

A one-pot synthesis of highly substituted tetrahydropyridines from *N*-benzylidenemethanamines, dialkyl acetylenedicarboxylates and benzylidenemalononitriles

Hossein Mehrabi* and Ahmad Mohebbi

Department of Chemistry, Vali-e-Asr University of Rafsanjan, 77176 Rafsanjan, Iran

E-mail: mehraby_h@yahoo.com

DOI: <http://dx.doi.org/10.3998/ark.5550190.p009.701>

Abstract

A simple and efficient synthesis of highly substituted tetrahydropyridines has been developed using a one-pot, two step reactions. The synthesis of a series of *N*-benzylidenemethanamines from benzylamines and benzaldehydes in the presence of acetic acid, followed by cyclization with dialkyl acetylenedicarboxylates and benzylidenemalononitriles, gave the corresponding tetrahydropyridines in good yields.

Keywords: Tetrahydropyridines, *N*-benzylidenemethanamines, dialkyl acetylenedicarboxylates, benzylidenemalononitriles

Introduction

Tetrahydropyridines are one of the fundamental heterocycles, which have been the subject of intense research for their outstanding biological properties and wide range of applications to pharmaceutical compounds and synthetic intermediates.¹⁻⁸ Tetrahydropyridine derivatives are also useful against several metabolic disorders and human ailments. The prominent biological activities associated with this pharmacophore are antiparasitic, antimicrobial, anticancer and antiviral. Further, these are intricately involved in MAO based mechanism in Parkinson's disease,²⁻¹³ as inhibitors of farnesyl transferase,¹⁴ dihydroorotate dehydrogenase^{15,16} and also play key roles in many disease processes.

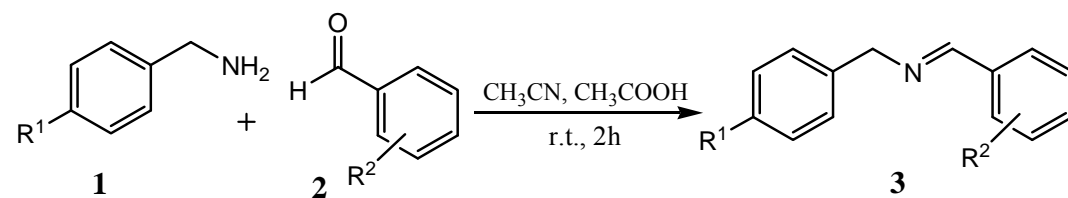
The first synthesis of dihydropyridines *via* a cyclocondensation reaction of acetoacetic ester, aldehyde and ammonia was reported by Arthur Hantzsch in 1882.¹⁷ Multi-component reactions (MCRs) have emerged as a powerful synthetic tool in organic synthesis due to their advantages over the conventional multi-step synthesis.¹⁸ Therefore, an strategy for the synthesis of the functionalized tetrahydropyridines is using MCRs. One of the most generally used approaches for the synthesis of this class of compounds is three-component reactions of anilines, aromatic aldehydes and acetoacetates in the presence of L-proline/TFA,¹⁹ bromodimethylsulfonium

bromide (BDMS),²⁰ tetrabutylammonium tribromide (TBATB),²¹ molecular iodine,²² indium chloride (InCl₃),²³ zirconium oxy chloride (ZrOCl₂),²⁴ ceric ammonium nitrate (CAN)²⁵ and silica-supported boron trifluoride (BF₃.SiO₂).²⁶ Four-component reactions of acetylenedicarboxylates, malononitrile, aldehydes and amines in the presence of polyethylene glycol (PEG),²⁷ L-proline/FeCl₃²⁸ and the base conditions,²⁹ is also reported to give tetrahydropyridines. The reaction of Meldrum's acid, acetoacetates, aromatic aldehydes and ammonium acetate by using Lawesson's reagent under microwave irradiation is also known to give tetrahydropyridines.³⁰ Although these methods have their own merits, but suffer from the drawbacks with respect to cost of reagents, reaction conditions, and reaction work-ups. Consequently, this tandem reaction still requires an efficient protocol for the synthesis of tetrahydropyridine derivatives. Herein we report a one-pot, two-step synthesis of substituted tetrahydropyridines *via* benzylamines and aldehydes with dialkyl acetylenedicarboxylates and benzylidenemalononitriles as starting materials under catalyst-free conditions.

Results and Discussion

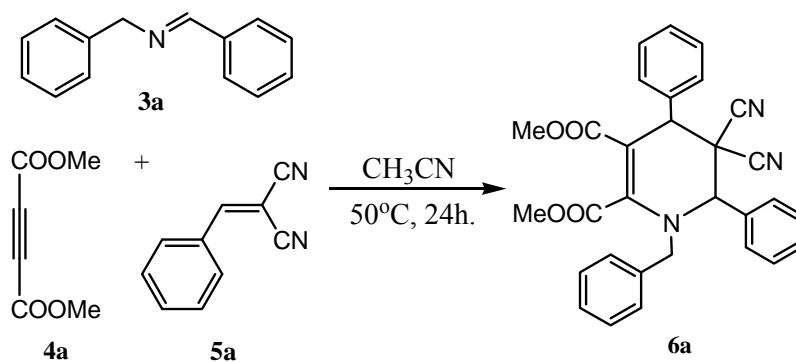
We began our investigation with the construction of *N*-benzylidenemethanamines, which are versatile synthetic intermediates, from benzylamines and benzaldehyde derivatives (Table 1). The initial reaction was attempted using benzylamine (**1a**) and benzaldehyde (**2a**) (Table 1, entry 1). When **1a** and **2a** were treated in the presence of two drops acetic acid in acetonitrile at room temperature, *N*-benzylidenemethanamine (**3a**) was obtained in 85% yield. Various *N*-benzylidenemethanamines **3** were prepared in good yields as shown in Table 1.

