Facile synthesis of Hantzsch 1,4-dihydropyridines with unsymmetrical 2,6- and 3,5-substituents

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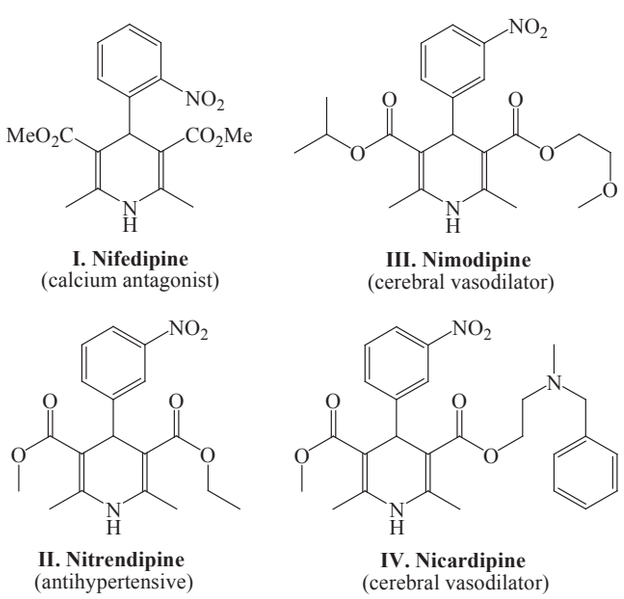
A facile synthesis of Hantzsch 1,4-dihydropyridines with unsymmetrical 2,6- and 3,5-substituents in a one-pot two-step tandem reaction under solvent-free conditions, promoted by microwave irradiation, has been developed. No catalysts are used and the work-up is easy. This approach provides a convenient, efficient and practical synthesis of 1,4-dihydropyridines having non-identical substituents at the 2,6- and 3,5- positions, which are not easily accessed by the classical Hantzsch synthesis.

Keywords: 1,4-dihydropyridines, Hantzsch reaction, one-pot two-step synthesis, microwave irradiation, solvent-free reaction

1,4-Dihydropyridines (DHPs), in particular 4-aryl-1,4-dihydropyridines, are an important class of organic compounds in the field of drugs and pharmaceuticals.[1,2] The DHP moiety is common in numerous bioactive compounds that include various antihypertensive, vasodilator, antimutagenic, bronchodilator, hepatoprotective, antiatherosclerotic, antitumour, geroprotective, and antidiabetic agents.[3–11] The most important class of calcium channel modulators is represented by nifedipine (**I**), a well-known commercialised calcium channel blocker of a unsymmetrically substituted 4-aryl-1,4-dihydropyridine.[12–14]

1,4-Dihydropyridines with non-identical 3,5-ester groups on the ring are in many cases superior to those with identical ester group substitution.[12] In fact, installation of different ester groups in the 3,5-positions of the DHP ring leads to the second generation of drugs for the treatment of cardiovascular and hypertension diseases, such as nitrendipine (**II**) (antihypertensive), nimodipine (**III**) (cerebral vasodilator), and nicardipine (cerebral vasodilator) (**IV**).[12] Some of these 1,4-DHPs are known to be useful for the regeneration of the reduced form of nicotinamine adenine dinucleotide (NADH), an essential compound for living organisms.[15,16]



I. Nifedipine
(calcium antagonist)

III. Nimodipine
(cerebral vasodilator)

II. Nitrendipine
(antihypertensive)

IV. Nicardipine
(cerebral vasodilator)

Fig. 1 Substituted 1,4-dihydropyridines used as drugs.

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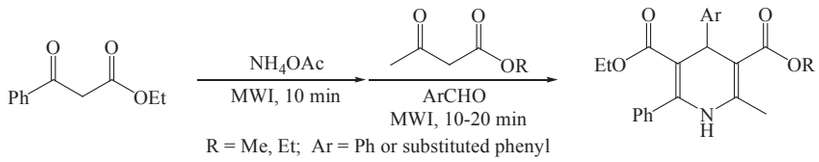
The classical synthesis of symmetrically substituted 1,4-dihydropyridines is the Hantzsch reaction, a one-pot three-component condensation of an aldehyde, β-ketoester, and ammonia catalysed by an acid. This reaction is usually conducted in refluxing ethanol.[17] However, this method cannot be applied for the preparation of differently substituted 1,4-DHPs because with two different types of β-ketoesters the Hantzsch reaction will give rise to a mixture of the DHP products. Several modifications have been made for this classical procedure.[12,18–24] Microwave irradiation has been successfully employed to accelerate the Hantzsch condensation reaction of 1,4-DHPs.[25–29] However, few reports on using a one-pot procedure for the preparation of unsymmetrically substituted 1,4-DHPs have been found. Hence, the development of new methods leading to DHPs with different substituents at the 2,6- and 3,5-positions on the dihydropyridine ring by a convenient and efficient way is of great interest for medicinal and synthetic organic chemists.

