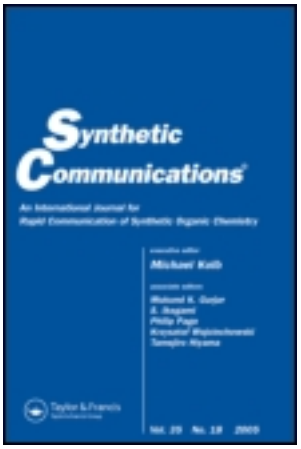

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Synthesis of 1,4-Dihydropyridine Derivatives Under Solvent-Free and Grinding Conditions

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SYNTHESIS OF 1,4-DIHYDROPYRIDINE DERIVATIVES UNDER SOLVENT-FREE AND GRINDING CONDITIONS

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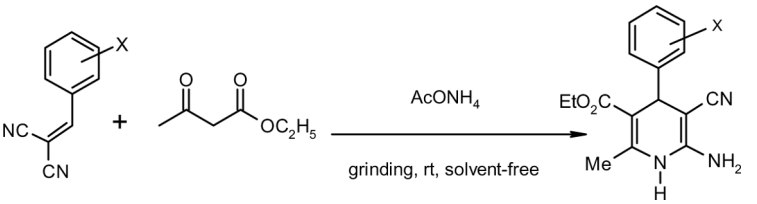
GRAPHICAL ABSTRACT



Abstract *An efficient and environmentally friendly synthesis of 6-amino-5-cyano-1,4-dihydropyridine derivatives was developed by the one-pot reaction of ethyl acetoacetate, [(2-aryl)methylene]malononitriles, and ammonium acetate at room temperature with grinding. The key advantages are the short reaction times, good yields, simple workup, and easy purification. The present method does not involve any hazardous solvent.*

Keywords 1,4-Dihydropyridines; grinding; Hantzsch reaction; multicomponent reaction; solvent-free

INTRODUCTION

1,4-Dihydropyridines (1,4-DHPs) are important class of compounds in the field of drugs and pharmaceuticals.[1–3] Hantzsch 1,4-DHPs (dialkyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates) are widely used clinically as calcium channel blockers for the treatment of cardiovascular diseases, including hypertension and angina pectoris. 1,4-DHPs possess a variety of biological activities,[4] such as vasodilator, bronchodilator, antiatherosclerotic, antitumor, and antidiabetic activities. Recent studies have revealed that 1,4-DHPs exhibit several medicinal applications,[5] which include neuroprotectant and platelet anti-aggregatory activity, in addition to cerebral anti-ischemic activity in the treatment of Alzheimer's disease and as a chemosensitizer in tumor therapy. Structure–activity relationships (SARs) show that the combination of the substituents at the C3, C4, and C5 positions of Hantzsch esters modulates the activity and tissue selectivity.[6,7] In general, the presence of an aryl

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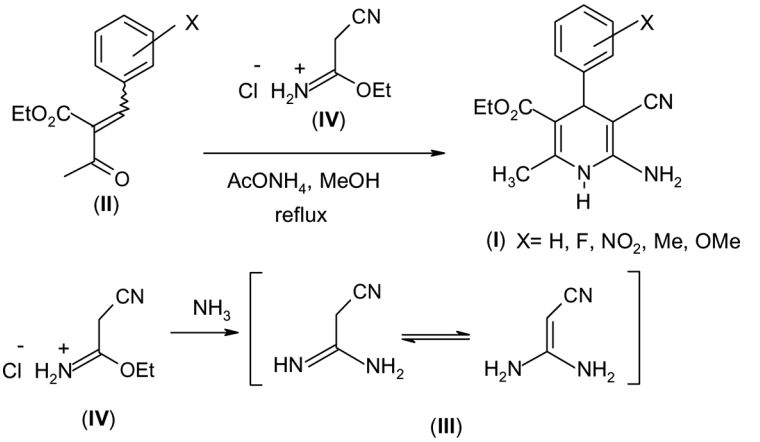
group at C4 and esters, acyl, sulfonyl, or nitrile groups at C3 and C5 of the 1,4-DHP ring has proved to be a fundamental requirement for the pharmacological activity.[8–10] In spite of the widely developed chemistry of the 1,4-DHPs, little is known about 1,4-DHPs bearing substituents other than hydrogen atoms or alkyl groups at C2 and C6.[11,12] A survey of the current literature has shown that the synthesis and pharmacology of 6-amino substituted 1,4-DHPs (**I**) have been described in the literature.[13,14] Most of these compounds induced a remarkable neuroprotective affect against toxicity caused by [k^+]-elicited [Ca^{2+}] overload, preventing calcium overload and neuronal death.

