Synthesis of Unsymmetrically Substituted 1,4-Dihydropyridines and Analogous Calcium Antagonists by Microwave Heating

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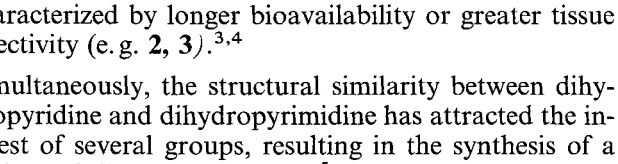
Rapid and efficient synthesis of 3,5-unsymmetrically substituted 1,4-dihydropyridines and imidazopyrimidine derivatives can be achieved under microwave irradiation using a household microwave oven.

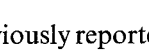
The 1,4-dihydropyridines are still the largest and most widely studied class of calcium channel blockers or "calcium antagonists",[1] and the work in this area has led to the development of many dihydropyridine derivatives, some of which have been successfully introduced as commercial products for the treatment of coronary diseases or hypertension (e.g. nifedipine, **1**).[2] Recent work in this field has been devoted to the study of unsymmetrically substituted 1,4-dihydropyridines, some of them being characterized by longer bioavailability or greater tissue selectivity (e.g. **2**, **3**).[3,4]

Simultaneously, the structural similarity between dihydropyridine and dihydropyrimidine has attracted the interest of several groups, resulting in the synthesis of a variety of dihydropyrimidines[5] and evaluation of their activity as calcium channel blockers. In addition, fused dihydropyridines and dihydropyrimidines **4** have also been recently evaluated.[6]



1: Nifedipine $R^1 = 2\text{-}NO_2$; $R^2 = R^3 = Me$

2: Nimodipine $R^1 = 3\text{-}NO_2$; $R^2 = CH_2CH_2OMe$; $R^3 = i\text{-}Pr$

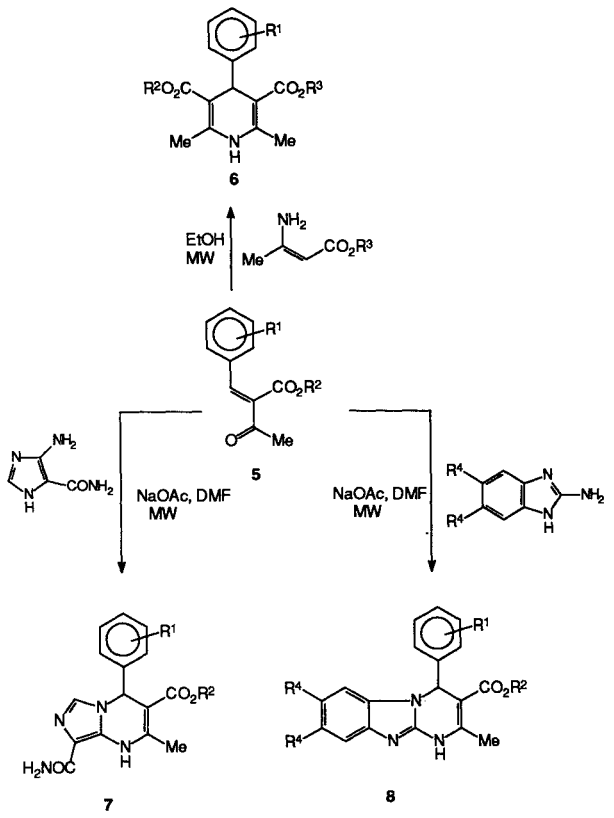
3: Furnidipine $R^1 = 2\text{-}NO_2$; $R^2 =$  ; $R^3 = Me$

4 X = C, N

Figure

In connection with our previously reported work on novel calcium channel blockers[4] and our interest in the use of nonconventional techniques in organic synthesis, we describe here the synthesis of the 3,5-unsymmetrically substituted 1,4-dihydropyridines **6**, imidazo[1,5-*a*]pyrimidine derivatives **7** and benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives **8** under microwave irradiation.

We have recently described the microwave preparation of symmetrically substituted 1,4-dihydropyridines using the one-pot condensation of an aldehyde with alkylacetoacetates and ammonia.[7] Initial attempts to prepare 3,5-unsymmetrically substituted derivatives by microwave heating resulted in disappointing yields. Under the various conditions tested (sealed and open vessels, and dry media) retro-Michael reaction and/or aromatization, leading either to the symmetrically substituted 1,4-dihydropyridines or to pyridine derivatives, were competing reactions. However, we now show how unsymmetrical 1,4-dihydropyridines **6** can be synthesized in excellent yields when a mixture of the arylmethyleneacetoacetate **5** and the β-aminocrotonate in ethanol is irradiated in a microwave oven.[8] Irradiation time, solvent amount and molar ratio of reactants were optimized for **6a** using a Simplex program.[9] The optimal conditions for **6a** were generally applied to compounds **6**, using a conventional method as control.[13] A marked rate enhancement was observed, when compared to conventional heating, as it is shown in the Table.



