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Stereoselective one-pot five-component synthesis of polysubstituted 1,4,5,6-tetrahydropyridines with two and three stereocenters

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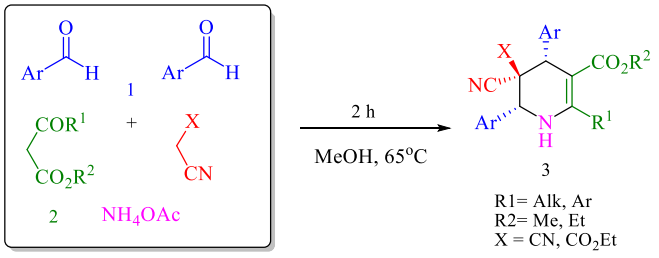
Abstract

A novel five-component stereoselective synthesis of polysubstituted tetrahydropyridines is reported. The Knoevenagel condensation – Michael addition – Mannich reaction – cyclization – dehydration cascade of aldehydes, esters of 3-oxocarboxylic acids C-H acids and ammonium acetate provides convenient access to 2-substituted alkyl (4*SR*,6*RS*)-4,6-diaryl-5,5-dicyano-1,4,5,6-tetrahydropyridi-ne-3-carboxylates with two stereocenters and 3,5-dialkyl (4*RS*, 5*SR*,6*RS*)-5-cyano-2,4,6-triaryl-1,4,5,6-tetrahydropyri-dine-5,3-carboxylates with three stereocenters in 57–84% yields. It was established that formation of products proceeds via substituted 2-hydroxypiperidines with four stereocenters. Ammonium acetate plays a dual role, acting as a base and as a nitrogen source. Five bonds are formed as a result of multicomponent process. Structures of new compounds were confirmed by ^{1}H, ^{13}C NMR, IR, and mass spectral studies. The formation of single diastereomers was confirmed by singe crystal X-ray diffraction studies and 2D-NMR spectroscopy.



Knoevenagel / Michael / Mannich /cyclization / dehydrataton cascade
Formation of 3 C-C, 2 C-N bonds
One diastereomer

Keywords: Multicomponent reactions, tetrahydropyridines, ammonium acetate, C-H acids, stereoselectivity

Introduction

A piperidine ring is a structural unit of a huge number of natural and synthetic biologically active compounds, many of which are widely used in medicine. About a third of all known alkaloids contain a piperidine ring in their structure.[1] Piperidine derivatives play a significant role in the discovery of drugs exhibiting various biological activities such as antihypertensive,[2] antimalarial,[3] neuroprotective,[4,5] antibacterial,[6] anticonvulsant[7] and anti-inflammatory activity.[8] Also piperidine containing drugs are important therapeutic agents in the treatment of influenza,[9-11] diabetes,[12,13] viral infections including AIDS,[14,15] and cancer metastases.[16,17] Among pharmaceutical drugs, substituted 4-arylpiperidine and 4,6-diarylpiperidine derivatives, resembling a pharmacophore fragment of morphine, are of great importance. A number of valuable medicines with various physiological properties have been obtained on their basis, for example, analgesics,[18] neuroleptics,[19] antidepressants,[20] antiallergic drugs,[21] and many others.

At present, many strategies are known for constructing six-membered heterocycles with one nitrogen atom as the only hetero atom, and the overwhelming majority of them are a sequence of classical two-component reactions. This approach has a number of significant disadvantages. In a two-component paradigm, even relatively small and not too complex molecules often have to be synthesized using complex multistep synthesis, which leads to great labor costs and small overall yields, resulting in high cost of final products. This problem becomes especially pressing if several stereocenters are present in the target molecule, which must have a strictly defined configuration. Multicomponent synthesis has already become an instrument of classical organic synthesis. Multicomponent reactions are important processes, in which more than three different reactants directly get converted into one new structure bearing most of the atoms of these reactants.[22-24]

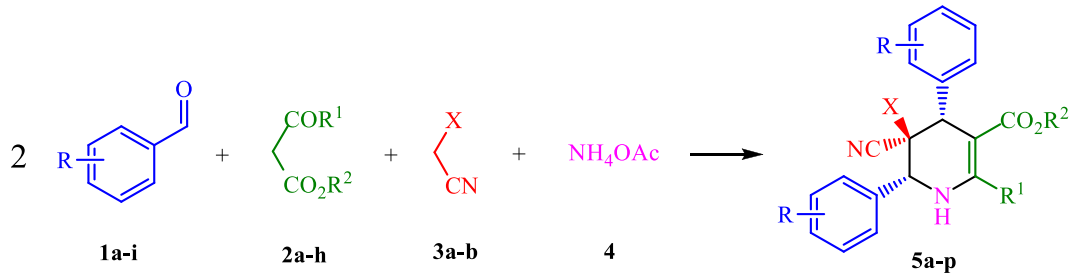
The success of a multicomponent approach in assembling a piperidine ring was demonstrated as far back as in 1917 when a three-component assembly of tropinone, a key compound in the synthesis of atropine, was accomplished. Later, the synthesis of tropinone was improved.[25] At present, this reaction is known as the Robinson-Schöpf reaction. Recently, a multicomponent synthesis of substituted piperidines was carried out applying ammonium acetate[26-32], water ammonia[33-35] or amines[36,37] as a source of nitrogen.

In continuation of our research on the multicomponent synthesis of alicyclic[38-41] and heterocyclic[42-48] derivatives from carbonyl compounds and C-H acids, we report the results of a novel one-pot five-component reaction between aromatic aldehydes, esters of 3-oxocarboxylic acid, nitriles and ammonium acetate for the direct highly stereoselective substituted 1,4,5,6-tetrahydropyridines formation.