All these facts prompted us to find a new ecofriendly method and to employ grinding at room temperature for the multicomponent synthesis of the ethyl 6-amino-4-aryl-5-cyano-1,4-dihydro-2-methyl-3-pyridinecarboxylic acids **2a**–**g** in a solvent-free environment.

RESULTS AND DISCUSSION

The synthesis of a number of 6-amino-4-aryl-5-cyano-1,4-dihydropyridines (**I**) has been reported.[13,14] The compounds of type **I** have been prepared by reacting 2-arylmethylene-3-oxo-butanoic acid ethyl esters (**II**) with 3,3-diaminoacrylonitrile (**III**), obtained in situ from ethyl 2-cyanoacetimidate hydrochloride (**IV**), in the presence of ammonium acetate in methanol under reflux (Scheme 1).

1,4-DHPs are generally synthesized by the classical Hantzsch reaction, which involves the condensation of an aldehyde with an active methylene carbonyl compound (e.g., ethyl acetoacetate) and ammonia (or a primary amine or ammonium acetate) in refluxing ethanol or other lower alcohols. A number of improved methods have been reported in the literature to modify this reaction.[15] To develop an efficient and environmentally benign methodology for the synthesis of Hantzsch esters, we initially examined the one-pot reaction of aromatic aldehydes (1 equiv.), ethyl acetoacetate (1 equiv.), and ammonium acetate (1.5 equiv.) under solvent-free

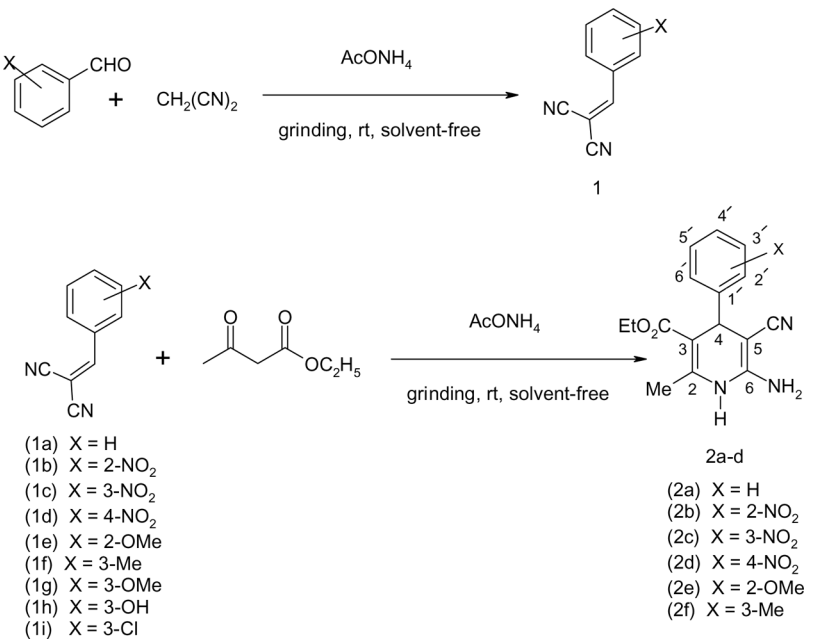


Scheme 1. Synthesis of 1,4-DHPs of type 1.