After the successful preparation of *N*-benzylidenemethanamines **3a-3f**, and with the aim to construct substituted tetrahydropyridines, we selected **3a** as a model compound to examine its reactions with a dimethyl acetylenedicarboxylate and a benzylidenemalononitrile under different conditions. Upon treatment of **3a** with dimethyl acetylenedicarboxylate (**4a**) and 2-benzylidenemalononitrile (**5a**) in acetonitrile solvent, the reaction furnished the desired product, dimethyl 1-benzyl-5,5-dicyano-1,4,5,6-tetrahydro-4,6-diphenylpyridine-2,3-dicarboxylate (**6a**) (Scheme 1).

Table 1. Synthesis of *N*-benzylidenemethanamines

Entry	R ₁	R ₂	Product	Yield (%) ^a
1	H	H		85
2	H	4-OMe		82
3	OMe	H		88
4	Cl	H		80
5	Cl	2-Cl		78
6	H	2-Cl		80

^a Yields are given for isolated product

**Scheme 1.** The optimization of the model reaction.

The optimization of the reaction conditions, including mmol of starting materials, reaction solvent, temperature, and the time of reaction, was then investigated. First, solvent-free conditions and various solvent were screened (Table 2, entries 1–6), with acetonitrile proving to be the best for this reaction. Then, we examined the influence of different temperature on this reaction. To our satisfaction, when the reaction was carried out at room temperature in 24h, the product was 62% yield but at 50°C and reflux conditions in the same time the product was 75% and 70% yield respectively (Table 2, entries 7-9). Finally, we observed that the ratio of starting materials also had an important influence on the reaction, a more amount of **4a** (for example, 1.5 mmol) in acetonitrile at 50°C resulted in a more yield, 80% (Table 2, entries 9-11).

Table 2. Optimization of the synthesis of highly substituted tetrahydropyridines

Entry	3a:4a:5a	Solvent/Temp (°C)	Time (h)	Yield ^a (%)
1	1:1:1	Solvent-free, rt	12	0
2	1:1:1	MeOH, rt	12	Trace
3	1:1:1	EtOH, rt	12	Trace
4	1:1:1	THF, rt	12	Trace
5	1:1:1	DCM, rt	12	30
6	1:1:1	MeCN, rt	12	50
7	1:1:1	MeCN, rt	24	62
8	1:1:1	MeCN, 50°C	24	75
9	1:1:1	MeCN, reflux	24	70
10	1:1.2:1	MeCN, 50°C	24	77
11	1:1.5:1	MeCN, 50°C	24	80

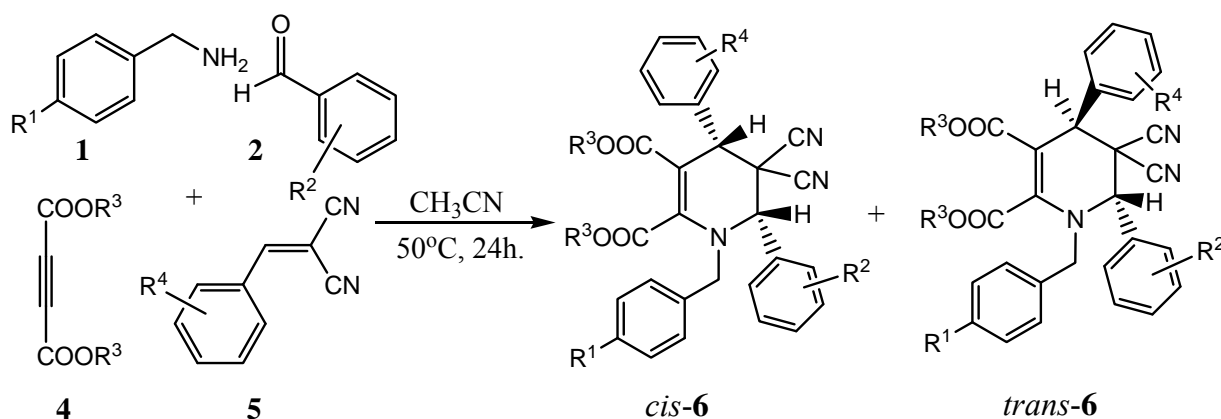
^aYields are given for isolated product.

With the optimized conditions in hand (Table 2, entry 11), we next investigated the possibility of the synthesis of substituted tetrahydropyridines *via* a one-pot reaction from benzylamines and aldehydes with dialkyl acetylenedicarboxylates and benzylidenemalononitriles. To explore the scope of this novel transformation, various benzylamines, aldehydes, dialkyl acetylenedicarboxylates and benzylidenemalononitriles were utilized under the optimized one-pot conditions. The results in Table 3 show that all the reactions proceeded smoothly to afford the diastereoisomeric substituted tetrahydropyridines (*cis*-**6** and *trans*-**6**) in good yields. Of course, we could not to separate the diastereoisomers from the mixture of reaction by column chromatography.