Scheme

It is noteworthy that unsymmetrically substituted 1,4-dihydropyridines were the reaction products obtained in all cases, except in derivatives containing a 4-(2′-nitrophenyl) substituent. These compounds are very sensitive to oxidation of the dihydropyridine ring under microwave conditions. For example, the reaction of 2-nitrophenylmethyleneacetoacetate with the corresponding β-aminocrotonate gave a mixture of 1,4-dihydropyridine **6e** (58%) and the pyridine derivative (28%). Similarly, in the formation of **6f** (64%), the corresponding pyridinedicarboxylate was obtained (26%).

Table. Preparation of 1,4-Dihydropyridines **6**, Imidazo[1,5-*a*]pyrimidine Derivatives **7** and Benzo[4,5]imidazo[1,2-*a*]pyrimidine Derivatives **8** Under Microwave Irradiation

Compound	R^1	R^2	R^3	R^4	Control[a] Yield (%)[b]	Control[a] Time (h)	Microwave[a] Yield (%)[b]	Microwave[a] mp (°C)	Time (min)	Lit. mp (°C)
6a	2-Cl	CH_2THF[c]	Me	–	81	12	82	166–167	4.5	165–167[13]
6b	3-Cl	CH_2THF[c]	Me	–	91	12	98	137–139	4.5	137–139[13]
6c	3-Br	CH_2THF[c]	Me	–	97	12	96	139–140	4.5	138–140[13]
6d	2,3-Cl_2	Et	Me	–	94	10	96	142–144	4.5	145[14]
6e	2-NO_2	CH_2THF[c]	Me	–	91	12	58	154–156	4.5	153–156[4,13]
6f	2-NO_2	Me	*i*-Pr	–	89	12	64	174–175	4.5	174[14]
6g	3-NO_2	CH_2THF[c]	Me	–	96	12	98	128–130	4.5	128–130[13]
6h	3-NO_2	CH_2THF[c]	$MeO(CH_2)_2$	–	95	12	94	108–110	4.5	109–111[13]
7a	2-NO_2	CH_2THF[c]	–	–	80	48	80	267–268	1	267–268[10]
7b	3-NO_2	*i*-Pr	–	–	74	24	78	253–255	1	254–256[10]
8a	3-NO_2	*i*-Pr	–	H	78	24	83	280–281	1	280–281[10]
8b	3-NO_2	$MeO(CH_2)_2$	–	H	68	48	73	>350	1	>350[10]
8c	2,3-Cl_2	Me	–	Me	70	24	75	294–296	1	294–296[10]

[a] Microwave and control reactions were carried out in EtOH for **6** and in dimethylformamide (DMF) for **7** and **8**; For compounds **6**, yields refer to product isolated by flash chromatography; for **7** and **8** to product after crystallization.
[b] All compounds were characterized by comparing with authentic samples.
[c] THF = tetrahydrofuran-2-yl.

We also tested the reaction between arylmethyleneacetoacetates and aminoheterocycles leading to the imidazo[1,5-*a*]pyrimidine derivatives **7** and benzo[4,5]imidazo[1,2-*a*]pyrimidine derivatives **8**, which showed promising activity as calcium channel blockers.[10] The reactions were explored using different solvents as energy-transfer media. The yields of these compounds were about 40–60% in alcoholic solvents, while in DMF the yields clearly increased and a significant reduction of the reaction time was observed (8 min versus 1 min). In these series, the optimal conditions found for **8c** were also generally applied and the oxidation of the dihydropyrimidine moiety was not observed in any case.

To summarize, microwave irradiation allows for the preparation of different families of classical and newer calcium antagonists in good yields and in much shorter periods of time than with conventional heating. The extension of this technique to the rapid synthesis of other biologically active heterocycles is currently under investigation.

All melting points were determined on a Buchi SMP-20 apparatus and are uncorrected. IR spectra were obtained as KBr disks on a Perkin-Elmer 1310 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Unity 300 and determined in $(CD_3)_2SO$ and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. Microwave digestion bomb model 4781 was obtained from Parr Instrument Company, Illinois, USA. A domestic microwave oven, Balay model BA HN991 AA703, was used. The oven has a variable timing cycle from 5 s to 45 min and a continuous variable heating cycle from 90 through 500 W of power output. The microwave frequency is 2.45 MHz and the oven's capacity is 18 L. Power generated by the oven was measured before every experiment by the method described by Watkins.[11] All chemicals were purchased from the Aldrich Chemical Co., Ltd., and were used without further purification. Silica gel (Merck, 230–400 mesh) was used as received. The arylmethyleneacetoacetates **5** were prepared as previously reported.[12,13] Compounds **6–8** exhibited physical and spectral properties in accordance with previously reported structures.

4-Aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates 6; General Procedure for Microwave Method:

The arylmethyleneacetoacetate **5** (8 mmol), β-aminocrotonate (4 mmol) and EtOH (4.5 mL) were charged to a Teflon vessel (23 mL capacity) and placed in the microwave digestion bomb. The mixture was irradiated in an oven at 400 W for the time shown in the Table. The digestion bomb was cooled in ice and the reaction mixture was chromatographed. Compounds **6** were eluted with hexane/EtOAc 7:3.