conditions at room temperature on grinding. No reaction was performed. Then, for the synthesis of 6-amino substituted 1,4-DHPs (**I**), we initiated our studies by reaction of aromatic aldehydes (1 equiv.), ethyl acetoacetate (1 equiv.), malononitrile (1 equiv.), and ammonium acetate (1.5 equiv.) in one pot under solvent-free conditions at room temperature with grinding. However, after workup and purification, the ^{1}H NMR spectrum of the obtained product did not show any aromatic protons. ^{1}H NMR data show only the reaction of ethyl acetoacetate and malononitrile. So we used a one-pot, two-stage synthesis of this specific group of 1,4-DHPs via a Knovenagel condensation involving malononitrile and a subsequent Micheal addition/cyclization. Treatment of aromatic aldehydes (1 equiv.) with malononitrile (1 equiv.) in the presence of ammonium acetate (1.5 equiv.) under solvent-free conditions at room temperature on grinding gave benzylidene malononitrile derivatives **1a**–**i** via the Knovenagel condensation without any purification. To the same reaction vessel, we added ethyl acetoacetate (1 equiv.) and followed this by grinding (Scheme 2). After workup and purification, the 6-amino-4-aryl-5-cyano-1,4-dihydropyridines **2a**–**f** were obtained in good yields. The results with different aldehydes are depicted in Table 1.

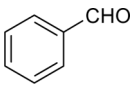
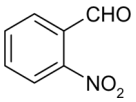
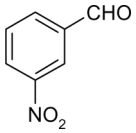
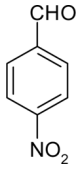
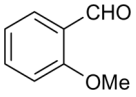
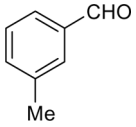
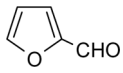
The reaction of ethyl acetoacetate with 3-methoxybenzylidene malononitrile (**1g**) and 3-hydroxybenzylidene malononitrile (**1h**) in the presence of ammonium acetate under solvent-free conditions at room temperature on grinding gave a complex mixture of products. We also prepared *m*-chlorobenzylidene malononitrile (**1i**) by this method. We did not continue the reaction with it, because it is very lachrymal.

To prove the mechanism/structures proposed as intermediates, identification of the proposed intermediates should be made. For this purpose, we performed



Scheme 2. Synthesis of 6-amino-4-aryl-5-cyano-1,4-dihydropyridines.

Table 1. Synthesis of 6-Amino-4-aryl-5-cyano-1,4-dihydropyridines **2a**–**g** by grinding

Entry	Aldehyde	Product	Yield (%)	Mp (°C)
1		**2a**	78	190–192
2		**2b**	57	177.5–178.5 (lit.[14b] mp 123–125)
3		**2c**	81	187–188 (lit.[14b] mp 218–220)
4		**2d**	76	175–176 (lit.[14b] mp 240–242)
5		**2e**	59	196–197 (lit.[14b] mp 209–211
6		**2f**	68	176–177
7		**2g**	68	204–205

the Knovenagel condensation of aromatic aldehydes and malononitrile in the presence of ammonium acetate by grinding under solvent-free conditions at room temperature. Reaction of aromatic aldehydes (1 equiv.) with malononitrile (1 equiv.) in the presence of ammonium acetate (1.2 equiv.) under solvent-free conditions at

Table 2. Knoevenagel condensation of aromatic aldehydes and malononitrile by grinding for preparation of benzylidene malononitrile derivatives **1**

Entry	X	Yield (%)
1	H	85
2	4-Me	71
3	2-MeO	75
4	3-MeO	77
5	3-NO_2	90
6	2-NO_2	70
7	3-Cl	87

room temperature by grinding gave benzylidene malononitrile derivatives **1** after recrystallization from ethanol 95% in good yields. The results with different aldehydes are depicted in Table 2.

CONCLUSIONS

In conclusion, we have developed a simple and efficient method for the synthesis of 6-amino substituted 1,4-DHPs at room temperature in solvent-free conditions. The experimental simplicity, mildness of conversion, efficient yields, short reaction times, low cost, simple workup, and easy purification make this procedure attractive to synthesize a variety of these derivatives.

EXPERIMENTAL

Preparation of Ethyl 6-Amino-5-cyano-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (2a), a Typical Procedure

A mixture of benzaldehyde (10 mmol, 1 ml), malononitrile (10 mmol, 0.66 g), and ammonium acetate (15 mmol, 1.15 g) was thoroughly mixed in a mortar by grinding until the completion of reaction as indicated by thin-layer condensation (TLC) (15 min). The mixture was solidified during the grinding. Then, ethyl acetoacetate (10 mmol, 1.26 ml) was added to the same vessel. The mixture, which was initially in a partial liquid state, solidified during the process of grinding (15 min). The pure product (**2a**) was obtained by recrystallized from ethanol (2.21 g, 78%).

