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Synthesis and characterization of poly(2,6-dimethyl-4-phenyl-1,4-dihydropyridinyl)arenes as novel multi-armed molecules

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ABSTRACT

A new series of poly(2,6-dimethyl-4-phenyl-1,4-dihydropyridinyl)arenes were synthesized in good yields using a one-pot, acid-catalyzed cyclocondensation reaction of the appropriate poly(aldehydes) with 3-aminobut-2-enenitrile in acetic acid at reflux.

Since the first reported synthesis of 1,4-dihydropyridines (1,4-DHPs) by Arthur Hantzsch in 1881, there has been a great deal of interest in this area.[1] This is mainly due to the fact that the 1,4-DHP motif has been found to exhibit significant biological activities in the treatment of cardiovascular disease and as calcium channel blockers.[2] More than twelve commercial, clinically important drugs such as Nifedipin **1**, Felodipine **2**, Nicardipine **3,** and Nimodipin **4** (Fig. 1), containing the 1,4-DHP parent nucleus have been manufactured and used worldwide.[3] These compounds also exhibit a variety of biological activities such as vasodilator, branchodilator, antitheroselerotic, antitumour, antidiabatic, hepatoprotective, geroprotective, and antituberclosis activities.[4]

Therefore, the preparation of novel 1,4-DHP derivatives is a reasonable target in medicinal and synthetic organic chemistry. Numerous attempts to improve the Hantzsch reaction using alternative catalysts and green reaction methods have been investigated.[5] Multicomponent reactions (MCRs) are among the most efficient strategies for the synthesis of 1,4-DHPs in terms of providing both sufficient structural diversity and a large number of compounds for libraries.[6]

Furthermore, over recent years there has been an increasing number of reports regarding so-called 'multi-armed' molecules[7] which are of interest in a range of contexts. For example, multi-armed molecules, in which an aromatic core is appended by long aliphatic arms, has found use as discotic liquid crystals.[7q] Benzene cores appended by six flexible arms, each terminated by an anionic group, have recently been shown to form micelles in aqueous solutions.[7a,7b] Multi-armed molecules, in which the arms contain suitable donor functionalities, have been used as ligands for metal ion complexation.[8] Multi-armed arenes have also been frequently used as core units for dendrimers.[9]

In connection with these findings, we report herein, the synthesis of novel three-, four-, and sixfold branched dihydropyridine-3,5-dicarbonitriles linked to a benzene core via phenoxylmethyl spacers. To the best of our knowledge, very little is known about the synthesis and properties of multi-armed dihydropyridine-3,5-dicarbonitrile derivatives.[10]

Two strategies were investigated for the synthesis of the target compounds. In the first strategy (Scheme 1) we studied the synthesis of 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile **7** via the cyclocondensation of *p*-hydroxybenzaldehyde **5** with 3-aminobut-2-enenitrile **6** in acetic acid at reflux according to the method described by Kuthan et al.[11] Subsequent reaction of three equivalents of the potassium salt of **7** with 1,3,5-tris-bromomethylbenzene[12] in DMF unfortunately did not lead to the clean formation of the corresponding tris (2,6-dimethyl-4-phenyl-1,4-dihydropyridinyl)benzene **9a**. The reaction instead gave a mixture of products that were not easily handled and were not characterized.

In search for an alternative pathway to prepare the target tris (2,6-dimethyl-4-phenyl-1,4-dihydropyridinyl)benzenes **9a,b**, our attention turned to utilizing tris-aldehydes **10a,b** as precursors which could then undergo acid-catalyzed condensation with