Results and Discussion

The Knoevenagel condensation – Michael addition – Mannich reaction – cyclization – dehydration cascade of aldehydes **1** (both with electron-withdrawing and electron-donating substituents), esters of 3-oxocarboxylic acids **2** malononitrile or ethylcyanoacetate and ammonium acetate afforded highly functionalized 1,4,5,6-tetrahydropyridines **5** (Scheme 1, Table 1). Refluxing of the starting compounds in methanol for 2 h leads to the selective formation of products. This technique was developed in the study of multicomponent synthesis of piperidin-2-ones using NH_4OAc as a nitrogen source for the piperidine cycle.[30]

The new multicomponent reaction allows to obtain 2-substituted alkyl 4,6-diaryl-5,5-dicyano-1,4,5,6-tetrahydropyridine-3-carboxylates **5a-n** with two stereocenters and 3,5-dialkyl 5-cyano-2,4,6-triaryl-1,4,5,6-tetrahydropyri-dine-5,3-carboxylates **5o,p** with three stereocenters in 57-84%. It should be noted, that **5a-n** were isolated by simple filtration of the reaction mixture and column chromatography was avoided entirely. **5o,p** have a higher solubility in methanol and their isolation was more laborious.



Scheme 1. Stereoselective formation of 2-alkyl (4*SR*,6*RS*)-4,6-diaryl-5-cyano-1,4,5,6-tetrahydropyridine-3-carboxylates **5** from aldehydes **1**, ester of 3-oxocarboxylic acid **2**, cyanides **3** and ammonium acetate **4**.

Table 1. Five-component stereoselective substituted 1,4,5,6-tetrahydropyridine **5** synthesis.[a]

Aldehyde	C-H acid	X	R	R^1	R^2	Product	Yield[b]
1a	**2a**	CN	H	Me	Me	**5a**	84
1b	**2a**	CN	3-Me	Me	Me	**5b**	78
1c	**2a**	CN	2-F	Me	Me	**5c**	69
1d	**2a**	CN	3-Cl	Me	Me	**5d**	72
1e	**2a**	CN	4-Br	Me	Me	**5e**	73
1f	**2a**	CN	4-NO_2	Me	Me	**5f**	76
1a	**2b**	CN	H	Me	Et	**5g**	84
1g	**2b**	CN	4-Me	Me	Et	**5h**	82
1h	**2c**	CN	4-Cl	Et	Me	**5i**	71
1f	**2c**	CN	4-NO_2	Et	Me	**5g**	62
1i	**2d**	CN	4-OMe	C_6H_5	Me	**5k**	58
1a	**2e**	CN	H	C_6H_5	Et	**5l**	65
1h	**2e**	CN	4-Cl	C_6H_5	Et	**5m**	81
1g	**2f**	CN	4-Me	4-BrC_6H_4	Me	**5n**	70
1e	**2g**	CO_2Et	4-Br	4-ClC_6H_4	Me	**5o**	66
1h	**2h**	CO_2Et	4-Cl	4-ClC_6H_4	Me	**5p**	57

[a] Reaction conditions: aldehyde **1** (6 mmol), ester of 3-oxocarboxylic acid **2** (3 mmol), malononitrile or ethylcyanoacetate **3** (3 mmol), ammonium acetate **4** (6 mmol) were reflux in methanol (10 mL) for 2 h. Monitored by TLC. [b] Isolated yields.

In the NMR spectra of compounds **5**, only a single set of signals was identified, assuming the stereoselective formation of individual diastereoisomers. The structure of compound **5i** is shown in Figure 1. The X-ray crystal diffraction data indicated that structure **5i** with two stereogenic centers should be determined as methyl (4*SR*,6*RS*)-5,5-dicyano-2-ethyl-4,6-bis(4-chloro)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate. In this conformation, bulky aryl substituents are located in sterically least hindered positions relative to each other.

The structure of **5o** with three stereogenic centers was determined by means of NMR spectroscopy. The full NMR signal assignment has been carried out using 2D NMR techniques such as ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC (See supplementary materials). First of all, it was found signals of the tetrahydropyridine ring in ^{1}H

and ^{13}C spectra. *p*-Hal-phenyl moieties are at the 2nd, 4th and 6th positions and C^2 is substituted by *p*-Cl-phenyl fragment. All respective cross-peaks from $H^o/C^{\#}$ in the ^1H-^{13}C HMBC spectrum are presented. Spatial arrangement of substitutions near C^5 was determined by analyzing ^1H-^{13}C spin coupling constant from the ^{13}C spectrum recorded with only ethyl CH_2 proton decoupling. It was found carboxyl (d, J = 3.4 Hz) and nitrile (t, J = 8.3 Hz) carbon signal (Fig. 3). It can be concluded that nitrile group is in *trans*-position to the axial H^4 and H^6 while COOEt is in *cis* one due to $J_{COO\text{-}H}$ is smaller than $J_{CN\text{-}H}$. Carboxyl carbon has a spin coupling interaction only with H^4. Thus, **5o** has 4*RS*,5*SR*,6*RS* configuration.

A possible reaction pathway is shown in Scheme 2. The Knoevenagel condensation of aromatic aldehyde **1** with malononitrile or ethyl cyanoacetate affords the corresponding cyano-olefin **A**. Michael addition of 3-oxocarboxylic acid ester **2** to the olefin generates alkyl 2-substituted 3-aryl-4-cyanobutanoates **B**, which undergo Mannich reaction of the intermediate arylimine to form amine **C**. Next intramolecular cyclization leads to the formation of 2-substituted 4,6-diaryl-5-cyano-2-hydroxypiperidine-3-carboxylate **6**. Finally, dehydration of alcohol **6** affords corresponding tetrahydropyridine **5**.