Mp 190–192 °C; IR (KBr) $\bar{\nu} = 3402$ (s), 3328 (s), 3223 (m), 2966 (w), 2189 (s), 1693 (s), 1259 (s), 1060 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.10$ (t, $J = 7.20$ Hz, 3H, CH_3 ester), 2.38 (s, 3H, CH_3-2), 4.05 (m, 2H, CH_2 ester), 4.45 [s, 1H, C(4)-H], 4.50 (br, s, 2H, NH_2), 7.17–7.35 (m, 5H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.86$ (CH_3 ester), 18.37 (CH_3-2), 38.75 (C-4), 60.64 (CH_2 ester), 62.58 (C-5), 108.00 (C-3), 118.80 (CN), 127.17 (C-4′), 127.50 (C-3′,5′), 128.56 (C-2′,6′), 143.72 (C-1′), 156.76, 157.39 (C-2, 6), 165.83 (CO) ppm.

Selected Data

Ethyl 6-amino-5-cyano-2-methyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (2b). Mp 177.5–178.5 °C; IR (KBr) $\bar{\nu} = 3453$ (s), 3294 (s), 3215 (s), 3185 (s), 2984 (w), 2208 (s), 1719 (s), 1684 (s), 1601 (s), 1530 (s), 1381 (s), 1225 (s), 1062 (s), 786 (s), 726 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.99$ (t, $J = 7.20$ Hz, 3H, CH_3 ester), 2.41 (s, 3H, CH_3-2), 3.96 (m, 2H, CH_2 ester), 4.67 (br, s, NH_2), 5.26 [s, 1H, C(4)-H], 7.32–7.40 (m, 2H, Ar-H4′, H6′), 7.58 (dt, $J_1 = 7.50$ Hz, $J_2 = 1.20$ Hz, 1H, Ar-H5′), 7.82 (dd, $J_1 = 7.70$ Hz, $J_2 = 1.20$ Hz, 1H, Ar-H3′) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.66$ (CH_3 ester), 18.45 (CH_3-2), 32.97 (C-4), 60.95 (CH_2 ester), 63.50 (C-5), 107.30 (C-3), 118.21 (CN), 124.06 (C-3′), 127.91 (C-4′), 130.61 (C-6′), 133.23 (C-5′), 139.08 (C-1′), 149.09 (C-2′), 158.05, 158.24 (C-2, 6), 165.04 (CO) ppm.

Ethyl 6-amino-5-cyano-2-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (2c). Mp 187–188 °C; IR (KBr) $\bar{\nu} = 3402$ (s), 3328 (s), 3221 (m),

2987 (w), 2190 (s), 1672 (s), 1531 (s), 1344 (s), 1063 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.12$ (t, $J = 7.20$ Hz, 3H, CH_3 ester), 2.41 (s, 3H, CH_3-2), 4.05 (m, 2H, CH_2 ester), 4.58 (s, 1H, C(4)-H), 4.69 (br, s, NH_2), 7.49 (t, $J = 8.00$ Hz, 1H, Ar-H5′), 7.58 (td, $J_1 = 8.00$ Hz, $J_2 = 0.80$ Hz, Ar-H6′), 8.06 (t, $J = 1.60$ Hz, 1H, Ar-H2′), 8.11 (md, $J = 8.00$ Hz, 1H, Ar-H4′) ppm; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 1.01$ (t, $J = 7.20$ Hz, 3H, CH_3 ester), 2.07 (s, 2H, NH_2), 2.34 (s, 3H, CH_3-2), 3.36 (s, 1H, NH), 3.95 (m, 2H, CH_2 ester), 4.52 [s, 1H, C(4)-H], 7.60–7.70 (m, 2H, Ar-H5′, H6′), 7.98 (s, 1H, Ar-H2′), 8.10 (dt, $J_1 = 7.50$ Hz, $J_2 = 1.92$ Hz, 1H, Ar-H4′) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.90$ (CH_3 ester), 17.64 (CH_3-2), 37.75 (C-4), 59.95 (CH_2 ester), 63.50 (C-5), 105.93 (C-3), 117.33 (CN), 121.39 (C-4′), 121.55 (C-2′), 128.51 (C-5′), 133.01 (C-6′), 145.10 (C-1′), 147.47 (C-3′), 159.77, 156.95 (C-2, 6), 164.26 (CO) ppm.

