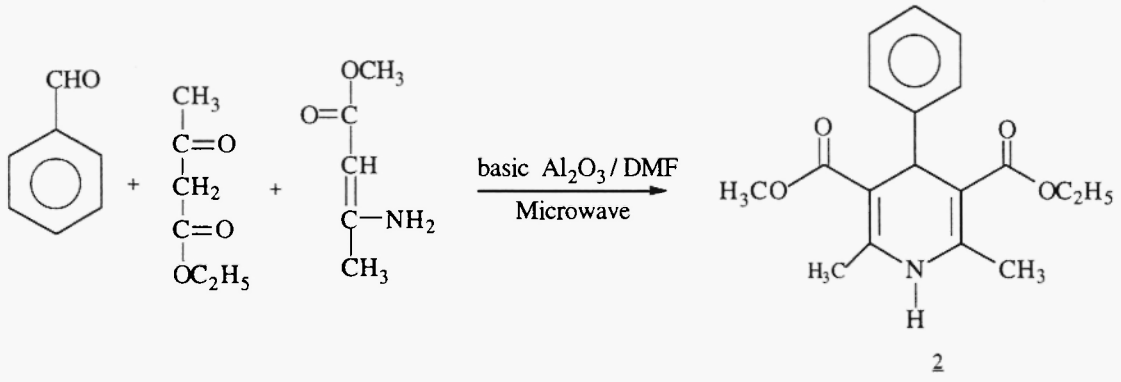
Results and Discussion.

The synthesis of hexahydroquinoleines and unsymmetrical 1,4-DHP were carried out according to schemes 1 and 2 respectively.



(1a R = H; 1b R = NO_2) 1

Scheme 1



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Scheme 2

Preliminary studies allowed us to optimize the substrate support relative amount and reaction times, and to establish the convenience to use a catalytic amount of DMF as an energy transfer medium in order to permit higher temperatures (14). All the reactions were followed by t.l.c. and yields were determined by g.c.. Experiments were replicated in order to ensure the reproducibility of

two mineral solid supports and a catalytic amount of DMF under microwave irradiation appear in Table 1.

Table 1 : Synthesis of hexahydroquinoleine 1a under microwave irradiation (6 min, power 560W).

Supports (2 g)	DMF (ml)	Final Temp. [a] (°C)	Yield (%) 1a
acidic Al_2O_3	-	80-90	~ 40
acidic Al_2O_3	0.5	120-130	≥ **95**
K10	-	70-80	< 10
K10	0.5	120-130	< 15

a) Final temperatures were measured immediately after the reaction using a glass thermometer.

According to the results shown in Table 1, synthesis of hexahydroquinoleine 1b was carried out on acidic alumina with DMF. However, the better yields in the synthesis of the unsymmetrical 1,4-DHP 2 were obtained using basic alumina with DMF. Results in the synthesis of compounds 1a, 1b and 2 appear in Table 2.

Table 2 : Synthesis of hexahydroquinoleines 1a and 1b, and unsymmetrical 1,4-DHP 2 under microwave irradiation (power 560 W).

Comp.	Support [a]	Reaction time (min)	Final temp. (°C)	Yield[b]
1a	acidic Al_2O_3	6	130-140	≥ **92** (**86**)
1b	acidic Al_2O_3	4	130-140	≥ **92** (**85**)
2	basic Al_2O_3	6	110-120	≥ **85** (**78**)

a) To the mixture of starting materials dispersed onto 2 g of the alumina were added 0.5 ml of DMF.

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

In order to show the advantages in use of acidic and basic alumina/DMF and of microwave heating mode, Table 3 shows results in the synthesis of hexahydroquinoleines and unsymmetrical 1,4-DHP respectively, compared to classical methods employing solvents under reflux. They are also compared to solvent-free reaction by classical heating in the same conditions as under microwaves.

Table 3 : Comparative results obtained in the synthesis of the compounds 1a, 1b and 2 using conventional methods (A) and microwave irradiation (B) (power = 560 W).

Comp.	Method	Solvent	Reaction time (min)	Temperature °C	Yield (%)
1a	A	EtOH	60	78	65
	B	**none**	**6**	**130**	**≥ 92**
	A	none	6	130	< 10[a]
	A	none	60	130	40[b]
1b	A	EtOH	60	78	62
	B	**none**	**4**	**130**	**≥ 92**
	A	none	4	130	< 10[a]
	A	none	60	130	45[b]
2	A	EtOH	840	78	55
	B	**none**	**6**	**120**	**≥ 85**
	A	none	6	120	≤ 5[a]
	A	none	60	120	30[b]

a) Complements to 100 % are starting materials

b) Conversions are > 90 %. Complement is constituted of decomposition and uncyclized products

Taking into account shorter reaction times and higher yields achieved by coupling acidic or basic alumina/DMF and microwave irradiation compared to those obtained by using classical methods, easier work-up, purity of derived products, it is possible to advise this method as an improvement for successful synthesis of hexahydroquinoleines 1a and 1b and unsymmetrical 1,4-DHP 2. Such an approach might be extended to other members of this important class of organic compounds.

In order to study the possible existence of a specific microwave effect in respect to conventional heating mode, a thermoregulated oil bath at 130°C was used as the source of heat in comparative experiments, under similar conditions as those carried out under microwave irradiation. Lower yields obtained with conventional heating mode, even after one hour of reaction, indicate that the effect of microwave irradiation is not purely thermal (see Tables 2 and 3).