To confirm the proposed mechanism, we monitored the reaction between 4-methylbenzaldehyde **1g**, ethylcyanoacetate, methyl 3-(4-bromophenyl)-3-oxopropanoate **2f** and ammonium acetate in methanol at room temperature. The starting compounds, symmetrical para-substituted in aromatic nuclei, were chosen for ease of identification of the reaction products by ^1H NMR spectroscopy. After 50 minutes of stirring, a thick white precipitate formed in the reaction mass. After filtration and drying, this compound (by high resolution mass spectrometry) was identified (by high resolution mass spectrometry) as $C_{29}H_{26}BrN_3O_3$, corresponding to methyl ester 5,5-dicyano-2-(4-bromo)phenyl-2-hydroxy-4,6-bis(4 -methyl)phenylpiperidine-3-carboxylic acid **6**. In the recorded spectra of ^1H and ^{13}C **6**, one set of signals was observed, which indicates the formation of one diastereomer.

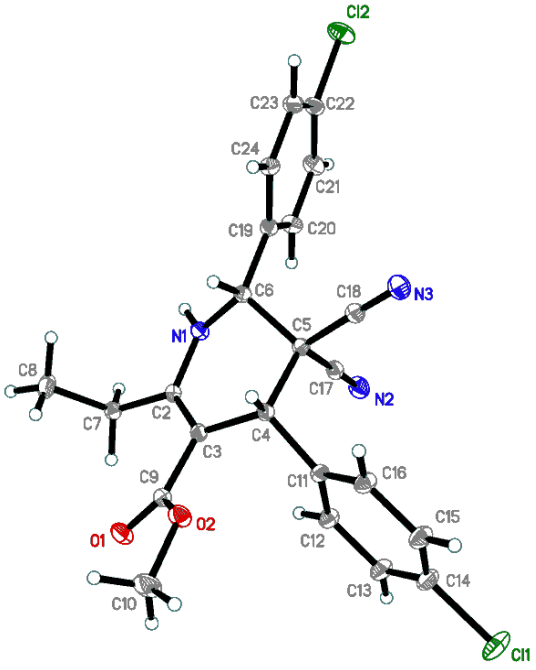


Fig 1. Structure of **5i**. p = 50%.

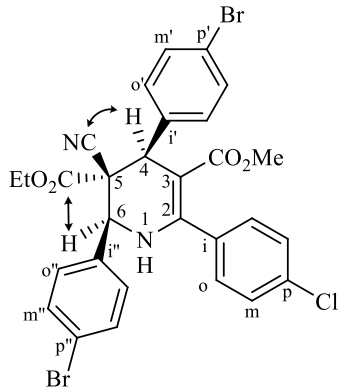


Fig. 2. ^{1}H-^{13}C correlation in HMBC NMR spectrum of **5o**.

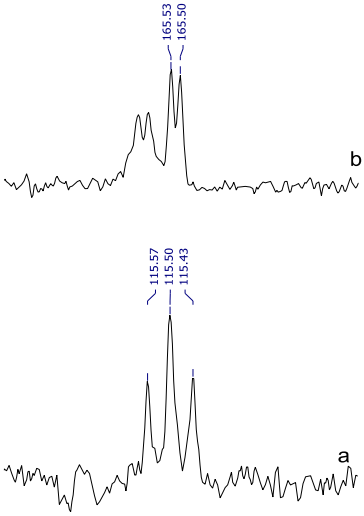
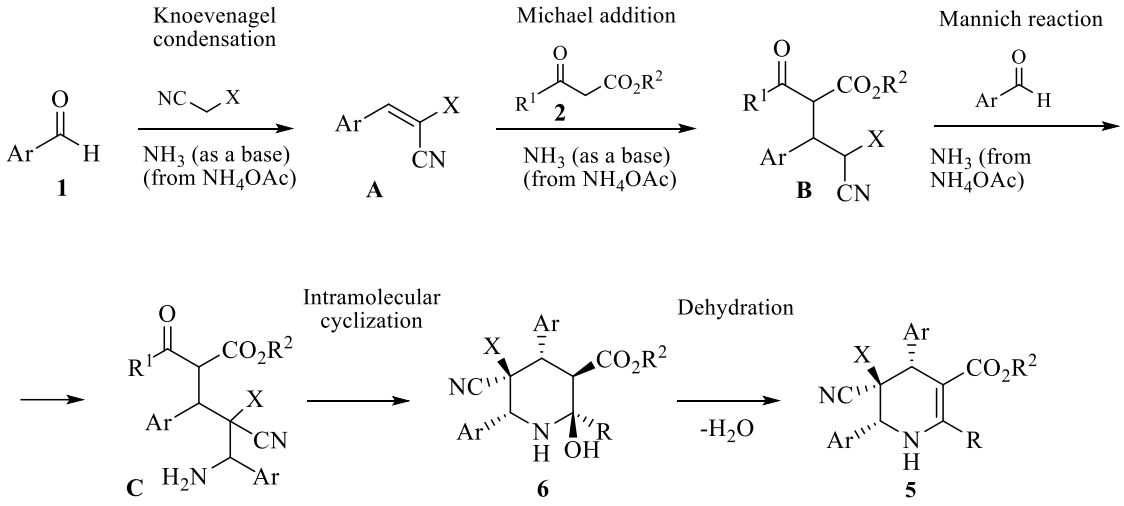


Fig. 3. Fragments of ^{13}C NMR spectra **5o** decoupled from ethyl CH_2 protons (scale is the same): a) CN signal at 115.5 ppm, b) COOEt signal at 165.5 ppm.



Scheme 2. Mechanism of stereoselective polysubstituted 1,4,5,6-tetrahydropyridines **5** formation.