The NMR spectra of the resulting mixture clearly showed the presence of two the diastereoisomeric *cis*-**6** and *trans*-**6**. The ratio of isomers was determined from the intensities of specific signals in ¹H NMR spectra. For instance, the ¹H NMR spectrum of the compound **6a** consisted of two singlet signals at δ 3.32 (3H, Minor isomer) and δ 3.51 (5H, Major isomer) ppm due to the methoxy groups, one singlet signal at δ 3.88 (3H, Minor isomer) ppm for the methoxy

group, a multiplet at δ 3.97-4.08 (9H, Major/Minor isomers) ppm due to the methoxy group, the CH chiral proton and the CH₂-Ph methylene protons, a multiplet at δ 4.36-4.54 (6H, Major/Minor isomers) ppm for the CH chiral proton and the CH₂-Ph methylene protons, and a multiplet at δ 6.98-7.42 (39H, Major/Minor isomers) ppm for the aromatic protons of the phenyl rings. The ¹H decoupled ¹³C NMR spectrum of compound **6a** showed 41 distinct signals in agreement with the proposed two isomer structure that characteristic 12 signals for the chiral, benzylic, and methoxy carbons at δ 29.71-63.29 ppm, 5 signals for cyanide and alkene carbons at δ 96.19-113.84 ppm, 20 signals due to the aromatic carbons of the phenyl rings at δ 128.23-149.91 ppm, and 4 signals for the carbonyl carbons at δ 165.01-165.81 ppm.

Table 3. Synthesis of highly substituted tetrahydropyridines

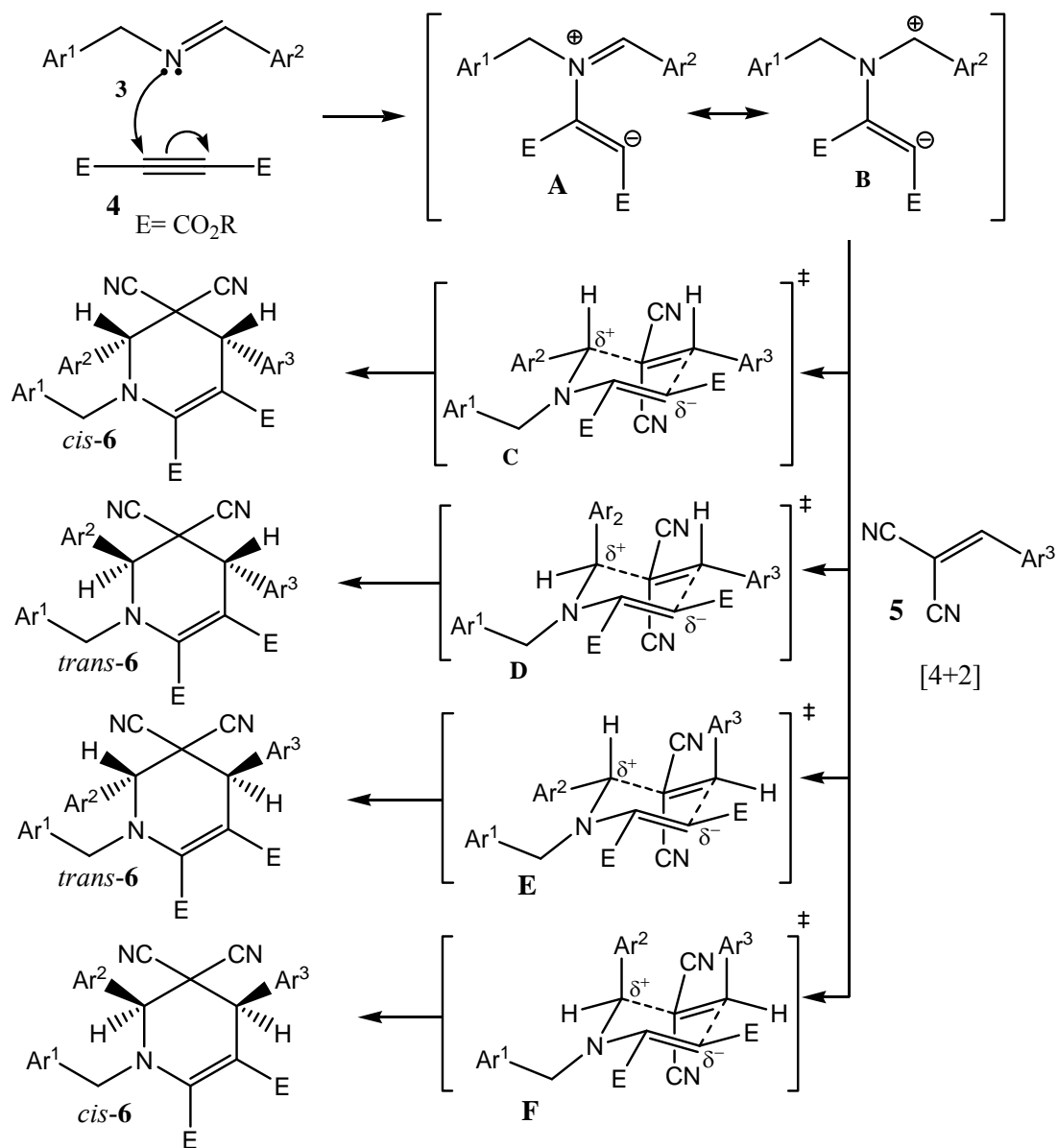


Entry	R ¹	R ²	R ³	R ⁴	Product	Yield ^a (%)	Major/Minor
1	H	H	Me	H	6a	80	1.7:1.0
2	H	H	Me	4-OMe	6b	73	2.0:1.0
3	H	H	Me	4-NO ₂	6c	77	3.3:1.0
4	H	4-OMe	Me	H	6d	72	1.8:1.0
5	OMe	H	Me	2-Cl	6e	83	1.7:1.0
6	H	H	Me	4-Cl	6f	85	1.9:1.0
7	Cl	H	Me	H	6g	75	1.6:1.0
8	Cl	2-Cl	Me	4-NO ₂	6h	82	2.5:1.0
9	H	2-Cl	Et	H	6i	85	2.2:1.0
10	Cl	H	Et	2-Cl	6j	75	2.4:1.0

^a Yields are given for isolated product.