Ethyl 6-amino-5-cyano-2-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (2d). Mp 175–176 °C; IR (KBr) $\bar{\nu} = 3404$ (s), 3333 (s), 3204 (s), 2983 (w), 2200 (s), 1690 (s), 1650 (s), 1518 (s), 1345 (s), 1270 (s), 1060 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.11$ (t, $J = 7.20$ Hz, 3H, CH_3 ester), 2.42 (s, 3H, CH_3-2), 4.05 (q, $J = 7.20$ Hz, 2H, CH_2 ester), 4.57 [s, 1H, C(4)-H], 4.67 (br, s, NH_2), 7.39 (d, $J = 7.70$ Hz, 2H, Ar-H2,6′), 8.18 (d, $J = 7.70$ Hz, 1H, Ar-H3′,5′) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.92$ (CH_3 ester), 18.61 (CH_3-2), 38.82 (C-4), 60.86 (C-5), 60.97 (CH_2 ester), 106.79 (C-3), 118.28 (CN), 123.99 (C-2′,6′), 128.42 (C-3′,5′), 147.09 (C-1′), 151.09 (C-4′), 157.73, 158.05 (C-2, 6), 165.26 (CO) ppm.

Ethyl 6-amino-5-cyano-2-methyl-4-(2-methoxyphenyl)-1,4-dihydropyridine-3-carboxylate (2e). Mp 196–197 °C; IR (KBr) $\bar{\nu} = 3403$ (s), 3326 (s), 3220 (m), 2967 (w), 2933 (w), 2187 (s), 1693 (s), 1606 (m), 1256 (s), 1063 (s), 713 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.06$ (t, $J = 7.20$ Hz, 3H, CH_3 ester), 2.38 (s, 3H, CH_3-2), 3.84 (s, 3H, OCH_3), 4.00 (m, 2H, CH_2 ester), 4.41 (br, s, 2H, NH_2), 4.88 [s, 1H, C(4)-H], 6.82–6.92 (m, 2H, Ar-H5′, 3′), 7.06 (dd, $J_1 = 7.50$ Hz, $J_2 = 1.50$ Hz, 1H, Ar-H6′), 7.19 (dt, $J_1 = 7.50$ Hz, $J_2 = 1.50$ Hz, 1H, Ar-H4′) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.77$ (CH_3 ester), 18.31 (CH_3-2), 32.61 (C-4), 55.58 (OCH_3), 60.42 (CH_2 ester), 61.81 (C-5), 107.06 (C-3), 111.05 (C-3′), 119.10 (CN), 120.65 (C-5′), 128.24 (C-4′), 128.68 (C-6′), 131.79 (C-1′), 157.07 (C-2), 157.45 (C-2′), 157.94 (C-6), 166.08 (CO) ppm.

Ethyl 6-amino-5-cyano-2-methyl-4-(3-methylphenyl)-1,4-dihydropyridine-3-carboxylate (2f). Mp 176–177 °C; IR (KBr) $\bar{\nu} = 3401$ (s), 3330 (m), 3222 (m), 2981 (w), 2192 (s), 1697 (s), 1675 (s), 1647 (m), 1604 (m), 1372 (m), 1266 (s), 1058 (s), 721 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.11$ (t, $J = 6.90$ Hz, 3H, CH_3 ester), 2.33 (s, 3H, CH_3-2), 2.38 (s, 3H, CH_3), 4.05 (m, 2H, CH_2 ester), 4.41 [s, 1H, C(4)-H], 4.45 (br, s, NH_2), 6.92–7.25 (m, 4H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.86$ (CH_3 ester), 18.37 (CH_3-2), 21.45 (CH_3), 38.68 (C-4), 60.61 (CH_2 ester), 62.52 (C-5), 108.08 (C-3), 118.91 (CN), 124.62 (C-4′), 127.96, 128.20, 128.40 (C-2′,5′,6′), 138.07 (C-3′), 143.64 (C-1′), 156.61, 157.45 (C-2,6), 165.91 (CO) ppm.