Reactions were faster in a microwave environment than under conventional heating mode at the same temperature (classical heating for about seven minutes only afforded starting materials and traces of the desired product as determined by chromatographic analyses).

Experimental procedure

Starting materials came from commercial sources. Uncorrected melting points were determined on an Electrothermal 9100 apparatus. Reactions were carried out in a Sanyo domestic 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 a mixture of hexane:ethyl 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). All solvents used employed for chromatographic analyses and DMF were HPLC grade from BDH.

The supports used for the synthesis experiments were acidic and basic alumina grades for column chromatography from Merck and montmorillonite K10 from Fluka. I. R. spectra were recorded on a Philips Analytical PU9600 FTIR spectrometer. ^1H and ^{13}C-nmr spectra were recorded on a Bruker AC (250- ^1H; 62.0-^{13}C) F using TMS as an internal standard and DMSO-d_6 as a solvent. The mass spectra were perfomed on a Delsi/Nermag Spectral 30 spectrometer.

Procedure to obtain hexahydroquinoleines 1a and 1b: equimolar amounts (3 mmol) of methyl β-aminocrotonate, dimedone and benzaldehyde (1a) or 3-nitrobenzaldehyde (1b) were smoothly mixed with 2 g of acidic alumina using a Teflon rod (to avoid any damage to the support particles); 0.5 ml of DMF were added to the mixture which was then placed into a pyrex-glass opened vessel and irradiated in the microwave domestic 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 dichloromethane until neither reactants nor products are detected in the support; the solvent was evaporated and the solid further recristallized from adequate solvent.

Procedure to obtain unsymmetrical 1,4-DHP (compound 2): the synthesis of 2 was similar to that described for 1a and 1b replacing dimedone for ethyl acetoacetate and using benzaldehyde as the starting aldehyde and basic alumina as a support.

3-Carbonylmethoxy-5-oxo-4-phenyl-2,7,7-trimethyl-1,4,6,6,8,8-hexahydroquinoleine 1a [m.p. = 268-70 ($CHCl_3$); yield = 86%].

IR (KBr) / cm^{-1} : 3279, 1709, 1647, 1631, 1480; ^1H-nmr (DMSO-d6) δ (ppm): 1.01 (s, 6H, CH_3), 1.16 (s, 6H, CH_3), 2.27 (m, 2H, CH_2), 2.32 (m, 2H, CH_2), 2.47 (s, 3H, CH_3), 3.69 (s, 3H, CH_30), 5.15 (s, 1H, H-4), 5.97 (s, 1H, NH), 7.21-7.35 (m, 5H, H aromatics); ^{13}C-nmr (DMSO-d6) δ (ppm): 19.5 (CH_3), 27.2 (CH_3), 29.4 (CH_3), 32.7 (C7), 36.4 (C4), 40.9 (C8), 50.7 (C6), 51.0 (CH_20), 105.8 (C3), 112.5 (C4a), 125.7, 127.2 (2), 127.8 (2C), 144.0 (aryl), 144.5 (C2), 147.8 (C8a), 167.9 (COO), 194.5 (C5); MS (m / z): 325 (M^+), 248, 83, 77, 51

3-Carbonylmethoxy-5-oxo-4-(3-nitrophenyl)-2,7,7-trimethyl-1,4,6,6,8,8-hexahydroquinoleine 1b [m.p. = 223-25 ($CHCl_3$) yield = 85%]

IR (KBr) / cm^{-1} : 3270, 1720, 1681, 1510, 1482; ^1H-nmr (DMSO-d6) δ (ppm): 0.83 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.10 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.40 (m, 2H, CH_2), 3.54 (s, 3H, CH_30), 5.00 (s, 1H, H-4), 7.537.99 (m, 4H, H aromatics), 9.28 (s, 1H, NH); ^{13}C-nmr (DMSO-d6) δ (ppm): 18.3 (CH_3), 26.2 (CH_3), 29.0 (CH_3), 32.1 (C7), 36.1 (C4), 39.3 (C8), 49.9 (C6), 50.7 (CH_30), 102.2 (C3), 109.2 (C4a), 125.8, 127.3 (2C), 128.0 (2C), 145.4 (aryl), 147.5 (C2), 150.1 (C8a), 166.9 (COO), 194.3 (C5); MS (m/z): 371 (M^+), 354, 248, 84, 76, 49

3-Carbonylethoxy-5-carbonylmethoxy-2,6-dimethyl-4-phenyl-1,4-dihydropyridine 2 [m.p. = 150-52 (CH_3OH) yield = 78%]

IR (KBr) / cm^{-1} : 3344, 1688, 1652, 1630, 1488, 1442; ^{1}H-nmr (DMSO-d6) δ (ppm): 1.24 (t, 3H, CH_3), 2.28 (s, 6H, 2 CH_3), 3.62 (s, 3H, CH_3), 4.12 (m, 2H, CH_20), 4.99 (s, 1H, H-4), 6.13 (s, 1H, NH), 7.1-7.4 (m, 5H, H aromatics); ^{13}C-nmr (DMSO-d6) δ (ppm): 14.2 (CH_3), 19.3 (CH_3), 19.4 (CH_3), 39.5 (C4), 50.9 (CH_30), 59.8 (CH_20), 103.7 (C5), 103.9 (C3), 125.9, 127.3, 127.8, 128.0, 128.6, 147.7 (aryl), 144.2 (C6), 144.5 (C2), 168.2 (COO);MS (m/z): 315 (M^+), 284, 209, 77, 51

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