A survey of the Hantzsch reaction mechanism reveals the intermediacy of the Knoevenagel condensation product between the aldehyde and β-ketoester and the 3-aminocrotonate resulting from the reaction of the β-ketoester with ammonia. This implies that the synthesis of 1,4-DHPs with non-identical substituents at the 2,6- or 3,5-positions might be achieved by the reaction of the two types of intermediate products bearing different ester groups. Such an approach, however, includes the independent formation and separation of the Knoevenagel condensation product and the 3-aminocrotonate as starting materials, respectively, which is obviously complicated and inconvenient. We report here a new synthetic procedure for the straightforward synthesis of 1,4-DHPs with different 2,6- and 3,5-substituents.

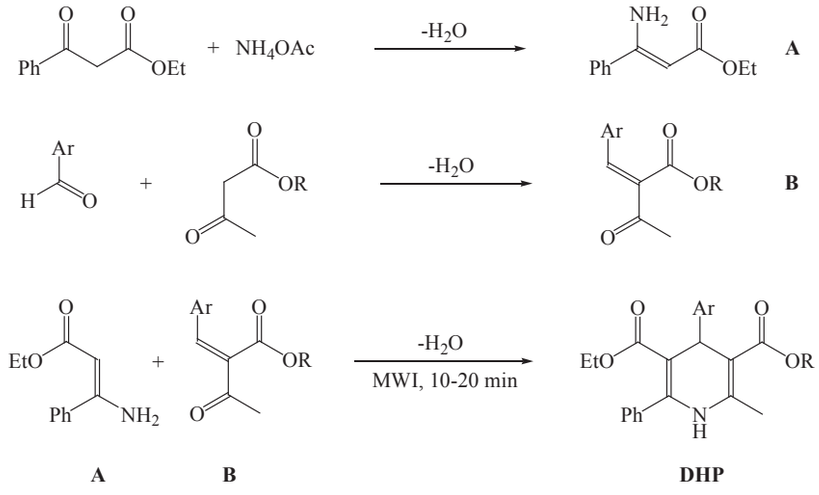
Results and discussion

This one-pot two-step protocol for the preparation of unsymmetrically substituted 1,4-DHPs can be carried out by first reacting ethyl benzoylacetate with ammonium acetate, and then methyl (ethyl) acetoacetate with an aromatic aldehyde being added. All the reactions are finished in one-pot with two steps under solvent-free conditions and are promoted by microwave irradiation without using any catalyst as shown in Scheme 1.

The results of the reactions are presented in Table 1. It is thought that the reaction proceeds first with the formation of aminocinnamate **A** from ethyl benzoylacetate and ammonium acetate; it is then followed by the Knoevenagel condensation of methyl or ethyl acetoacetate with the aromatic aldehyde leading to arylmethylideneacetoacetate **B** (Scheme 2).



Scheme 1 One-pot two step synthesis of an unsymmetrically substituted 1,4-dihydropyridine DHP.



Scheme 2 Formation route of unsymmetrically substituted 1,4-dihydropyridine DHP.

The conjugate addition of aminocinnamate **A** to arylmethylideneacetoacetate **B** and subsequent intramolecular cyclisation affords the final products, namely 4-aryl-2-methyl-6-phenyl-1,4-dihydropyridine-3,5-dicarboxylates in moderate to high yields. The successive preparation procedure of one-pot with two steps reactions in the same pot eliminates the necessity of separating the two intermediate products **A** and **B** and averts the problem of forming mixed DHP products. Table 1 shows that a wide range of substituents can be incorporated in the 4-aryl ring, including the hydroxyl and the azido groups.

Conclusions

In summary, we have presented a facile protocol for the straightforward synthesis of Hantzsch 1,4-DHPs with unsymmetrical 2,6- and 3,5-substituents, which is characterised by a one-pot, two-step and four-component tandem reactions under solvent-free conditions promoted by microwave irradiation. No catalysts are used and the work-up is easy. This provides a convenient, efficient and practical synthesis to the differently substituted 2,6- and 3,5-dihydropyridines, which are otherwise difficult to access by the classical Hantzsch 1,4-dihydropyridine synthesis. Further expanding the reaction scope, the applications of this strategy in the synthesis of biologically active asymmetrically substituted DHP derivatives and the reaction mechanism will be investigated.

Experimental

^{1}H and ^{13}C NMR spectra were determined with a Bruker Avance 300 spectrometer in DMSO-d_6 solutions unless otherwise stated with TMS as internal reference (300 MHz for ^{1}H and 75 MHz for ^{13}C). The chemical shifts (δ) are reported in ppm and coupling constants (J) are given in Hz. IR spectra were recorded on a Bruker Tensor 27 spectrometer in KBr plates. Mass spectra were recorded with an Agilent 5973N MSD spectrometer in EI mode at 70 eV. Elemental analyses were carried out on a Perkin-Elmer PE-2400 II HONS