Ethyl 6-amino-5-cyano-2-methyl-4-(2-furyl)-1,4-dihydropyridine-3-carboxylate (2g). Mp 204–205 °C; IR (KBr) $\bar{\nu} = 3393$ (m), 3370 (m), 3202 (m), 2963 (m), 2193 (s), 1693 (s), 1685 (s), 1261 (s), 1065 (s), 802 (s) cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$): $\delta = 1.23$ (t, $J = 7.20$ Hz, 3H, CH_3 ester), 2.37 (s, 3H, CH_3-2), 4.16 (m, 2H, CH_2 ester), 4.53 (br, s, 2H, NH_2), 4.64 [s, 1H, C(4)-H], 6.102 (d, $J = 3.30$ Hz, 1H, Ar-H5′), 6.28 (m, 1H, Ar-H4′), 7.31 (s, 1H, Ar-H3′) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.00$ (CH_3 ester), 18.43 (CH_3-2), 32.37 (C-4), 59.53 (C-5), 60.78 (CH_2 ester), 105.71 (C-3), 105.93 (C-5′), 110.33 (C-4′), 118.62 (CN), 141.93 (C-3′), 155.13 (C-1′), 157.78, 158.54 (C-2,6), 165.63 (CO) ppm.

General Procedure for the Knovenagel Reaction

A mixture of aromatic aldehyde (10 mmol), malononitrile (10 mmol, 0.66 g), and ammonium acetate (15 mmol, 1.15 g), was thoroughly mixed in a mortar by grinding until the completion of reaction as indicated by TLC (15 min). The mixture solidified during the grinding. The pure product was obtained by recrystallized from ethanol 95%. The identity of these compounds was easily established by comparison of their ^1H NMR spectra with those of authentic samples.[16]

Selected Data

2-Benzylidenemalononitrile. Mp 84 °C (lit.[16] 84–85 °C); IR (KBr) $\bar{\nu} = 3032$ (w), 2223 (s), 1654 (s), 1591 (s), 1450 (s), 755 (s), 678 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.55$ (t, $J = 7.20$ Hz, 2H, Ar-H3′,5′), 7.65 (t, $J = 7.20$ Hz, 1H, Ar-H4′), 7.89 (s, 1H, =CH), 7.92 (d, $J = 7.20$ Hz, 2H, Ar-H2′,6′) ppm.

2-(4-Methylbenzylidene)malononitrile. Mp 135 °C (lit.[16] 140 °C); IR (KBr) $\bar{\nu} = 3035$ (m), 2222 (s), 1605 (m), 1588 (s), 1221 (m), 1192 (m), 814 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.47$ (s, 3H, CH_3), 7.35 (d, $J = 7.25$ Hz, 2H, Ar-H3′,5′), 7.34 (s, 1H, =CH), 7.82 (d, $J = 7.25$ Hz, 2H, Ar-H2′,6′) ppm.

2-(2-Methoxybenzylidene)malononitrile. Mp 86 °C (lit.[16] 86 °C); IR (KBr) $\bar{\nu} = 3046$ (m), 2944 (w), 2842 (w), 2224 (s), 1579 (s), 1252 (s), 1021 (s), 755 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.94$ (s, 3H, OCH_3), 7.00 (d, $J = 8.70$ Hz, 1H, Ar-H3′), 7.08 (t, $J = 7.80$ Hz, 1H, Ar-H5′), 7.18 (dt, $J_1 = 7.80$ Hz, $J_2 = 1.50$ Hz, 1H, Ar-H4′), 8.19 (dd, $J_1 = 8.1$ Hz, $J_2 = 1.50$ Hz, 1H, Ar-H6′), 8.31 (s, 1H, =CH) ppm.

