

Multicomponent synthesis of 1,4-dihydropyridine-3,5-dicarbonitriles

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Abstract

1,4-Dihydropyridines are one of the most used classes of antihypertensive drugs. The present communication describes the autocatalytic four-component reaction of 2,6-dihalogen-substituted benzaldehydes, malononitrile and cyclic amines results in the formation of previously unknown 1,4-dihydropyridine-3,5-dicarbonitriles. The structure of these previously unknown compounds was confirmed by means of ¹H and ¹³C NMR and IR spectroscopy, mass spectrometry and elemental analysis.



Keywords: Benzaldehyde, malononitrile, cyclic amine, 1,4-dihydropyridine, multicomponent reaction, autocatalytic process

Introduction

Systemic arterial hypertension is characterized by persistently high blood pressure (BP) in the systemic arteries.¹ Approximately one in four adults have hypertension.² The Global Burden of Disease study has shown that non-optimal BP continues to be the biggest single risk factor contributing to the global burden of disease and to global all-cause mortality, leading to 9.4 million deaths and 212 million lost healthy life years (8.5% of the global total) each year.³

Antihypertensive pharmacotherapy has evolved over several decades driven by the development of various antihypertensive medication classes and large-scale outcomes trials proving their benefits on cardiovascular diseases morbidity and mortality.⁴ Dihydropyridines (DHPs) are one of the classes of antihypertensive drugs. DHP drugs are inhibitors of L-type voltage-dependent calcium channel that are mainly spread outside the central nervous system.⁵ Nowadays these are the most used drugs in the treatment of hypertension. The most used DHPs are Amlodipine, Felodipine, and Nifedipine (Figure 1) with a substituent in the *o*-position.





However, 1,4-dihydropyridines have some disadvantages, such as relatively low bioavailability, insufficient tissue selectivity, and rapid elimination.⁶

Thus, the synthesis of a new type of 1,4-dihydropyridines is an important challenge for researchers.

4-Substituted pyridine-3,5-dicarbonitriles have a high conductance-type of calcium-activated K-channel opening effect and a smooth muscle relaxant effect for bladder based on the K-channel opening effect, which can be used in treating pollakiuria and urinary incontinence.⁷

Multicomponent reactions have proven to be the best strategy for the construction of large and complex, heterocyclic structures with easy and comparatively simple steps.^{8,9,10} These reactions have been employed in various synthetic transformations where classical methods usually involve many steps with tedious procedures. The MCR approach provides high yields, atom-/step economy, reduced reaction time, is eco-friendly, and acts as an amenable tool for the generation of a library of new chemical entities, especially in the drug discovery process.¹¹

The first multicomponent synthesis of 1,4-dihydropyridines (or perhaps even the first multicomponent process) was carried out by A. Hantzsch in 1881.¹² He carried out the preparation of dihydropyridine derivatives by condensation of an aldehyde with two equivalents of a θ -ketoester in the presence of ammonia.

Modern methods for the synthesis of 1,4-dihydropyridine using modifications of the Hantzsc synthesis.^{13,14,15} In recent years, malononitrile and its derivatives have been increasingly used to carry out such transformations. ^{16,17,18}

We previously carried out different types of multicomponent processes leading to substituted piperidines and tetrahydropyridines.¹⁹⁻²² These processes are three- and four-component reactions occurring under mild conditions.

Now, we wish to report our results on the efficient autocatalytic four-component transformation of benzaldehydes **1**, malononitrile and cyclic amines **2** into the previously unknown 1,4-dihydropyridine-3,5-dicarbonitriles **3** in EtOH at 78 °C, as shown in Scheme 1. The corresponding cyclic amine in this reaction is both a reagent and a catalyst.



Scheme 1. Multicomponent synthesis of 1,4-dihydropyridine-3,5-dicarbonitriles 3.

Results and Discussion

For the study, we have chosen 2,6-dihalogen-substituted benzaldehydes. This is due to the fact that compounds with *ortho*- or *meta*-substituents of electron-withdrawing nature possess optimum activity, while *para*-substitution shows a decrease in activity according to its electronic and steric effect.²³ The importance of the *ortho*-substituents is to "lock" the conformation of the 1,4-DHP such that the C-4 position of the aromatic ring is perpendicular to the 1,4-DHP ring. This perpendicular conformation has been proposed to be essential for the activity of the 1,4-DHPs.²⁴

Transformation of 2,6-diclorobenzaldehyde **1b**, malononitrile and morpholine **2b** was chosen as a model reaction (Table 1). We studied this reaction in alcohols (Table 1, entries 1-3), as well as in the presence of an excess of amine (Table 1, entry 4). Under these conditions, compound **3d** was obtained in 61-78% yields. It was found that the reaction proceeds better in ethanol and *n*-propanol, and the use of an excess of amine has practically no effect on the reaction yield. In addition, the effect of the reaction time was also considered (Table 1, entries 5 and 6). It was found that the reaction time also has little effect on the yield of the process.