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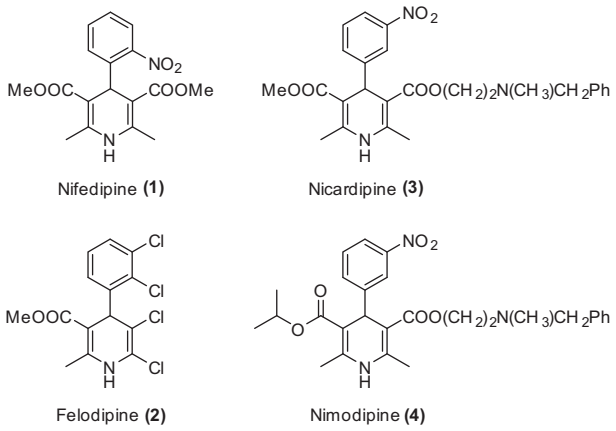


Figure 1. 1,4-DHPs used as clinical drugs.

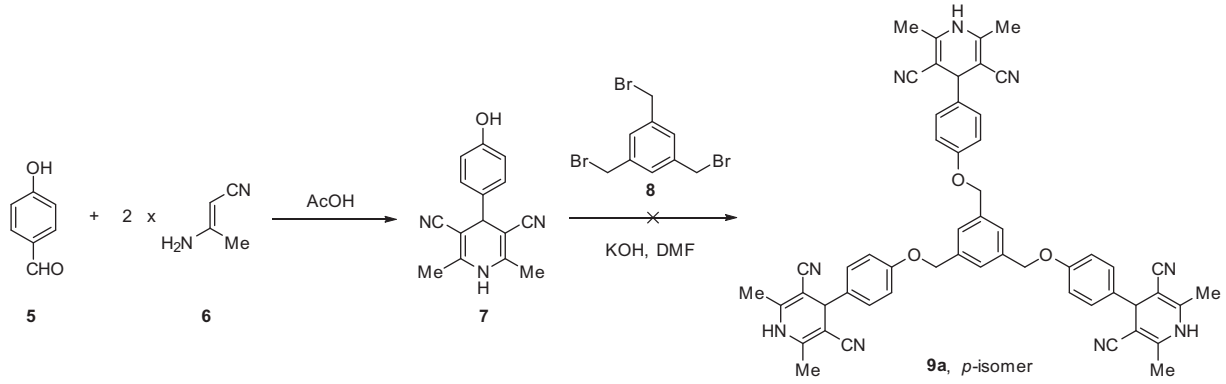
3-aminobut-2-enenitrile **6** to yield the target molecules. Thus, tris (4-formylphenoxymethyl)benzenes **10a,b** were prepared by reacting the potassium salt of 4-hydroxybenzaldehyde **5** or salicylaldehyde with tris(bromomethyl)benzene in DMF at reflux.[13] In the next step, acid-catalyzed condensation of each of the tris-aldehydes **10a** and **10b** with six equivalents of 3-aminobut-2-enenitrile gave the corresponding tris(2,6-dimethyl-4-phenyl-1,4-dihydropyridinyl)benzenes **9a** and **9b** in 78% and 76% yields, respectively, as pale yellow crystals (Scheme 2).[13]

Tetrakis(4-formylphenoxymethyl)benzenes **14** and **15** were prepared in 79% and 82% yields, respectively, by fourfold substitution of tetrakis(bromomethyl)benzene **11**[12] with four equivalents of the potassium salt of 4-hydroxybenzaldehyde **5** and salicylaldehyde **13**, respectively. Similarly, hexakis(4-formylphenoxymethyl)benzenes **16** and **17** were prepared in 80% and 84% yields, respectively, by sixfold substitution of hexakis(bromomethyl)benzenes **12**[12] with six equivalents of the potassium salt of 4-hydroxybenzaldehyde and salicylaldehyde, respectively, (Scheme 3).[13]