A mechanistic rationalization for the reaction is given in Scheme 2. nucleophilic attack of **3** on the electron-deficient triple bond **4** could lead to the formation of intermediate **A**, which possessed a resonance structure **B** as a 1,4-dipolar synthon. When the benzyldenemalononitrile **5** existed in the mixture of **3** and **4**, a subsequent [4+2] cycloaddition occurred. In this way, the

corresponding substituted tetrahydropyridine derivatives **6** were prepared. During the process of the cycloaddition, there are four possible transition states **C**, **D**, **E**, and **F**, which might lead to the formation of four possible products, *cis*-**6** and *trans*-**6** accordingly. **C** presented the lowest energy while **F** had the highest energy.



Scheme 2. Proposed mechanism for the synthesis of highly substituted tetrahydropyridines.

Conclusions

We have developed an efficient and facile method for the synthesis of highly substituted tetrahydropyridine derivatives by treatment of *N*-benzylidenemethanamines, dialkyl acetylenedicarboxylates, and benzylidenemalononitriles under catalyst-free conditions. The mild reaction conditions, low cost of the starting materials, operational simplicity and good yields are advantages of the protocol.

Experimental Section

General. All chemicals were purchased from Aldrich and Merck with high-grade quality, and used without any purification. All melting points were obtained by Bamslead Electrothermal 9200 apparatus and are uncorrected. The reactions were monitored by TLC and all yields refer to isolated products. ¹H and ¹³C NMR spectra were recorded in CDCl₃ on a Bruker 400 MHz spectrometer. Infrared spectra were recorded on a Bruker FT-IR Equinax-55 spectrophotometer in KBr with absorption in Cm⁻¹. Elemental analyses were performed using a Carlo Erba EA 1108 instrument. All products were characterized by their spectra and physical data.

General procedure for the synthesis of substituted tetrahydropyridines. To a 25 mL round-bottom flask were added appropriate benzylamine (**1**) (1.0 mmol), benzaldehyde (**2**) (1.0 mmol), two drops acetic acid, acetonitrile (5.0 mL) and the mixture was stirred vigorously at room temperature. After the benzylamine had been consumed (monitored by TLC), acetonitrile (5.0 mL), dialkyl acetylenedicarboxylate (**4**) (1.5 mmol) and 2-benzylidenemalononitrile (**5**) (1.0 mmol) were added. The mixture was then allowed to stir at 50°C for 24 h. After completion of the reaction, determined by TLC, the solvent was removed under reduced pressure, and the resulting crude product (72-85%) was recrystallized from ethanol to give the pure compounds **6a-j**.

Dimethyl 1-benzyl-5,5-dicyano-1,4,5,6-tetrahydro-4,6-diphenylpyridine-2,3-dicarboxylate (6a). Mp 146-149 °C. IR ν /cm⁻¹ (KBr): 3032, 2952, 2246, 1749, 1703, 1592, 1456, 1434, 1257. ¹H NMR (400 MHz, CDCl₃): δ 3.32 (3H, s, OCH₃, Minor isomer), 3.51 (5H, s, OCH₃, Major isomer), 3.88 (3H, s, OCH₃, Minor isomer), 3.97-4.08 (9H, m, Major/Minor isomers), 4.36-4.54 (6H, m, Major/Minor isomers), 6.98-7.42 (39H, m, ArH, Major/Minor isomers) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 29.71, 44.31, 45.25, 47.23, 51.59, 51.94, 53.38, 53.41, 53.60, 54.16, 59.10, 63.29, 96.19, 112.34, 112.61, 113.33, 113.84, 128.23, 128.34, 128.42, 128.50, 128.54, 128.82, 128.95, 129.03, 129.32, 129.55, 130.16, 130.29, 130.63, 131.00, 133.10, 134.19, 135.04, 135.50, 149.84, 149.91, 165.01, 165.19, 165.28, 165.81 ppm. Anal. Calcd for C₃₀H₂₅N₃O₄ (491.54): C, 73.30; H, 5.13; N, 8.55. Found: C, 73.18; H, 5.09; N, 8.61.

Dimethyl 1-benzyl-5,5-dicyano-1,4,5,6-tetrahydro-4-(4-methoxyphenyl)-6-phenylpyridine-2,3-dicarboxylate (6b). Mp 135-137 °C. IR ν /cm⁻¹ (KBr): 3029, 2949, 2245, 1743, 1704, 1593,

1513, 1457, 1435, 1254. ^1H NMR (400 MHz, CDCl_3): δ 3.45 (3H, s, OCH_3 , Minor isomer), 3.62 (6H, s, OCH_3 , Major isomer), 3.76 (3H, s, OCH_3 , Minor isomer), 3.79 (6H, s, OCH_3 , Major isomer), 3.97 (3H, s, OCH_3 , Minor isomer), 4.05-4.16 (11H, m, Major/Minor isomers), 4.44-4.62 (7H, m, Major/Minor isomers), 6.69-7.52 (42H, m, ArH, Major/Minor isomers) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 44.56, 44.71, 46.62, 51.69, 51.97, 53.30, 53.35, 53.59, 54.15, 55.16, 55.22, 58.94, 63.14, 96.56, 112.45, 112.77, 113.40, 113.60, 113.83, 126.97, 127.38, 127.96, 128.02, 128.23, 128.35, 128.43, 128.49, 128.82, 128.86, 128.90, 129.28, 129.57, 130.02, 130.11, 130.40, 130.54, 130.60, 131.06, 133.15, 134.22, 149.55, 149.72, 159.41, 159.96, 165.05, 165.24, 165.32, 165.89 ppm. Anal. Calcd for $\text{C}_{31}\text{H}_{27}\text{N}_3\text{O}_5$ (521.56): C, 71.39; H, 5.22; N, 8.06. Found: C, 71.53; H, 5.26; N, 8.04.