It is optimal to carry out the reaction in ethanol at reflux for 3 h and the amine **2** is taken in an equivalent amount (Table 1, entry 2). Under these conditions, 1,4-dihydropyridine-3,5-dicarbonitrile **3d** is formed in 75% yield.

Table 1. Search for the optimal reaction conditions for the synthesis of 3 a

CI CI CI	+	$\begin{pmatrix} CN \\ CN \end{pmatrix}$ + $\begin{pmatrix} O \\ N \\ H \end{pmatrix}$		CI CI CI NC CN H_2N N N N H $3d$ O
Nº	Solvent	Amount of 2b (mmol)	Time (h)	Yield (%)
1	MeOH	1	3	61
2	EtOH	1	3	75
3	<i>n</i> -PrOH	1	3	76
4	EtOH	1.2	3	78
5	EtOH	1	2	62
6	EtOH	1	4	78

^a Reaction conditions: 2,6-diclorobenzaldehyde **1b** (1 mmol), malononitrile (2 mmol), morpholine **2b** were refluxed in 3 mL of solvent. Isolated yields.

Compounds **3a–d** were synthesized in 68–79% yields in optimal conditions (Table 2). The structure of these previously unknown 1,4-dihydropyridine-3,5-dicarbonitriles **3** was confirmed by means of ¹H and ¹³C NMR and IR spectroscopy, mass spectrometry and elemental analysis. For all compounds, only one set of signals was observed in ¹H and ¹³C NMR spectra.

The autocatalytic reaction process is environmentally friendly because no amine catalyst becomes waste when reacted. This transformation is easily accomplished; the isolated compounds **3** do not require additional purification.

The process of isolating the final 1,4-dihydropyridine-3,5-dicarbonitriles **3** is an easy work-up procedure, the reaction mixture was cooled to 0°C, the precipitated residue was separated by simple filtration.

The pseudo four-component reaction has a high bond-forming index²⁵ equal to 4: in one stage, two C-C bonds and two C-N bonds are formed.

Table 2. Pseudo four-component reaction of benzaldehydes 1a,b, malononitrile and amines 2a,b ^a



^a Reaction conditions: benzaldehyde **1a,b** (1 mmol), malononitrile (2 mmol), cyclic amine **2** (1 mmol) were refluxed in 3 mL of EtOH. Isolated yields.

The reaction described above for obtaining new compounds **3** compares favorably with the fact that it proceeds in the green solvent ethanol, without a catalyst, and at the same time with good yields. In addition,

during the reaction, a second heterocyclic fragment appears in the final compound, and no preliminary synthesis of the starting materials containing this fragment is required.

Taking into consideration the results of our colleagues in the synthesis of 6-sulfanyl-1,4dihydropyridines¹⁶, the following mechanism for the autocatalytic pseudo four-component reaction of benzaldehyde **1**, malononitrile and cyclic amines **2** was proposed, as shown in Scheme 2.

The first stage was a rapid Knoevenagel condensation of benzaldehyde **1** and malononitrile anion **A**, and then the formation of adduct **4** with the expulsion of a hydroxide anion. After that, the heterocyclization of adduct **4** and anion **A** occurs with the addition of amine **2**. The formed anion **B** undergoes protonation and tautomerization to 1,4-dihydropyridine-3,5-dicarbonitrile **3**. In this autocatalytic process, the amine **2** deprotonates malononitrile, and also acts as a reagent, adding to dihydropyridine at the cyclization stage.



Scheme 2. Proposed mechanism of benzaldehydes **1**, malononitrile and amines **2** transformation into 1,4dihydropyridine-3,5-dicarbonitriles **3**.

If the studied pseudo four-component reaction is carried out with benzaldehyde under the found optimal conditions, then pyridine-3,5-dicarbonitrile **5** are formed, as shown in Scheme 3.



Scheme 3. Multicomponent synthesis of 4-phenylpyridine-3,5-dicarbonitrile 5.

Presumably, compounds **3** are not oxidized, since this would lead to the formation of sterically crowded *bis-ortho,ortho'*-disubstituted biaryl systems.