Table 1 One-pot two-step synthesis of mixed 2,6- and 3,5-substituted 1,4-DHPs

Entry	Ar	R	Time /min	Yield /%	M.p./°C
1	C_6H_5	Me	20	81	156–157
2	4-FC_6H_4	Me	20	85	169–170
3	4-ClC_6H_4	Me	20	86	168–169
4	4-BrC_6H_4	Me	20	85	154–156
5	4-IC_6H_4	Me	20	80	167–169
6	2-$O_2NC_6H_4$	Me	30	62	142–144
7	3-$O_2NC_6H_4$	Me	25	86	170–171
8	4-$O_2NC_6H_4$	Me	20	85	112–114
9	3-HOC_6H_4	Me	20	85	234–235
10	4-HOC_6H_4	Me	20	83	218–210
11	4-$MeOC_6H_4$	Me	20	86	158–159
12	3,4-$Cl_2C_6H_3$	Me	20	81	169–171
13	4-$Me_2NC_6H_4$	Me	25	75	169–170
14	4-HO-3-$MeOC_6H_3$	Me	20	87	197–199
15	3,5-Br_2-4-HOC_6H_2	Me	20	81	180–182
16	2-Furanyl	Me	20	80	132–134
17	3-ClC_6H_4	Me	20	76	153–155
18	3-$N_3C_6H_4$	Me	20	81	158–160
19	4-$N_3C_6H_4$	Me	20	82	126–128
20	C_6H_5	Et	25	75	119–121
21	4-FC_6H_4	Et	20	76	136–138
22	4-ClC_6H_4	Et	20	76	161–163
23	4-BrC_6H_4	Et	20	74	156–157
24	4-IC_6H_4	Et	20	70	144–146
25	3-$O_2NC_6H_4$	Et	20	76	199–202, 200–201[30]
26	4-$O_2NC_6H_4$	Et	20	75	135–137
27	3-HOC_6H_4	Et	20	78	131–133
28	4-HOC_6H_4	Et	25	75	180–182
29	4-$Me_2NC_6H_4$	Et	30	71	178–180
30	4-$MeOC_6H_4$	Et	20	83	130–132
31	3,4-$Cl_2C_6H_3$	Et	20	72	152–154
32	3-ClC_6H_4	Et	20	74	168–170
33	3-$N_3C_6H_4$	Et	20	75	124–126
34	4-$N_3C_6H_4$	Et	20	77	108–109
35	4-HO-3-$MeOC_6H_3$	Et	20	79	175–176
36	3,5-Br_2-4-HOC_6H_2	Et	20	89	177–179
37	2-Furanyl	Et	20	76	105–106

analyser. Melting points are uncorrected. 2-Furaldehyde, ethyl and methyl acetoacetate, and ethyl benzoylacetate were all reagent grades and were redistilled *in vacuo* before use. The synthetic reactions were carried out in a Computer Microwave Solid-Liquid Synthesizer/ Extraction Work Station XH-200A (0–1000 W and 0–300 °C) (Beijing Xianghu Science and Technology Development Company, Ltd.) and performed in open vessels. The reaction temperature was set as needed and monitored automatically.

General procedure

A mixture of ethyl benzoylacetate (0.96 g, 5 mmol) and ammonium acetate (0.77 g, 10 mmol) was irradiated with microwave (600 W) at 80 °C for 10 min. Methyl (ethyl) acetoacetate (5 mmol) and the appropriate aromatic aldehyde (5 mmol) were added to the resulting mixture and heating was continued at 80 °C for 10–20 min with microwave irradiation (600 W). Upon completion of the reaction as monitored by TLC, the crude mixture was purified by flash column chromatography on silica gel (300–400 mesh) eluted with petroleum ether–ethyl acetate to afford the pure products. All the new compounds prepared have been characterised by ^{1}H NMR, ^{13}C NMR, IR, and MS spectra and elemental analysis.

3-Ethyl 5-methyl 1 4-dihydro-6-methyl-2,4-diphenylpyridine-3,5-dicarboxylate **(1)**: Yellow crystals, m.p. 156–157 °C, yield 81%. δ_H 9.11 (s, 1 H, NH), 7.28 (m, 10 H, ArH), 4.97 (s, 1 H, CH), 3.68 (q, 2 H, J=6.9 Hz, OCH_2), 3.58 (s, 3 H, OCH_3), 2.30 (s, 3 H, CH_3), 0.69 (t, 3 H, J=6.9 Hz, CH_3); δ_C 167.3, 166.7, 149.6, 145.8, 144.3, 139.6, 136.7, 129.4, 129.2, 128.3, 127.8, 124.7, 118.5, 117.1, 104.4, 103.5, 59.9, 59.7, 39.9, 19.5, 14.3, 13.6 ppm; ν_{max} 3344, 2982, 1674, 1224, 799, 702 cm^{-1}. Anal. Calcd for $C_{23}H_{23}NO_4$: C 73.19, H 6.14, N 3.71. Found: C 73.37, H 6.07, N 3.82%.

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Electronic Supplementary Information

Physical and spectroscopic data for the compounds given in Table 1 are provided as ESI available through: stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

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