Dimethyl 1-benzyl-5,5-dicyano-1,4,5,6-tetrahydro-4-(4-nitrophenyl)-6-phenylpyridine-2,3-dicarboxylate (6c). Mp 139-142 $^\circ\text{C}$. IR ν/cm^{-1} (KBr): 3033, 2951, 2248, 1743, 1702, 1593, 1524, 1456, 1435, 1262. ^1H NMR (400 MHz, CDCl_3): δ 3.46 (3H, s, OCH_3 , Minor isomer), 3.58 (10H, s, OCH_3 , Major isomer), 4.02 (3H, s, OCH_3 , Minor isomer), 4.09-4.22 (18H, m, Major/Minor isomers), 4.49-4.71 (9H, m, Major/Minor isomers), 7.12-8.08 (60H, m, ArH, Major/Minor isomers) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 15.29, 43.75, 44.47, 51.83, 52.03, 53.59, 53.76, 53.87, 54.62, 59.54, 65.87, 95.08, 112.22, 112.59, 123.18, 123.73, 128.57, 128.80, 128.95, 129.08, 129.21, 129.25, 129.35, 129.47, 129.55, 130.05, 130.24, 130.43, 130.61, 130.92, 132.82, 142.64, 148.22, 150.41, 164.72, 164.77 ppm. Anal. Calcd for $\text{C}_{30}\text{H}_{24}\text{N}_4\text{O}_6$ (536.53): C, 67.16; H, 4.51; N, 10.44. Found: C, 67.20; H, 4.52; N, 10.37.

Dimethyl 1-benzyl-5,5-dicyano-1,4,5,6-tetrahydro-6-(4-methoxyphenyl)-4-phenylpyridine-2,3-dicarboxylate (6d). Mp 140-142 $^\circ\text{C}$. IR ν/cm^{-1} (KBr): 3031, 2952, 2242, 1742, 1699, 1591, 1514, 1454, 1435, 1255. ^1H NMR (400 MHz, CDCl_3): δ 3.40 (3H, s, OCH_3 , Minor isomer), 3.60 (5.4H, s, OCH_3 , Major isomer), 3.82 (3H, s, OCH_3 , Minor isomer), 3.88 (5.4H, s, OCH_3 , Major isomer), 3.95 (3H, s, OCH_3 , Minor isomer), 4.02-4.18 (11H, m, Major/Minor isomers), 4.44-4.59 (6H, m, Major/Minor isomers), 6.84-7.38 (39H, m, ArH, Major/Minor isomers) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 44.53, 45.26, 47.57, 51.53, 51.92, 53.29, 53.33, 53.58, 53.90, 55.29, 55.37, 55.41, 58.60, 63.38, 95.96, 112.41, 112.75, 113.21, 113.50, 113.82, 113.85, 114.25, 114.63, 122.18, 122.56, 128.16, 128.28, 128.32, 128.37, 128.53, 128.71, 128.79, 128.91, 129.09, 129.53, 129.98, 130.38, 130.67, 133.26, 134.48, 135.41, 135.63, 149.99, 150.03, 160.86, 161.19, 165.03, 165.22, 165.34, 165.82 ppm. Anal. Calcd for $\text{C}_{31}\text{H}_{27}\text{N}_3\text{O}_5$ (521.56): C, 71.39; H, 5.22; N, 8.06. Found: C, 71.79; H, 5.27; N, 8.03.

Dimethyl 1-(4-methoxybenzyl)-4-(2-chlorophenyl)-5,5-dicyano-1,4,5,6-tetrahydro-6-phenylpyridine-2,3-dicarboxylate (6e). Mp 125-128 $^\circ\text{C}$. IR ν/cm^{-1} (KBr): 3029, 2955, 2240, 1743, 1701, 1593, 1511, 1451, 1436, 1258. ^1H NMR (400 MHz, CDCl_3): δ 3.37 (3H, s, OCH_3 , Minor isomer), 3.61 (5.1H, s, OCH_3 , Major isomer), 3.84 (3H, s, OCH_3 , Minor isomer), 3.89 (5.1H, s, OCH_3 , Major isomer), 3.94 (3H, s, OCH_3 , Minor isomer), 4.09-4.20 (10H, m, Major/Minor isomers), 4.45-4.63 (6H, m, Major/Minor isomers), 6.83-7.44 (35H, m, ArH, Major/Minor isomers) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 40.81, 42.97, 43.04, 51.53, 51.59, 52.03, 53.34, 53.64, 54.01, 55.38, 55.42, 58.64, 60.21, 63.74, 96.16, 98.63, 102.73, 112.14, 112.39, 113.05,

113.18, 114.31, 114.53, 114.67, 122.04, 122.22, 126.74, 126.82, 127.94, 128.30, 128.43, 128.81, 128.87, 129.02, 129.60, 129.66, 129.87, 129.97, 130.07, 130.15, 130.78, 133.15, 133.63, 134.21, 134.37, 135.02, 135.46, 150.02, 150.22, 161.03, 161.24, 164.85, 165.11, 165.18, 165.39 ppm. Anal. Calcd for C₃₁H₂₆ClN₃O₅ (556.01): C, 66.97; H, 4.71; N, 7.56. Found: C, 67.09; H, 4.72; N, 7.53.