Conclusions

The title compounds, 1,4-dihydropyridine-3,5-dicarbonitriles, were synthesized in good yield using the facile and efficient autocatalytic pseudo four-component approach with simple equipment and available starting compounds. The compounds **3** were characterized by spectroscopic methods and elemental analysis. The synthesis of dihalogen-substituted 1,4-dihydropyridine-3,5-dicarbonitriles allows new potential antihypertensive drugs, which are inhibitors of L-type voltage-dependent calcium channel.

Experimental Section

General. The solvents and reagents were purchased from commercial sources and used as received.

All melting points were measured with Gallenkamp melting-point apparatus (London, UK) and were uncorrected. ¹H and ¹³C NMR spectra were recorded in DMSO- d_6 with Bruker AM300 spectrometer (Billerica, MA, USA) at ambient temperature. Chemical shift values are relative to Me₄Si. The MS spectra (EI = 70 eV) were obtained directly with a Kratos MS-30 spectrometer (Manchester, UK). For elemental analysis, a 2400 Elemental Analyzer (Perkin Elmer Inc., Waltham, MA, USA) was used. The IR spectra were recorded with a Bruker ALPHA-T FT-IR spectrometer (Billerica, MA, USA) in KBr pellet.

Multicomponent synthesis of 1,4-dihydropyridine-3,5-dicarbonitriles 3

A solution of benzaldehyde **1** (1 mmol), malononitrile (0.132 g, 2 mmol), and the corresponding cyclic amine **2** (1 mmol) in ethanol (3 mL) was refluxed in a round-bottom flask for 3 h. After the reaction was finished, the reaction mixture was chilled to 0 °C to crystallize the solid compound **3**, which was then filtered off, twice rinsed with ice-cold ethanol (2×2 mL) and dried under reduced pressure.

2-Amino-4-(2-chloro-6-fluorophenyl)-6-(piperidin-1-yl)-1,4-dihydropyridine-3,5-dicarbonitrile (3a). Yellowish solid; yield 68% (0.243 g); mp 203–204 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ 1.47-1.75 (m, 6H, 3 CH₂ pip), 3.01 (t, ³*J* = 5.7 Hz, 4H, 2 CH₂ pip), 4.88 (s, 1H, CH), 6.04 (s, 2H, NH₂), 7.13–7.23 (m, 1H, CH Ar), 7.24-7.37 (m, 2H, 2 CH Ar), 7.82 (br s, 1H, NH) ppm; ¹³C NMR (75 MHz, DMSO-*d*₆): δ 21.8 (C(4[`])H₂ pip), 22.4 (2C, C(3[`])H₂ and C(5[`])H₂ pip), 35.0 (C(4)H), 43.9 (2C, 2 CH₂N pip), 52.1 (<u>C</u>(3)-CN), 62.5 (<u>C</u>(5)-CN), 115.1 (d, ²*J*_{C-F} = 22.6 Hz, C(5[`])H Ar), 120.7 (C(3)-<u>C</u>N), 121.2 (C(5)-<u>C</u>N), 121.5 (C(3[°])H Ar), 125.7 (C(2[°])-Cl), 129.0 (d, ³*J*_{C-F} = 10.2 Hz, C(4[`])H Ar), 129.9 (d, ²*J*_{C-F} = 14.2 Hz, C(4[`])H Ar), 148.0 (C(2)-NH₂), 151.6 (C(6)-pip), 161.9 (d, ¹*J*_{C-F} = 249.6 Hz, C(6[°])-F) ppm; IR (KBr): v 3425, 3337, 3230, 2170, 2146, 1667, 1648, 1598, 1491, 1347, 783 cm⁻¹; MS (*m/z*, relative intensity %): 340 [³⁷Cl, M – F]⁺ (2), 338 [³⁵Cl, M – F]⁺ (11), 303 [M – F – Cl]⁺ (3), 145 [C₇H₅N₄]⁺ (3), 132 [³⁷Cl, C₆H₄ClF]⁺ (20), 130 [³⁵Cl, C₆H₄ClF]⁺ (55), 84 [C₅H₁₀N]⁺ (100), 28 [CH₂N]⁺ (52); Anal. calcd. for C₁₈H₁₇ClFN₅: C, 60.42; H, 4.79; N, 19.57%; found: C, 60.53; H, 4.85; N, 19.52%.