2-(3-Methoxybenzylidene)malononitrile. Mp 107–109 °C (lit.[16] 130 °C); IR (KBr) $\bar{\nu} = 3038$ (w), 2229 (m), 1571 (s), 1279 (s), 1040 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.88$ (s, 3H, OCH_3), 7.18 (dt, $J_1 = 7.20$ Hz, $J_2 = 2.10$ Hz, 1H, Ar-H6′), 7.40–7.53 (m, 3H, Ar-H2′,4′,5′), 7.76 (s, 1H, =CH) ppm.

2-(3-Nitrobenzylidene)malononitrile. Mp 140 °C (lit.[16] 140 °C); IR (KBr) $\bar{\nu} = 3084$ (w), 3046 (w), 2225 (m), 1596 (s), 1527 (s), 1355 (s), 1152 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.80$ (t, $J = 7.10$ Hz, 1H, Ar-H5′), 7.90 (s, 1H, =CH), 8.34 (d, $J = 7.10$ Hz, 1H, Ar-H6′), 8.48 (m, 1H, Ar-H4′), 8.67 (t, $J = 2.1$ Hz, 1H, Ar-H2′) ppm.

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REFERENCES

1. Reddy, G. M.; Shiradkar, M.; Chkravarthy, A. K. Chemical and pharmacological significance of 1,4-dihydropyridines. *Curr. Org. Chem.* **2007**, *11*(10), 847–852.
2. Bossert, F.; Meyer, H.; Wehinger, E. Substituted -1,4-dihydropyridines and pharmaceutical compositions containing them. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 762–769.
3. Lanis, R. A.; Triggle, D. A. New developments in Ca^{2+} channel antagonists. *J. Med. Chem.* **1983**, *25*, 775–785.
4. (a) Godfraid, T.; Miller, R.; Wibo, M. Calcium antagonism and calcium entry blockade. *Pharmacol. Rev.* **1986**, *38*(4), 321–416; (b) Sausins, A.; Duburs, G. Synthesis of 1,4-dihydropyridines by cyclocondensation reactions. *Heterocycles* **1988**, *27*, 269–289; (c) Mager, P. P.; Coburn, R. A.; Solo, A. J.; Triggle, D. J.; Rothe, H. QSAR, diagnostic statistics, and molecular modelling of 1,4-dihydropyridine calcium antagonists: A difficult road ahead. *Drug Des. Discov.* **1992**, *8*(4), 273–289; (d) Mannhold, R.; Jablonka, B.; Voigt, W.; Schonafinger, K.; Schraven, K. Calcium- and calmodulin-antagonism of elnadipine derivatives: A comparison of structure–activity relationships. *Eur. J. Med. Chem.* **1992**, *27*, 229–235.
5. Klusa, V. Chemoenzymatic synthesis of enantiopure 1,4-dihydropyridine. *Drugs Future* **1995**, *20*, 135–138.
6. Ferry, D. R.; Glossmann, H. Evidence for multiple receptor sites within the putative calcium channel. *Naunyn.-Schmiedeberg's Arch. Pharmacol.* **1982**, *321*(1), 80–83.
7. Itil, T. M.; Michael, S. T.; Hoffmeister, F.; Kunitz, A.; Eralp, E. Nimodipine, a calcium antagonist vasodilator with psychotropic properties (a controlled quantitative pharmaco-EEG study). *Curr. Ther. Res.* **1984**, *35*, 405–422.
8. Goldmann, S.; Stoltefuss, J. 1,4-Dihydropyridines: Effects of chirality and conformation on the calcium antagonist and calcium agonist activities. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1559–1578.
9. Schramm, M.; Thomas, G.; Towart, R.; Franckowiak, G. Novel dihydropyridines with positive inotropic action through activation of Ca^{2+} channels. *Nature* **1983**, *303*, 535–537.
10. Budriesi, R.; Bisi, A.; Ioan, P.; Rampa, A.; Gobbi, S.; Belluti, F. Piazzi, L.; Valenti, P.; Chiarini, A. 1,4-Dihydropyridine derivatives as calcium channel modulators: The role of 3-metoxy-flavone moiety. *Bioorg. Med. Chem.* **2005**, *13*, 3423–3430.
11. Guzmán, A.; Romero, M.; Maddox, A.; Muchowski, J. Vilsmeier–Haack reaction with glutarimides: Synthesis of 2,6-dichloro-1,4-dihydropyridine-3,5-dicarboxaldehydes. *J. Org. Chem.* **1990**, *55*, 5793–5797; (b) Nguyen, J.-T.; Velázquez, C. A.; Knaus, E. E. Hantzsch 1,4-dihydropyridines containing a diazen-1-ium-1,2-diolate nitric oxide donor moiety to study calcium channel antagonist structure–activity relationships and nitric oxide release. *Bioorg. Med. Chem.* **2005**, *13*, 1725–1738.
12. (a) Moshtaghi, Z. A.; Raisossadat, O. M.; Mollazadeh, S. Synthesis of novel unsymmetrical 1,4-dihydropyridine derivatives. *Synth. Commun.* **2005**, *35*, 2895–2903; (b) Moshtaghi, Z. A.; Raisossadat, O. M.; Sadeghi, S. Q. Synthesis of novel unsymmetrically substituted 1,4-dihydropyridines and separation of the enantiomers of racemic 1,4-dihydropyridine containing isothioureido group. *Arkivoc* **2006**, *14*, 15–21.
13. Troschutz, R. Darstellung von pyrido[2,3-d]pyrimidinen mit Trimethoprimpartial struktur. *Arch. Pharm.* **1989**, *322*, 285–290.
14. (a) León, R.; de los Ríos, C.; Marco-Contelles, J.; López, M. G.; García, A. G.; Villarroya, M. Synthesis of 6-amino-1,4-dihydropyridines that prevent calcium over load and neuronal death. *Eur. J. Med. Chem.* **2008**, *43*, 668–674; (b) Marco-Contelles, J.; León, R.; de los Ríos, C.; Guglietta, A.; Terencio, J.; López, M. G.; García, A. G.; Villarroya, M. Novel multipotent tacrine-dihydropyridine hybrids with improved acetylcholinesterase