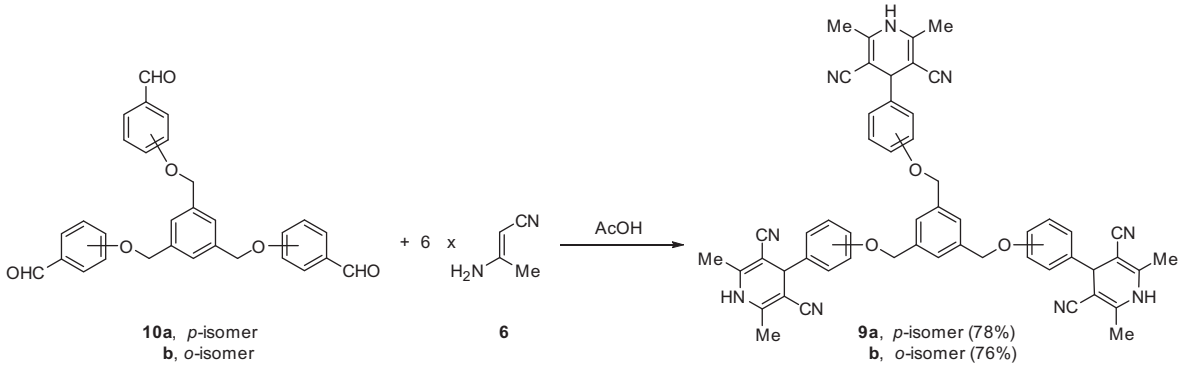
The same methodology was extended to the preparation of tetrakis- and hexakis(2,6-dimethyl-4-phenyl-1,4-dihydropyridinyl) benzenes **18a,b** and **19a,b**, respectively.[13] Thus, acid-catalyzed condensation of the appropriate poly(aldehyde) derivative **14**–**17** with eight or twelve equivalents, respectively, of 3-aminobut-2-enenitrile in acetic acid at reflux afforded **18a,b** and **19a,b**, respectively, in 74–82% yield (Scheme 4).[13]

It was noteworthy that the amount of acetic acid used in the above reactions played an important role in determining the reaction products. For example in the presence of excess acetic acid, most of the reactions gave a mixture of products. Analysis of the ^{1}H NMR spectra of the reaction products indicated the presence of the target products together with additional signals for the corresponding benzylidene-3-oxobutanenitrile derivatives as well as other unknown by-products. Fortunately, (benzene-1,2,4,5-tetrayltetrakis-(methylene))tetrakis-(oxy)tetrakis(benzene-2,1-diyl))tetrakis-(methan-1-yl-1-ylidene)tetrakis(3-oxobutanenitrile) **20** was isolated as a single product in 73% yield upon treatment of **15** with 3-aminobut-2-enenitrile **6** in excess acetic acid (Scheme 5). On the other hand, **18b** was obtained as the sole product in high yields by carrying out the same reaction using catalytic acetic acid.