Felodipine **(6d)**: mp 142–144°C (isopropyl ether) (Lit.[14] 145°C).

IR (KBr): ν = 3340, 1680, 1620, 1500, 1440, 1310, 1280, 1040, 990 cm^{-1}.

^{1}H NMR (300 MHz): δ = 6.7–7.3 (m, 3H); 6.25 (bs, 1H); 5.37 (s, 1H); 3.98 (q, 2H); 3.56 (s, 3H); 2.21 (s, 6H); 1.08 (t, 3H).

Furnidipine **(6e)**: mp 154–156°C (EtOH) (Lit.[13] 153–156°C).

IR (KBr): ν = 3284, 3095, 2889, 1694, 1525, 1496, 1352, 1304, 1201, 1092 cm^{-1}.

^{1}H NMR (300 MHz): δ = 7.6–7.1 (m, 5H, Ar and NH); 5.67 (s, 1H); 4.4–4.2 (m, 2H); 3.86 (t, 2H); 3.7–3.1 (dd, 1H); 3.49 (s, 3H); 2.36 (s, 3H); 2.17 (s, 3H), 2.0–1.4 (m, 4H).

1,4-Dihydroimidazo[1,5-*a*]pyrimidine Derivatives 7 and 1,4-Dihydrobenzo[4,5]imidazo[1,2-*a*]-pyrimidine Derivatives 8; General Procedure:

A mixture of the arylmethyleneacetoacetate **5** (2.25 mmol), 4-amino-5-carbamoylimidazole[15] or 2-aminobenzimidazole or 2-amino-5,6-dimethylbenzimidazole (2.25 mmol), NaOAc (4.8 mmol) and DMF (2.7 mL) were irradiated under the conditions indicated above for **6**. The reaction mixture was poured into ice–water (15 mL) and the precipitate formed was collected by filtration, washed with water (3 × 5 mL) and recrystallized from DMF/H_2O, affording pure compounds **7** and **8**.

7a: mp 267–268°C (Lit.[10] 267–268°C).

IR (KBr): ν = 1658, 1586, 1525 cm^{-1}.

^{1}H NMR (300 MHz): δ = 9.37 (bs, 1H, NH); 7.9–7.3 (m, 5H, Ar–H nitrophenyl and 5-H); 7.20 and 7.11 (two bs, 2H, $CONH_2$); 6.77 and 6.76 (two s, 1H, 4-H diastereomeric); 3.9–3.4 (m, 5H, CO_2CH_2, 2′-CH and 5′-CH_2); 1.8–1.2 (m, 4H, 3′-CH_2 and 4′-CH_2).

8a: mp 280–281°C (Lit.[10] 280–281°C).

IR (KBr): ν = 1572, 1521, 1247 cm^{-1}.

^{1}H NMR (300 MHz): δ = 10.90 (bs, 1 H, NH); 8.3–7.5 (m, 4 H, Ar–H nitrophenyl); 7.34 and 7.29 (2 d, 2 H, J = 7.8 Hz, 392 (21)5-H and 8-H); 7.03 and 6.78 (2 dt, 2 H, J = 7.8, 1.1 Hz, 6-H and 7-H); 6.61 (s, 1 H, 4-H); 4.83 (m, 1 H, J = 6.2 Hz, OCH); 2.45 (s, 3 H, =C–Me); 1.24 (d, 3 H, J = 6.2 Hz, CHMe); 0.97 (d, 3 H, J = 6.2 Hz, CHMe).

8c: mp 294–296 °C (Lit.[10] 294–296 °C).

IR (KBr): ν = 1583, 1265, 1246 cm^{-1}.

^{1}H NMR (300 MHz): δ = 10.89 (bs, 1 H, NH); 7.5–6.7 (m, 6 H, Ar–H dichlorophenyl, benzimidazole and 4-H); 3.50 (s, 3 H, CO_2Me); 2.42 (s, 3 H, =C–Me); 2.17 (s, 3 H, Me benzimidazole); 2.13 (s, 3 H, Me benzimidazole).

4-Aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates 6; General Procedure for Controls:

The arylmethyleneacetoacetate **5** (5 mmol) and β-aminocrotonate (6 mmol) in ethanol (6 mL) were refluxed for the time shown in the Table. The reaction mixture was worked up as indicated above in the microwave method.

1,4-Dihydroimidazo[1,5-*a*]pyrimidine Derivatives 7 and 1,4-Dihydrobenzo[4,5]imidazo[1,2-*a*]-pyrimidine Derivatives 8; General Procedure for Controls:

A mixture of arylmethyleneacetoacetate **5** (2.25 mmol), 4-amino-5-carbamoylimidazole (2.25 mmol) or 2-aminobenzimidazole or 2-amino-5,6-dimethylbenzimidazole and NaOAc (380 mg, 4.72 mmol) in DMF (2.6 mL) was stirred at r.t. for 15 min and then heated at 65 °C for 24 h. The reaction mixture was worked up as above indicated in the microwave method.

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