The structure of **6** was confirmed by NMR spectroscopy methods including 2D NMR techniques such as ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC and ^{1}H-^{1}H NOESY (Figure 4). The full assignment of NMR signals has been made (See supplementary materials). In the proton spectrum it was found signals from three *para*-substituted

phenyls in aromatic region, two singlets from protons at heteroatoms (OH at 6.16 ppm and NH at 3.64 ppm), three signals from piperidine ring (δ5.05, 4.33 and 3.41 ppm) and three methyl signals (δ3.09, 2.33 and 2.28 ppm). Protons H^4 and H^3 are axial ones for the characteristic spin coupling constant (J = 12.3 Hz). Location of phenyl rings was determined by observing respective $H^o/C^{\#}$ and $H^{\#}/C^o$ cross-peaks. In addition, OH/C^i ($\delta_{H/C}$ 6.16/143.9 ppm) cross-peak was found. The cross-peak from H^4 and H^6($\delta_{H/H}$ 5.05/4.33 ppm) in NOESY indicate that the protons are in the same half-space relatively piperidine ring. Thus, intermediate 2-hydroxypiperidine has the 2*SR*,3*RS*,4*SR*,6*RS* configuration.

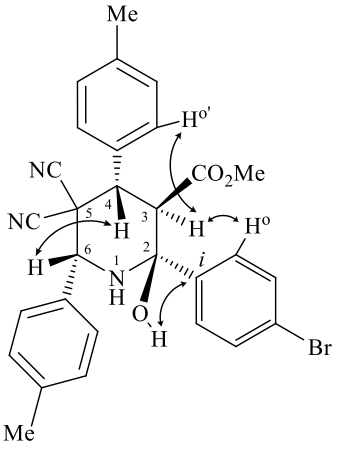


Fig. 4. ^{1}H-^{1}H and ^{1}H-^{13}C correlation in 2D NMR spectra of **6**.

Conclusions

We have developed a *one-pot* five-component stereoselective synthesis of substituted 1,4,5,6-tetrahydropyridine, utilizing aldehydes (both with electron-withdrawing and electron-donating substituents), malononitrile or ethylcyanoacetate, esters of 3-oxocarboxylic acids and ammonium acetate, which played dual role, acting as a base and as a nitrogen source for six-membered nitrogen-containing ring. Five bonds are formed as a result of multicomponent process. Our method allows to obtain 2-substituted alkyl (4*SR*,6*RS*)-4,6-diaryl-5,5-dicyano-1,4,5,6-tetrahydropyridine-3-carboxylates with two stereogenic centers and 3,5-dialkyl (4*RS*, 5*SR*,6*RS*)-5-cyano-2,4,6-triaryl-1,4,5,6-tetrahydropyridine-5,3-carboxylates with three stereocenters in 57–84%. We have proved that 1,4,5,6-tetrahydropyridines formation proceeds via stereoselective formation of substituted (2*SR*,3*RS*,4*SR*,6*RS*)-2-hydroxypiperidines.

Experimental Section

General. All melting points were measured with a Stuart SMP30 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AM300 and Bruker DRX 500 at ambient temperature in DMSO-$d_6$or $CDCl_3$ solutions. Chemical shift values are given in δ scale relative to Me_4Si. The J values are given in hertz. Only discrete or characteristic signals for the 1H NMR are reported. IR spectra were recorded with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. HR-ESI-MS was measured on a Bruker microTOF II instrument; external or internal calibration was done with electrospray calibrant solution (Fluka). All starting materials were obtained from commercial sources and used without purification. All reactions were monitored with thin layer chromatography (TLC) and carried out with Merck precoated plates DC-AlufolienKieselgel60 F254. X-ray crystallographic analyses were performed with Bruker Quest D8 diffractometer.

General procedure for preparation of polysubstituted 1,4,5,6-tetrahydropyridines 5.

Synthesis of 3a-n (General method). A mixture of aldehyde **1** (6 mmol), malononitrile (3 mmol, 0.198 g), ester of 3-oxocarboxylic acid **2** (3 mmol) and ammonium acetate (6 mmol, 0.462) was refluxed in methanol (10 mL)

for 2 h. After the reaction completion, the mixture was maintained at –10 °C for 30 min for the complete precipitation of the product. The precipitate was collected by filtration and dried to give pure tetrahydropyridines **5a-n**.

Synthesis of 5p,o. A mixture of aldehyde **1** (6 mmol), ethylcyanoacetate (3 mmol, 0.339 g), ester of 3-oxocarboxylic acids **2** (3 mmol), and ammonium acetate (6 mmol) was refluxed in methanol (10 mL) for 2 h. After the reaction completion, the methanol was evaporated under reduce pressure. The residue was purified by column chromatography (eluent: hexane/ethylacetate = 3/01) to give pure tetrahydropyridines **5p,o**.

Methyl (4*SR*,6*RS*)-5,5-dicyano-2-methyl-4,6-diphenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (5a). White solid; yield: 0.89 g (84%); mp 218–219 °C. (lit. mp[35] 218–219 °C). ^{1}H-NMR (DMSO-d_6, 300.13 MHz): 2.32 (s, 3H, CH_3), 3.11 (s, 3H, OCH_3), 4.83 (s, 1H, CH), 5.27 (s, 1H, CH), 7.28-7.34 (m, 4H, Ar + NH), 7.52 (dd, 4 H,Ar, J^1 5.9Hz, J^2 1.6 Hz,), 7.63 (m, 2H, Ar) ppm.