2-Amino-4-(2,6-dichlorophenyl)-6-(piperidin-1-yl)-1,4-dihydropyridine-3,5-dicarbonitrile (3b). Yellow solid; yield 79% (0.296 g); mp 192–193 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ 1.47-1.70 (m, 6H, 3 CH₂ pip), 2.96 (t, ³*J* = 5.2 Hz, 4H, 2 CH₂ pip), 5.30 (s, 1H, CH), 6.05 (s, 2H, NH₂), 7.29 (t, ³*J* = 8.0 Hz, 1H, CH Ar), 7.45 (d, ³*J* = 8.0 Hz, 2H, 2 CH Ar), 7.51-8.01 (br s, 1H, NH) ppm; ¹³C NMR (75 MHz, DMSO-*d*₆): δ 1.47-1.70 (m, 6H, 3 CH₂ pip), 2.96 (t, ³*J* = 5.2 Hz, 4H, 2 N-CH₂ pip), 5.30 (s, 1H, CH), 6.05 (s, 2H, NH₂), 7.29 (t, ³*J* = 8.0 Hz, 1H, CH Ar), 7.45 (d, ³*J* = 8.0 Hz, 2H, 2 CH Ar), 7.51-8.01 (br s, 1H, NH) ppm; ¹³C NMR (75 MHz, DMSO-*d*₆): δ 22.1 (C(4``)H₂ pip), 22.9 (2C, C(3``)H₂ and C(5``)H₂ pip), 38.1 (C(4)H), 44.2 (2C, 2 CH₂N pip), 51.6 (<u>C</u>(3)-CN), 62.3 (<u>C</u>(5)-CN), 120.4 (C(3)-<u>C</u>N), 121.0 (C(5)-<u>C</u>N), 121.7 (C(4`)H Ar), 128.7 (br s, C(2`)-CI), 128.9 (2C, C(3`)H and C(5`)H Ar), 130.3 (br s, C(6`)-CI), 137.8 (C(1`) Ar), 148.4 (C(2)-NH₂), 151.9 (C(6)-pip) ppm; IR (KBr): *v* 3425, 3338, 3227, 2171, 2142, 1654, 1600,

1493, 1344, 786, 773 cm⁻¹; MS (*m*/*z*, relative intensity %): 338 [37 Cl, M – HCl – H]⁺ (1), 336 [35 Cl, M – HCl – H]⁺ (6), 255 [37 Cl, M – Cl – C₅H₁₁N]⁺ (1), 253 [35 Cl, M – Cl – C₅H₁₁N]⁺ (3), 146 [C₇H₆N₄]⁺ (28), 113 [37 Cl, C₆H₄Cl]⁺ (5), 111 [35 Cl, C₆H₄Cl]⁺ (12), 84 [C₅H₁₀N]⁺ (100), 27 [C₂H₃]⁺ (91); Anal. calcd. for C₁₈H₁₇Cl₂N₅: C, 57.77; H, 4.58; N, 18.71%; found: C, 57.89; H, 4.69; N, 18.63%.

2-Amino-4-(2-chloro-6-fluorophenyl)-6-morpholino-1,4-dihydropyridine-3,5-dicarbonitrile (3c). Yellowish solid; yield 69% (0.248 g); mp 209–210 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ 2.97 (t, ³*J* = 4.0 Hz, 4H, 2 N-CH₂ morph), 3.68 (t, ³*J* = 4.0 Hz, 4H, 2 O-CH₂ morph), 4.88 (s, 1H, CH), 6.04 (s, 2H, NH₂), 7.13-7.23 (m, 1H, CH Ar), 7.24-7.37 (m, 2H, 2 CH Ar), 7.82 (s, 1H, NH) ppm; ¹³C NMR (75 MHz, DMSO-*d*₆): δ 35.0 (C(4)H), 43.9 (2C, 2C, 2 CH₂N), 52.1 (<u>C</u>(3)-CN), 62.5 (<u>C</u>(5)-CN), 64.6 (2C, 2 CH₂O), 115.1 (d, ²*J*_{C-F} = 22.6 Hz, C(5')H Ar), 120.7 (C(3)-<u>C</u>N), 121.2 (C(5)-<u>C</u>N), 121.6 (C(3')H Ar), 125.7 (C(2')-Cl), 129.4 (d, ³*J*_{C-F} = 10.3 Hz, C(4')H Ar), 130.0 (d, ²*J*_{C-F} = 13.3 Hz, C(4')H Ar), 148.1 (C(2)-NH₂), 151.6 (C(6)-morph), 161.9 (d, ¹*J*_{C-F} = 252.6 Hz, C(6')-F) ppm; IR (KBr): *v* 3389, 3341, 3204, 2171, 2146, 1647, 1596, 1487, 1421, 1348, 784 cm⁻¹; MS (*m/z*, relative intensity %): 296 [³⁵Cl, M – F – C₂H₄O]⁺ (1), 132 [³⁷Cl, C₆H₄ClF]⁺ (24), 130 [³⁵Cl, C₆H₄ClF]⁺ (100), 95 [C₄H₅N₃]⁺ (38), 87 [C₃H₈N]⁺ (20), 57 [C₃H₅O]⁺ (34), 29 [CH₃N]⁺ (36); Anal. calcd. for C₁₇H₁₅ClFN₅O: C, 56.75; H, 4.20; N, 19.47%; found: C, 56.84; H, 4.27; N, 19.41%.