Dimethyl 1-benzyl-4-(4-chlorophenyl)-5,5-dicyano-1,4,5,6-tetrahydro-6-phenylpyridine-2,3-dicarboxylate (6f). Mp 147-150 °C. IR ν/cm^{-1} (KBr): 3035, 2952, 2246, 1743, 1702, 1594, 1492, 1457, 1435, 1266. ¹H NMR (400 MHz, CDCl₃): δ 3.46 (3H, s, OCH₃, Minor isomer), 3.61 (5.7H, s, OCH₃, Major isomer), 3.98 (3H, s, OCH₃, Minor isomer), 4.06-4.19 (10.6H, m, Major/Minor isomers), 4.45-4.65 (6.7H, m, Major/Minor isomers), 7.07-7.53 (40.6H, m, ArH, Major/Minor isomers) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 29.70, 44.15, 44.60, 46.44, 51.71, 51.98, 53.44, 53.50, 53.65, 54.36, 59.15, 62.85, 95.94, 112.30, 112.49, 113.06, 113.74, 128.39, 128.48, 128.60, 128.69, 128.80, 128.86, 128.92, 129.12, 129.28, 129.39, 129.50, 129.71, 129.75, 129.82, 130.06, 130.23, 130.62, 130.74, 130.84, 133.02, 133.60, 133.98, 134.10, 134.28, 135.12, 150.02, 150.10, 164.85, 165.00, 165.05, 165.57 ppm. Anal. Calcd for C₃₀H₂₄ClN₃O₄ (525.98): C, 68.50; H, 4.60; N, 7.99. Found: C, 68.27; H, 4.53; N, 7.98.

Dimethyl 1-(4-chlorobenzyl)-5,5-dicyano-1,4,5,6-tetrahydro-4,6-diphenylpyridine-2,3-dicarboxylate (6g). Mp 130-132 °C. IR ν/cm^{-1} (KBr): 3030, 2951, 2238, 1737, 1710, 1687, 1588, 1511, 1435, 1352, 1225. ¹H NMR (400 MHz, CDCl₃): δ 3.41 (3H, s, OCH₃, Minor isomer), 3.57 (4.8H, s, OCH₃, Major isomer), 3.92 (3H, s, OCH₃, Minor isomer), 4.02-4.15 (10.2H, m, Major/Minor isomers), 4.39-4.57 (5H, m, Major/Minor isomers), 7.05-7.52 (36.4H, m, ArH, Major/Minor isomers) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 29.17, 29.37, 29.52, 29.70, 31.93, 47.82, 51.92, 52.11, 52.46, 53.34, 55.41, 58.99, 96.25, 109.65, 126.77, 126.99, 127.50, 127.84, 127.97, 128.07, 128.15, 128.27, 128.38, 128.44, 128.51, 128.62, 128.75, 128.84, 128.90, 129.01, 129.17, 129.67, 133.79, 138.53, 139.10, 152.77, 164.15, 164.21, 164.26, 167.94 ppm. Anal. Calcd for C₃₀H₂₄ClN₃O₄ (525.98): C, 68.50; H, 4.60; N, 7.99. Found: C, 68.61; H, 4.62; N, 8.04.

Dimethyl 1-(4-chlorobenzyl)-6-(2-chlorophenyl)-5,5-dicyano-1,4,5,6-tetrahydro-4-(4-nitrophenyl)pyridine-2,3-dicarboxylate (6h). Mp 139-142 °C. IR ν/cm^{-1} (KBr): 3035, 2956, 2247, 1740, 1703, 1593, 1517, 1451, 1434, 1252. ¹H NMR (400 MHz, CDCl₃): δ 3.39 (3H, s, OCH₃, Minor isomer), 3.51 (7.5H, s, OCH₃, Major isomer), 4.00 (3H, s, OCH₃, Minor isomer), 4.11-4.24 (14H, m, Major/Minor isomers), 4.43-4.68 (7.5H, m, Major/Minor isomers), 7.10-8.09 (42H, m, ArH, Major/Minor isomers) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 44.12, 44.37, 51.38, 51.97, 52.47, 53.06, 53.49, 54.18, 55.14, 55.46, 58.54, 63.06, 96.76, 112.29, 112.87, 113.01, 113.05, 113.44, 126.99, 127.48, 127.98, 128.02, 128.24, 128.30, 128.39, 128.74, 128.82, 128.96, 129.26, 129.42, 129.79, 130.03, 130.12, 130.58, 131.67, 132.10, 133.78, 134.29, 147.58, 148.72, 159.48, 159.64, 163.13, 163.24, 164.31, 164.80 ppm. Anal. Calcd for C₃₀H₂₂Cl₂N₄O₆ (605.42): C, 59.52; H, 3.66; N, 9.25. Found: C, 59.73; H, 3.69; N, 9.21.