Methyl (4*SR*,6*RS*)-5,5-dicyano-2-methyl-4,6-bis(3-methyl)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (5b). White solid; yield: 0.90 g (78%); mp 191-193 °C. IR (KBr): *v* 3422, 2252, 1655, 1453, 1248 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300.13 MHz): 2.38 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.30 (s, 3H, OCH_3), 4.43 (s, 1H, NH), 4.57 (s, 1H, CH), 4.72 (s, 1H, CH), 7.11-7.48 (m, 8H, Ar) ppm. ^{13}C-NMR ($CDCl_3$, 75.47 MHz): 20.3, 21.5 (s, 2C), 48, 50, 51, 51.1, 61.9, 97.8, 111.9, 113.8, 125 (s, 2C), 128.4, 128.5, 129.2, 129.2, 131.5, 133.6, 137.7, 138.1, 139.3, 151.9, 166.9 ppm. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{24}H_{24}N_3O_2^+$: 386.1863; found: 386.1857.

Methyl (4*SR*,6*RS*)-5,5-dicyano-2-methyl-4,6-bis(2-fluoro)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (5c). White solid; yield: 0.81 g (69%); mp 191-193 °C. IR (KBr): *v* 3355, 2253, 1688, 1458, 1249, 1187 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300.13 MHz): 2.42 (s, 3H, CH_3), 3.29 (s, 3H, OCH_3), 4.42 (s, 1H, CH), 5.18 (s, 1H, NH), 5.33 (s, 1H, CH), 7.10-7.38 (m, 5H, Ar), 7.42-7.56 (m, 2H, Ar), 7.85 (t, *J* 7.19Hz, 1H, Ar) ppm. ^{13}C-NMR($CDCl_3$, 75.47 MHz): δ 20.2, 45.9, 50.6, 53.8, 53.9, 97.2, 112.1, 112.5, 115.6 (d, $J^2_{C\text{-}F}$ 22.8 Hz, 1C), 116.3 (d, $J^2_{C\text{-}F}$ 21.9 Hz, 1C), 120.9 (d, $J^3_{C\text{-}F}$ 11.6 Hz, 1C), 124.3 (d, $J^5_{C\text{-}F}$ 3.5 Hz, 1C), 125.1 (d, $J^3_{C\text{-}F}$ 12.9 Hz, 1C), 125.3 (d, $J^5_{C\text{-}F}$ 3.7 Hz, 1C), 127.6 (d, $J^6_{C\text{-}F}$ 1.3 Hz, 1C), 127.9, 130 (d, $J^4_{C\text{-}F}$ 8.4 Hz, 1C), 132.3 (d, $J^4_{C\text{-}F}$ 8.6 Hz, 1C), 153.1, 160.6 (d, $J^1_{C\text{-}F}$ 250.5 Hz, 1C), 160.9 (d, $J^1_{C\text{-}F}$ 248 Hz, 1C), 166.4 ppm. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{22}H_{18}F_2N_3O_2^+$: 394.1362; found: 394.1369.

Methyl (4*SR*,6*RS*)-5,5-dicyano-2-methyl-4,6-bis(3-chloro)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (5d). White solid; yield: 0.92 g (72%); mp 210-213°C. IR(KBr): *v* 3411, 2240, 1712, 1458, 1247, 711 cm^{-1}. ^{1}H-NMR (DMSO-d_6,300.13 MHz): 2.34 (s, 3H, CH_3), 3.18(s, 3H, OCH_3), 4.86 (s, H, CH), 5.31 (s, H, CH), 7.25-7.63 (m, 7H, Ar + NH), 7.68 (d, *J* 10.15Hz, 2H, Ar) ppm. ^{13}C-NMR ($CDCl_3$, 75.47 MHz): 20.3, 47, 48, 50.5, 50.7, 61.2, 97.2, 111.4, 113.2, 125, 86, 126.3, 128.1 (s, 2C), 128.8, 129.9, 130.7, 131.1, 134.5, 135.2, 135.4, 139.7, 152.7, 166.4 ppm. HRMS (ESI) *m/z* $[M + H]^+$(for ^{35}Cl) 426.0765 calcd for $C_{22}H_{18}Cl_2N_3O_2^+$: 426.0765, (for ^{35}Cl and ^{37}Cl) 428.0740 calcd for $C_{22}H_{18}Cl_2N_3O_2^+$: 428.0742.

Methyl (4*SR*,6*RS*)-5,5-dicyano-2-methyl-4,6-bis(4-bromo)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (5e). White solid; yield: 1.13 g (73%); mp 197–198 °C. (lit.mp[35] 197–198 °C). ^{1}H-NMR (DMSO-d_6, 300.13 MHz): 2.34 (s, 3H, CH_3), 3.19 (s, 3H, OCH_3), 4.85 (s, 1H, CH), 5.31 (s, 1H, CH), 7.27 (d, *J* 8.5 Hz, 2H, Ar), 7.60 (dd, J_1 8.5 Hz, J_2 2.9 Hz, 4H, Ar), 7.66 (s, 1H, NH), 7.79 (d, *J* 8.5 Hz, 2H, Ar) ppm.

Methyl (4*SR*,6*RS*)-5,5-dicyano-2-methyl-4,6-bis(4-nitro)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (5f) White solid; yield: 1.02g (76%); m.p 250-251°C. (lit.mp[35] 250-251°C). ^{1}H-NMR (DMSO-d_6, 300.13MHz): δ = 2.4 (s, 3H, CH_3), 3.19 (s, 3H, OCH_3), 5.1 (s, H, CH),5.55 (s, H, CH), 7.02 (d, 3 H, Ar + NH, *J* 8.8 Hz), 7.61 (d, *J* 8.8Hz, 2H, Ar), 8.31 (s, 2 H, Ar, *J* 8.8 Hz), 8.46 (d, 2 H, Ar, *J* 8.8 Hz) ppm.