2-Amino-4-(2,6-dichlorophenyl)-6-morpholino-1,4-dihydropyridine-3,5-dicarbonitrile (3d). Yellow solid; yield 75% (0.282 g); mp 162–163 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ 3.09 (t, ³*J* = 4.4 Hz, 4H, 2 N-CH₂ morph), 3.75 (t, ³*J* = 4.4 Hz, 4H, 2 O-CH₂ morph), 5.29 (s, 1H, CH), 6.04 (s, 2H, NH₂), 7.28 (t, ³*J* = 8.0 Hz, 1H, CH Ar), 7.44 (d, ³*J* = 8.0 Hz, 2H, 2 CH Ar), 7.79 (s, 1H, NH) ppm; ¹³C NMR (75 MHz, DMSO-*d*₆): δ 38.3 (C(4)H), 43.4 (2C, 2 CH₂N), 52.0 (<u>C</u>(3)-CN), 62.6 (<u>C</u>(5)-CN), 63.8 (2C, 2 CH₂O), 120.7 (C(3)-<u>C</u>N), 121.2 (C(5)-<u>C</u>N), 121.9 (C(4`)H Ar), 128.8 (br s, C(1`) Ar), 129.2 (C(3`)H Ar), 130.9 (br s, C(2`)-CI), 135.2 (br s, C(6`)-CI), 138.0 (C(5`)H Ar), 148.7 (C(2)-NH₂), 152.2 (C(6)-morph) ppm; IR (KBr): *v* 3416, 3337, 3224, 2168, 2146, 1654, 1594, 1491, 1344, 786, 773 cm⁻¹; MS (*m/z*, relative intensity %): 321 [³⁷Cl, ³⁵Cl, M – C₃H₄O]⁺ (1), 319 [³⁵Cl, ³⁵Cl, M – C₃H₄O]⁺ (6), 252 [³⁵Cl, M – C₄H₉NO – Cl – NH]⁺ (1), 150 [³⁷Cl, ³⁷Cl, C₆H₄Cl₂]⁺ (3), 148 [³⁷Cl, ³⁵Cl, C₆H₄Cl₂]⁺ (22), 146 [³⁵Cl, ³⁵Cl, C₆H₄Cl₂]⁺ (32), 87 [C₄H₉NO]⁺ (42), 57 [C₃H₅O]⁺ (63), 29 [CH₃N]⁺ (100); Anal. calcd. for C₁₇H₁₅Cl₂N₅O: C, 54.27; H, 4.02; N, 18.61%; found: C, 54.37; H, 4.10; N, 18.53%.

Multicomponent synthesis of 4-phenylpyridine-3,5-dicarbonitrile 5

A solution of benzaldehyde **1c** (0.106 g, 1 mmol), malononitrile (0.132 g, 2 mmol), and morpholine **2b** (0.087 g, 1 mmol) in ethanol (3 mL) was refluxed in a round-bottom flask for 3 h. After the reaction was finished, the reaction mixture was chilled to 0 °C to crystallize the solid compound **5**, which was then filtered off, twice rinsed with ice-cold ethanol (2×2 mL) and dried under reduced pressure.

2-Amino-6-morpholino-4-phenylpyridine-3,5-dicarbonitrile (5). Yellow solid; yield 52% (0.159 g); mp 192–193 °C (lit. [15]) mp 190–192 °C); ¹H NMR (300 MHz, DMSO-*d*₆): δ 3.11 (t, ³*J* = 4.9 Hz, 4H, 2 CH₂), 3.77 (t, ³*J* = 4.9 Hz, 4H, 2 CH₂), 6.89 (s, 2H, 2-NH₂), 7.36–7.45 (m, 2H, 2 CH Ar), 7.47–7.59 (m, 3H, 3 CH Ar) ppm.

Supplementary Material

Copies of ¹H and ¹³C NMR spectra of compounds **3a-d** are given in the Supplementary Material file associated with this manuscript.

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