inhibitory and neurotective activities as potential drugs for the treatment of Alzheimer's disease. *J. Med. Chem.* **2006**, *49*(26), 7607–7610.

15. Recent examples, see: (a) Chari, M. A.; Syamasundar, K. Silica gel/$NaHSo_4$ catalyzed one-pot synthesis of Hantzsch 1,4-dihydropyridines at ambient temperature. *Catal. Commun.* **2005**, *6*, 624–626; (b) Donelson, J. L.; Gibbs, R. A.; De, S. K. An efficient one-pot synthesis of polyhydroquinoline derivatives through the Hantzsch four-component condensation. *J. Mol. Catal. A: Chem.* **2006**, *256*, 309–311; (c) Wang, L.-M.; Sheng, J.; Zhang, L.; Han, J.-W.; Fan, Z.-Y.; Tian, H.; Qian, C.-T. Facile Yb(OTf)3 promoted one-pot synthesis of polyhydroquinoline derivatives through Hantzsch reaction. *Tetrahedron* **2005**, *61*, 1539–1543; (d) Lee, J. H. Synthesis of Hantzsch 1,4-dihydropyridines by fermenting bakers' yeast. *Tetrahedron Lett.* **2005**, *46*, 7329–7330; (e) Ko, S.; Sastry, M. N. V.; Lin, C.; Yao, C.-F. Molecular iodine-catalyzed one-pot synthesis of 4-substituted-1,4-dihydropyridine derivatives via Hantzsch reaction. *Tetrahedron Lett.* **2005**, *46*, 5771–5774; (f) Vohra, R. K.; Bruneau, C.; Renaud, J.-L. Lewis acid-catalyzed sequential transformations: Straightforward preparation of functional dihydropyridines. *Adv. Synth. Catal.* **2006**, *384*, 2571–2574; (g) Kikuchi, S.; Iwai, M.; Murayama, H.; Fukuzawa, S.-I. Catalytic synthesis of 1,4-dihydropyridine derivatives using scandium(III) triflate. *Tetrahedron Lett.* **2008**, *49*, 114–116.
16. Hosseini-Sarvari, M.; Sharghi, H.; Etemad, S. Solvent-free Knovenagel condensations over TiO_2. *Chin. J. Chem.* **2007**, *25*, 1563–1567.