Ethyl (4*SR*,6*RS*)-5,5-dicyano-2-methyl-4,6-diphenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (5g). White solid; yield: 0.93 g (84%); mp 200-202 °C. IR (KBr): *v* 3312, 2252, 1644, 1470, 1456, 1247 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 500.13 MHz): 0,57 (t, *J* 7.12Hz, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.64 (m, 2HCH_2), 4.86 (s 1HCH), 5.31 (s, 1H, CH),

7.31-7.72 (m, 11H, Ar + NH) ppm. ^{13}C-NMR (DMSO-d_6, 75.47 MHz): 13.8, 19.4, 48.2, 49.6, 58.6, 60, 94.9, 113.4, 114.4, 128.3 (s, 3C), 128.6 (s, 2C), 128.8 (s, 2C), 129.1 (s, 2C), 130.4, 134.8, 139.7, 154.3, 166.3 ppm. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{23}H_{22}N_3O_2^+$: 372.1707; found: 372.1700.

Ethyl (4*SR*,6*RS*)-5,5-dicyano-2-methyl-4,6-bis(4-methyl)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (5h) White solid; yield: 0.98 g (82%); mp 224–225 °C. (lit. mp[35] 224–225 °C). ^{1}H-NMR (DMSO-d_6, 300.13 MHz): 0.59 (t, *J* 7.3 Hz, 3H, CH_3),2.31 (s, 6H, $2CH_3$),2.37 (s, 3H, CH_3),3.64 (qd, J_1 12.2 Hz, J_2 6.6 Hz, 2H, OCH_2), 4.76 (s, 1H, CH),5.21 (s, 1H, CH),7.20 (dd, $J_1$8.8Hz, J_2 2.2 Hz, 4H, Ar),7.33 (d, *J* 8.1 Hz, 2H, Ar), 7.42 (s, 1H, NH),7.52 (d, *J* 8.1 Hz, 2H, Ar) ppm.

Methyl (4*SR*,6*RS*)-5,5-dicyano-2-ethyl-4,6-bis(4-chloro)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (5i). White solid; yield: 0.93 g (71%); mp 132-135°C. IR (KBr): *v* 3420, 2255, 1705, 1464, 1260, 837 cm^{-1}. ^{1}H-NMR ($CDCl_3$ 300.13 MHz): ppm. 1.33 (t, *J* 7.5 Hz, 3H, CH_3), 2.93-2.65 (m, 2H, CH_2), 3.32 (s, 3H, OCH_3), 4.50 (s, 1H, NH), 4.60 (s, 1H, CH), 4.75 (s, 1H, CH), 7.35-7.38 (m, 4H, Ar), 7.5 (d, *J* 8.5 Hz, 2H, Ar), 7.59 (d, *J* 8.5 Hz, 2H, Ar) ppm. ^{13}C-NMR ($CDCl_3$, 75.47 MHz): 13.4, 27, 47.8, 50.2, 50.7, 60.9, 96.3, 111.5, 113.4, 128.9 (s, 2C), 129.1 (s, 2C), 129.2 (s, 2C), 129.7 (s, 2C), 131.9, 134.3, 136.3, 136.9, 158, 166.1 ppm. HRMS (ESI) m/z $[M + H]^+$ (for ^{35}Cl) 440.0922 calcd for $C_{27}H_{20}Cl_2N_3O_2^+$: 440.0927.

X-ray diffraction data were collected at 100K on a Bruker Quest D8 diffractometer equipped with a Photon-III area-detector (graphite monochromator, shutterless φ- and ω-scan technique), using Mo K_a-radiation. The intensity data were integrated by the SAINT program[49] and were corrected for absorption and decay using SADABS.[50] The structure was solved by direct methods using SHELXT[51] and refined on F^2 using SHELXL-2018.[52] All non-hydrogen atoms were refined with individual anisotropic displacement parameters. The location of atom H1 was found from the electron density-difference map; it was refined with an individual isotropic displacement parameter. All other hydrogen atoms were placed in ideal calculated positions and refined as riding atoms with relative isotropic displacement parameters. The SHELXTL program suite[48] was used for molecular graphics. **Crystal Data** for $C_{24}H_{23}Cl_2N_3O_3$ **5i**, Formula weight 472.35, T = 100(2) K, Wavelength 0.71073 Å, Crystal system Monoclinic, Space group $P2_1/c$, Unit cell dimensions a = 12.5724(4) Å a= 90°; b = 16.7206(5) Å b= 95.6182(11)°; c = 11.2121(4) Å g = 90°, Volume 2345.66(13) Å3, Z = 4, Density (calculated) 1.338 g/cm3, Absorption coefficient 0.307 mm-1, F(000) 984, Crystal size 0.59 x 0.59 x 0.56 mm3, Theta range for data collection 2.033 to 38.575°, Index ranges -22<=h<=22; -29<=k<=29; -19<=l<=19, Reflections collected 98467, Independent reflections 13254 [R(int) = 0.0312], Observed reflections 11486, Completeness to theta = 25.242° 99.9 %, Absorption correction Semi-empirical from equivalents, Max. and min. transmission 0.6085 and 0.5229, Refinement method Full-matrix least-squares on F2, Data / restraints / parameters 13254 / 0 / 301, Goodness-of-fit on F2 1.036, Final R indices [I>2sigma(I)] R1 = 0.0367, wR2 = 0.0964, R indices (all data) R1 = 0.0443, wR2 = 0.1021, Extinction coefficient 0.0028(7), Largest diff. peak and hole 0.608 and -0.681 e.Å-3. Obtained crystal structure was deposited in CCDC No. 2032520