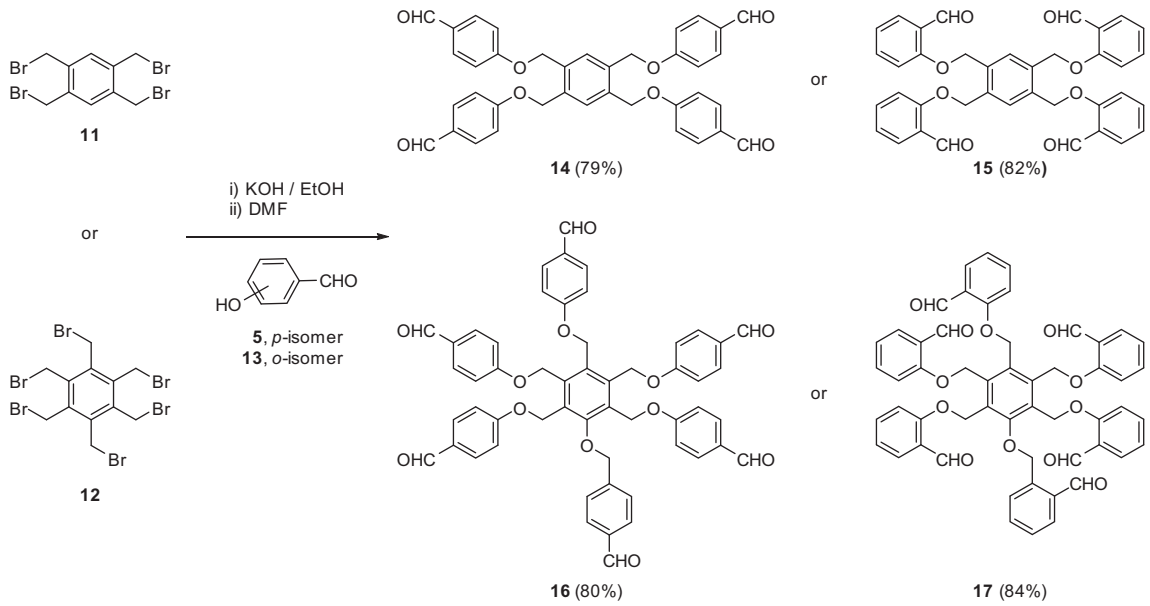
The structures of the newly synthesized compounds were confirmed by IR, NMR, mass spectra, and elementary analysis.[14,15] The symmetry of compounds **9a,b**, **18a,b,** and **19a,b** manifested as a single set of signals in the NMR spectra that were characteristic of the equivalent OCH_2, CH, NH and Me groups.



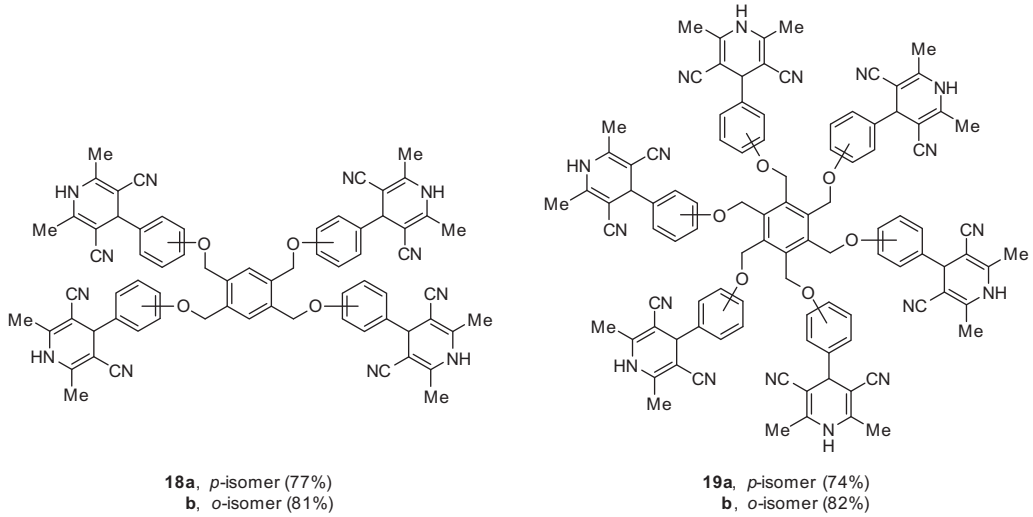
Scheme 1.



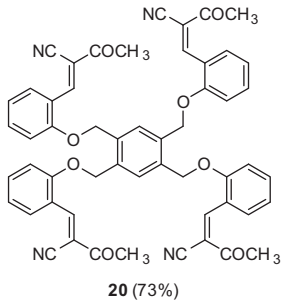
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

In conclusion, we have developed a simple and efficient method for the synthesis of tris-, tetrakis-, and hexakis(formylphenoxymethyl)benzenes. The synthetic utility of these compounds as building blocks for novel (2,6-dimethyl-4-phenyl-1,4-dihydropyridinyl)arenes has also been investigated. These new classes of 1,4-dihydropyridines are interesting both in their own right as unusual molecules and for their promising pharmacological and biological activities. They offer the advantage of easy synthesis using a simple one step procedure from inexpensive starting materials. Studies directed at examining the biological activities and inclusion behavior of these compounds as well as to extend the scope of the described synthetic method to additional multi-armed heterocyclic compounds are currently in progress.