Diethyl 1-benzyl-6-(2-chlorophenyl)-5,5-dicyano-1,4,5,6-tetrahydro-4-phenylpyridine-2,3-dicarboxylate (6i). Mp 157-159 °C. IR ν/cm^{-1} (KBr): 3036, 2957, 2238, 1748, 1704, 1596, 1513,

1459, 1431, 1242. ^1H NMR (400 MHz, CDCl_3): δ 1.31-1.37 (6H, m, 2CH_3 , Minor isomer), 1.46-1.50 (13.2H, m, 2CH_3 , Major isomer), 4.01-4.13 (8H, m, Major/Minor isomers), 4.21-4.30 (4.8H, m, Major/Minor isomers), 4.36-4.41 (4H, m, 2OCH_2 , Minor isomer), 4.47-4.51 (8.8H, m, 2OCH_2 , Major isomer), 7.11-7.56 (44.8H, m, ArH, Major/Minor isomers) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 43.19, 45.71, 48.62, 51.72, 51.98, 53.14, 53.76, 54.12, 54.90, 55.12, 55.54, 56.51, 58.20, 59.24, 62.73, 63.62, 94.41, 112.18, 112.35, 113.31, 113.52, 113.72, 113.95, 114.51, 114.80, 122.10, 123.51, 128.14, 128.38, 128.42, 128.57, 128.60, 128.74, 128.89, 128.96, 129.17, 129.43, 129.78, 130.38, 130.87, 132.26, 134.72, 135.06, 135.82, 148.31, 153.41, 160.74, 162.52, 165.81, 165.94, 166.12, 166.87 ppm. Anal. Calcd for $\text{C}_{32}\text{H}_{28}\text{ClN}_3\text{O}_4$ (554.04): C, 69.37; H, 5.09; N, 7.58. Found: C, 69.40; H, 5.07; N, 7.55.

Diethyl 1-(4-chlorobenzyl)-4-(2-chlorophenyl)-5,5-dicyano-1,4,5,6-tetrahydro-6-phenylpyridine-2,3-dicarboxylate (6j). Mp 144-147 °C. IR ν/cm^{-1} (KBr): 3034, 2957, 2238, 1745, 1700, 1591, 1513, 1452, 1435, 1250. ^1H NMR (400 MHz, CDCl_3): δ 1.30-1.39 (6H, m, 2CH_3 , Minor isomer), 1.44-1.51 (14.4H, m, 2CH_3 , Major isomer), 4.02-4.15 (8.6H, m, Major/Minor isomers), 4.22-4.31 (5H, m, Major/Minor isomers), 4.37-4.43 (4H, m, 2OCH_2 , Minor isomer), 4.46-4.53 (9.6H, m, 2OCH_2 , Major isomer), 7.04-7.83 (44.2H, m, ArH, Major/Minor isomers) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 42.29, 43.92, 49.66, 50.42, 51.63, 52.14, 53.03, 54.89, 55.37, 55.83, 56.24, 56.72, 58.94, 59.20, 61.78, 63.22, 96.72, 112.64, 112.81, 113.17, 113.54, 113.71, 115.51, 117.52, 122.18, 123.49, 128.11, 128.34, 128.51, 128.65, 128.70, 128.84, 128.88, 129.13, 129.54, 129.98, 130.14, 130.77, 133.29, 134.12, 135.63, 136.52, 149.74, 152.73, 161.34, 161.51, 164.74, 165.33, 165.54, 166.12 ppm. Anal. Calcd for $\text{C}_{32}\text{H}_{27}\text{Cl}_2\text{N}_3\text{O}_4$ (588.48): C, 65.31; H, 4.62; N, 7.14. Found: C, 65.46; H, 4.66; N, 7.12.

Acknowledgements

We are thankful to the Office of Graduate Studies of the Vali-e-Asr University of Rafsanjan for partial support of this work.

References

1. Aridoss, G.; Amirthaganesan, S.; Jeong, Y. T. *Bioorg. Med. Chem. Lett.* **2010**, (20), 2242. <http://dx.doi.org/10.1016/j.bmcl.2010.02.015>
2. Malviya, M.; Sunil K. Y. C.; Mythri, R. B.; Venkateshappa, C.; Subhash, M. N.; Rangappa, K. S. *Bioorg. Med. Chem. Lett.* **2009**, (17), 5526. <http://dx.doi.org/10.1016/j.bmc.2009.06.032>
3. Ishida, J.; Hattori, K.; Yamamoto, H.; Iwashita, A.; Mihara, K.; Matsuoka, N. *Bioorg. Med. Chem. Lett.* **2005**, (15), 4221. <http://dx.doi.org/10.1016/j.bmcl.2005.06.094>