Methyl (4*SR*,6*RS*)-5,5-dicyano-2-ethyl-4,6-bis(4-nitro)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (5j). White solid; yield: 0.86 g (62%); mp 243-248°C. IR (KBr): *v* 3387, 2250, 1685, 1484, 1349, 1256 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300.13 MHz): 1.27 (t, *J* 7.3Hz, 3H, CH_3), 2.65-2.88 (m, 2H, CH_2), 3.16 (s, 3H, OCH_3), 5.08 (s, 1H, CH), 5.52 (s, 1H, CH), 7.58 (d, *J* 8.5 Hz, 2H, Ar), 7.9 (d, *J* 8.9 Hz, 2H, Ar), 7.92 (s, 1H, NH), 8.3 (d, *J* 8.8 Hz, 2H, Ar), 8.44 (d, *J* 8.7 Hz, 2H, Ar) ppm. ^{13}C-NMR (DMSO-d_6, 75.47 MHz): 14.5, 26.2, 47, 48.8, 50.5, 58.9, 92.8, 112.5, 113.5, 124 (s, 2C), 124.1 (s, 2C), 129.2 (s, 2C), 130.3 (s, 2C), 141, 147.2, 149.1, 161.3, 166 ppm. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{23}H_{20}N_5O_6^+$: 462.1408; found: 462.1401.

Methyl (4*SR*,6*RS*)-5,5-dicyano-2-phenyl-4,6-bis(4-methoxy)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (5k). White solid; yield: 0.83 g (58%); mp 133-137°C. IR(KBr): *v* 3440, 2250, 1460, 1263, 1133cm^{-1}. ^{1}H-NMR ($CDCl_3$ 500.13MHz): 3.17 (s, 3H, OCH_3), 3.83 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 4.68 (s, 1H, NH), 4.71 (s, 1H, CH), 4.92 (s, 1H,

CH), 6.95 (d, *J* 8.7Hz, 2H, Ar), 7 (d, *J* 8.7Hz, 2H, Ar), 7.43-7.53 (m, 7H, Ar), 7.58 (d, *J* 8.7Hz, 2H, Ar) ppm. ^{13}C-NMR ($CDCl_3$, 125.76 MHz): 48.8, 50.5, 50.9, 55.2, 55.4, 61.7, 99.1, 112.1, 113.9, 114.1 (s, 2C), 114.5 (s, 2C), 125.3, 128.3 (s, 2C), 128.4 (s, 2C), 129.1, 129.2 (s, 4C), 129.7, 136.6, 153.9, 159.7, 161.3, 166.2 ppm. HRMS (ESI) [M + H]$^+$ calcd for $C_{29}H_{26}N_3O_4^+$: 480.1918; found: 480.1913.

Ethyl (4*SR*,6*RS*)-5,5-dicyano-2-phenyl-4,6-diphenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (5l). White solid; yield: 0.84 g (65%); mp 118-121°C. IR (KBr): *v* 3385, 2240, 1699, 1466, 1260 cm^{-1}. ^{1}H-NMR ($CDCl_3$ 300.13 MHz): 0.6 (t, *J* 7.1 Hz, 3H, CH_3), 3.56-3.75 (m, 2H CH_2), 4.6 (s, 1H, NH), 4.79 (s, 1H, CH), 4.98 (s, 1H, CH), 7.34-7.72 (m, 15H, Ar) ppm. ^{13}C-NMR ($CDCl_3$, 75.47 MHz): 13.3, 48.2, 51.3, 59.5, 62.2, 99.2, 111.8, 113.7, 127.9 (s, 2C), 128.2 (s, 4C), 128.51 (s, 2C), 128.6, 128.7 (s, 2C), 129.4 (s, 2C), 129.7, 130.8, 133.3, 136.5, 137.3, 153.9, 165.4 ppm. HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{28}H_{24}N_3O_2^+$: 434.1863; found: 434.1850.

Ethyl (4*SR*,6*RS*)-5,5-dicyano-2-phenyl-4,6-bis(4-chloro)phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (5m) White solid; yield: 1.22g (81%); m.p 193-197°C. IR (KBr): *v* 3334, 2250, 1700, 1259, 771 cm^{-1}. ^{1}H-NMR ($CDCl_3$ 300.13MHz): 0.64 (t, *J* 7.1 Hz, 3H, CH_3), 3.57-3.76 (m, 2HCH_2), 4.55 (s, 1H, NH), 4.75 (s, 1H, CH), 4.96 (s, 1H, CH), 7.4 (d, *J* 8.4 Hz, 2H, Ar), 7.45-7.53 (m, 9H, Ar), 7.61 (d, *J* 8.5 Hz, 2H, Ar) ppm. ^{13}C-NMR ($CDCl_3$, 75.47 MHz): 13.4, 48, 50.5, 59.7, 61.5, 98.9, 111.5, 113.3, 128.3 (s, 4C), 129 (s, 2C), 129.3 (s, 2C), 129.5 (s, 2C), 129.7 (s, 2C), 129.8, 131.6, 134.6, 135.7, 136.3, 137, 154.1, 165.2 ppm. HRMS (ESI) *m/z* [M + H]$^+$ (for ^{35}Cl) 502.1075 calcd for $C_{28}H_{22}Cl_2N_3O_2^+$: 502.1084, (for ^{35}Cl and ^{37}Cl) 504.1053 calcd for $C_{28}H_{22}Cl_2N_3O_2^+$: 504.1056.

Methyl (4*SR*,6*RS*)-5,5-dicyano-2-(4-bromo)phenyl-4,6-diphenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (5n). White solid; yield: 1.04 g (70%); mp 167-170°C. IR(KBr): *v* 3305, 2258, 1713, 1262, 1212, 704 cm^{-1}. ^{1}H-NMR ($CDCl_3$ 300.13MHz): 3.17 (s, 3H, OCH_3), 4.57 (s, 1H, NH), 4.75 (s, 1H, CH), 4.96 (s, 1H, CH), 7.33-7.69 (m, 14H, Ar) ppm. ^{13}C-NMR ($CDCl_3$, 75.47 MHz): 48.1, 50.8, 51.2, 62.2, 99.5, 111.7, 113.5, 124.2, 127.9 (s, 2C), 128 (s, 2C), 128.7 (s, 2C), 129.6 (s, 2C), 130.2 (s, 2C), 130.9 (s, 2C), 131.5 (s, 2C), 133.05, 135.1, 136.1, 152.8, 165.7 ppm. HRMS (ESI) *m/z* [M + H]$^+$ (for ^{79}Br) 498.0806 calcd for $C_{23}H_{20}Br_2N_3O_2^+$: 498.0812, (for ^{81}Br) 500.0793 calcd for $C_{23}H_{20}Br_2N_3O_2^+$: 500.0793.