Acknowledgments

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13. Aldehydes **10a,b, 14–17** were synthesized following reported methods, described by our group or by modification of literature procedures. (a) Kocyigit, O.; Guler, E. *J. Incl. Phenom. Macrocycl. Chem.* **2010**, *67*, 29–37; (b) Rajakumar, P.; Srisailas, M. *Tetrahedron Lett.* **2002**, *43*, 1909–1913; (c) Chand, D. K.; Bharadwaj, P. K. *Tetrahedron Lett.* **1996**, *37*, 8443–8446; (d) Finocchiaro, P.; Consiglio, G. A.; Imbrogiano, A.; Failla, S. *Phosphorus Sulfur Silicon Relat. Elem.* **2007**, *182*, 1689–1701; (e) Elwahy, A. H. M. *Tetrahedron Lett.* **2001**, *42*, 5123–5126. Typical experimental procedure for the synthesis of poly (dihydropyridinyl)arenes **9a,b**, **18a,b** and **19a,b**: To a warm solution of the appropriate poly-aldehyde **10a**, **10b**, **14**, **15**, **16** and **17** (10 mmol) in glacial acetic (5 mL), 3-aminobut-2-enenitrile **6** (6, 8 and 12 equiv, respectively) was added. The resulting yellowish solution was heated at reflux for 2 h then allowed to cool to room temperature. The formed precipitate was filtered, dried, and purified by recrystallization from acetic acid to afford pale yellow crystals of **9a,b**, **18a,b,** and **19a,b,** respectively. Compound (**9a**): Pale yellow solid (78%); m.p. = 286–288 °C. IR (KBr) ν = 3356 (NH), 2202 (CN) cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.03 (s, 18H), 4.34 (s, 3H), 5.15 (s, 6H), 7.06 (d, 6H, J = 6.8 Hz), 7.20 (d, 6H, J = 6.8 Hz), 7.54 (s, 3H), 9.45 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 17.7, 40.0, 69.2, 83.0, 115.0, 119.3, 126.5, 128.8, 136.7, 137.7, 146.4, 157.9. Compound (**18a**): Pale yellow solid (77%); m.p. 294–296 °C; IR (KBr) ν 3358 (NH), 2198 (CN) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.02 (s, 24H), 4.32 (s, 4H), 5.26 (s, 8H), 7.04 (d, 8H, J = 8.4 Hz), 7.18 (d, 8H, J = 8.4 Hz), 7.75 (s, 2H), 9.44 (s, 4H); ^{13}C NMR (DMSO-d_6) δ 17.7, 40.2, 66.9, 82.9, 115.0, 119.3, 128.7, 130.6, 135.0, 136.7, 146.3, 157.7. Compound (**19a**): Pale yellow solid (74%); m.p. 238–240 °C; IR (KBr) ν 3352 (NH), 2202 (CN) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.01 (s, 36H), 4.26 (s, 6H), 5.29 (s, 12H), 6.93 (d, 12H, J = 8.7 Hz), 7.13 (d, 12H, J = 8.7 Hz), 9.42 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 17.7, 40.0, 63.9, 82.9, 115.1, 119.3, 128.8, 136.9, 137.6, 146.4, 157.7.
14. The infrared spectra were recorded on potassium bromide disks using a Pye Unicam SP 3–300 and Shimadzu FTIR 8101 PC infrared spectrophotometer. The ^1H NMR spectra were determined on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard and DMSO-d6 as a solvent. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV.
15. All new compounds gave correct analytical data (^1H NMR, ^{13}C NMR, IR, MS, and elemental analyses).