5-ethyl 3-methyl (4*RS*,5*SR*,6*RS*)-5-cyano-2-(4-chloro)phenyl-4,6-bis(4-bromo)phenyl-1,4,5,6-tetrahydro-pyridine-5,3-carboxylate (5o). White solid; yield: 1.21 g (66%); mp 205-208°C.IR (KBr): *v* 3333, 2247, 1739, 1259, 810, 500cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 0.89 (t, *J* 7.1 Hz, 3H, CH_3), 3.00 (s, 3H, OMe), 3.82-4.02 (m, 2H, CH_2), 4.75 (s, 1H), 5.02 (d, *J* 1.8 Hz, 1H), 7.18 (d, *J* 8.0 Hz, 2H), 7.45 – 7.39 (m, 4H), 7.47 (d, *J* 8.6 Hz, 2H), 7.52 (d, *J* 8.6 Hz, 2H), 7.63 (d, *J* 8.6 Hz, 2H), 7.77 (d, *J* 1.8 Hz, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 13.5, 48.3, 49.9, 58.4, 60.4, 62.8, 96.6, 115.2, 120.4, 122.7, 127.5 (2C),129.4 (2C), 130.5 (2C), 130.8 (2C), 131.1 (2C), 131.2 (2C), 133.4, 133.5, 135.6, 138.9, 154.8, 165.5, 165.6 ppm. HRMS (ESI) *m/z* [M + H]$^+$ (for ^{35}Cl and ^{79}Br) 656.9786 calcd for $C_{29}H_{24}Br_2ClN_2O_4^+$: 656.9776.

5-ethyl-3-methyl (4*RS*,5*SR*,6*RS*)-5-cyano-2-(4-chloro)phenyl-4,6-bis(4-chloro)phenyl-1,4,5,6-tetrahydro-pyridine-5,3-carboxylate (5p). White solid; yield: 0.97 g (57%); mp 190-192°C. IR (KBr): *v* =3334, 2250, 1740, 1260, 811 cm^{-1}. ^{1}H-NMR ($CDCl_3$ 300.13MHz): 0.89 (t, *J* 7,1 Hz, 3H, CH_3), 3.17 (s, 3H, OCH_3), 3.93 (q, *J* 7 Hz, 2H, OCH_2), 4.49 (s, 1H, NH), 4.85 (s, 1H, CH), 4.89 (s, 1H, CH), 7.26-7.53 (m, 12H, Ar) ppm.^{13}C-NMR($CDCl_3$, 75.47 MHz): 13.57, 49.17, 50.54, 57.80, 61.27, 63.06, 100.4, 114.89, 128.46 (s, 2C), 128.61 (s, 2C), 129.04 (s, 2C), 129.23 (s, 2C), 129.32 (s, 2C), 129.89 (s, 2C), 132.71, 133.65, 135.24, 135.61, 136.18, 137.01, 152.41, 166.12 (s, 2C) ppm. HRMS (ESI) *m/z* [M + H]$^+$ (for ^{35}Cl) 569.0796 calcd for $C_{29}H_{24}Cl_3N_2O_4^+$: 569.0779.

Synthesis of 6. A mixture of 4-methylbenzaldehyde **1g** (3 mmol, 0.36 g), malononitrile (3 mmol, 0.198 g), methyl 3-(4-bromophenyl)-3-oxopropanoate **2f** (3 mmol, 0.771 g) and ammonium acetate (6 mmol, 0.462 g) was stirred in methanol (7 mL) at r.t for 50 min. The precipitate was collected by filtration and dried to give pure 2-OH-piperidine **6**.

Methyl (2*SR*,3*RS*,4*SR*,6*RS*)-5,5-dicyano-2-(4-bromo)phenyl-2-hydroxy-4,6-bis(4-methyl)phenyl-piperidine-3-carboxylate (6). White solid; yield: 1.34 g (82%); mp 144-146°C. IR (KBr): *v* = 3490, 3316, 2250, 1715, 512 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 2.28 (s, 3H, CH_3),2.33 (s, 3H, CH_3), 3.09 (s, 3H, OCH_3),3.41 (d, *J* 12.3 Hz, 1H), 3.64 (s, 1H, NH), 4.33 (d, *J* 12.3 Hz, 1H), 5.05 (s, 1H), 6.16 (s, 1H, OH), 7.19 (d, *J* 7.9 Hz, 2H), 7.27 (d, *J* 7.9 Hz, 2H), 7.31 (d, *J* 8.0 Hz, 2H), 7.59 (d, *J* 7.9 Hz, 2H), 7.63 (m, 4H) ppm. ^{13}C NMR (DMSO-d_6, 101 MHz,) δ: 20.6, 20.8, 45.7, 49.0, 51.1, 54.1, 58.6, 83.7, 113.0, 113.7, 121.3, 128.2 (2C), 128.3 (4C), 128.9 (2C), 129.2 (2C), 130.7 (2C), 132.8, 133.4, 138.2, 139.0, 143.9, 168.1 ppm. HRMS (ESI) m/z $[M + H]^+$ (for ^{79}Br) 544.1230 calcd for $C_{29}H_{27}BrN_3O_3^+$: 544.1217.

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