4. Suleman, N. K.; Flores, J.; Tanko, J. M.; Isin, E. M.; Castagnoli, N., Jr. *Bioorg. Med. Chem.* **2008**, (16), 8557.
5. Wimalasena, D. S.; Perera, R. P.; Heyen, B. J.; Balasooriya, I. S.; Wimalasena, K. *J. Med. Chem.* **2008**, (51), 760.
<http://dx.doi.org/10.1021/jm070875p>
6. Dunbar, P. G.; Durant, G. J.; Rho, T.; Ojo, B.; Huzl, J. J.; Smith, D. A. *J. Med. Chem.* **1994**, (37), 2774.
<http://dx.doi.org/10.1021/jm00043a016>
7. Chao, Y. X.; He, B. P.; Tay, S. S. W. *J. Neuroimmunol.* **2009**, (216), 39.
<http://dx.doi.org/10.1016/j.jneuroim.2009.09.003>
8. Roberts, E.; Sanc, J. P.; Sweeney, J. B.; Workman, J. A. *Org. Lett.* **2003**, (5), 4775.
Rodinovskaya, L. A.; Shestopalov, A. M.; Chunikihn, K. S. *Tetrahedron* **2002**, (58), 4273.
9. Beeler, A. B.; Gadepalli, R. S. V. S.; Steyn, S.; Castagnoli, N., J.; Rimoldi, J. M. *Bioorg. Med. Chem.* **2003**, (11), 5229.
10. Deskus, J. A.; Epperson, J. R.; Charles, P. S.; Joseph, A. C.; Dextraze, P.; Qian-Cutrone, J.; Gao, Q.; Ma, B.; Beno, B. R.; Mattson, G. K.; Molski, T. F.; Krause, R. G.; Taber, M. T.; Lodge, N. J.; Mattson, R. J. *Bioorg. Med. Chem. Lett.* **2007**, (17), 3099.
<http://dx.doi.org/10.1016/j.bmcl.2007.03.040>
11. Seyfried, C. A.; Greiner, H. E.; Haase, A. F. *Eur. J. Pharmacol.* **1989**, (160), 31.
[http://dx.doi.org/10.1016/0014-2999\(89\)90651-1](http://dx.doi.org/10.1016/0014-2999(89)90651-1)
12. Jaen, J. C.; Wise, L. D.; Heffner, T. G.; Pugsley, T. A.; Meltzer, L. T. *J. Med. Chem.* **1988**, (31), 1621.
<http://dx.doi.org/10.1021/jm00403a022>
13. Jaen, J. C.; Caprathe, B. W.; Wise, L. D.; Meltzer, L. T.; Pugsley, T. A.; Heffner, T. G. *Bioorg. Med. Chem. Lett.* **1993**, (3), 639.
[http://dx.doi.org/10.1016/S0960-894X\(01\)81245-2](http://dx.doi.org/10.1016/S0960-894X(01)81245-2)
14. Gwaltney, S. L., II; O'Connor, S. J.; Nelson, L. T. J.; Sullivan, G. M.; Imade, H.; Wang, W.; Hasvold, L.; Li, Q.; Cohen, J.; Gu, W.-Z.; Tahir, S. K.; Bauch, J.; Marsh, K.; Ng, S.-C.; Frost, D. J.; Zhang, H.; Muchmore, S.; Jakob, C. G.; Stoll, V.; Hutchins, C. *Bioorg. Med. Chem. Lett.* **2003**, (13), 1359.
[http://dx.doi.org/10.1016/S0960-894X\(03\)00095-7](http://dx.doi.org/10.1016/S0960-894X(03)00095-7)
15. Kamei, K.; Maeda, N.; Katsuragi-Ogino, R.; Koyama, M.; Nakajima, M.; Tatsuoka, T.; Ohno, T.; Inoue, T. *Bioorg. Med. Chem. Lett.* **2005**, (15), 2990.
<http://dx.doi.org/10.1016/j.bmcl.2005.04.059>
16. Van Voorhis, W. C.; Rivas, K. L.; Bendale, P.; Nallan, L.; Hornéy, C.; Barrett, L. K.; Bauer, K. D.; Smart, B. P.; Ankala, S.; Hucke, O.; Verlinde, C. L. M. J.; Chakrabarti, D.; Strickland, C.; Yokoyama, K.; Buckner, F. S.; Hamilton, A. D.; Williams, D. K.; Lombardo, L. J.; Floyd, D.; Gelb, M. H. *J. Med. Chem.* **2005**, (48), 3704.
17. Hantzsch, A. *Chem. Ber.* **1881**, (14), 1637.
<http://dx.doi.org/10.1002/cber.18810140214>

18. Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, (39) 3168.
[http://dx.doi.org/10.1002/1521-3773\(20000915\)39:18<3168::AID-ANIE3168>3.0.CO;2-U](http://dx.doi.org/10.1002/1521-3773(20000915)39:18<3168::AID-ANIE3168>3.0.CO;2-U)
19. Misra, M.; Pandey, S. K.; Pandey, V. P.; Pandey, J.; Tripathi, R.; Tripathi, R. P. *Bioorg. Med. Chem.* **2009**, (17), 625.
<http://dx.doi.org/10.1016/j.bmc.2008.11.062>
20. Khan, A. T.; Parvin, T.; Choudhary, L. H. *J. Org. Chem.* **2008**, (73), 8398.
<http://dx.doi.org/10.1021/jo8014962>
21. Khan, A. T.; Lal, M.; Khan, M. M. *Tetrahedron Lett.* **2010**, (51), 4419.
<http://dx.doi.org/10.1016/j.tetlet.2010.06.069>
22. Khan, A. T.; Khan, M. M.; Karthi, K. R. B. *Tetrahedron* **2010**, (66), 7762.
<http://dx.doi.org/10.1016/j.tet.2010.07.075>
23. Clarke, P. A.; Zaytzev, P. A.; Whitwood, A. C. *Tetrahedron Lett.* **2007**, (48), 5209.
<http://dx.doi.org/10.1016/j.tetlet.2007.05.141>
24. Mishra, S.; Ghosh, R. *Tetrahedron Lett.* **2011**, (52), 2857.
<http://dx.doi.org/10.1016/j.tetlet.2011.03.116>
25. Hong-Juan, W.; Li-Ping, M.; Zhan-Hui, Z. *ACS Comb. Sci.* **2011**, (13), 181.
26. Ramachandran, R.; Jayanth, S.; Jeong, Y. T. *Tetrahedron* **2012**, (68), 363.
<http://dx.doi.org/10.1016/j.tetlet.2011.03.116>
27. Pal, S.; Singh, V.; Das, P.; Choudhury, L. H. *Bioorg. Chem.* **2013**, (48), 8.
<http://dx.doi.org/10.1016/j.bioorg.2013.03.003>
28. Jiang, H. F.; Li, J. H.; Chen, Z. W. *Tetrahedron* **2010**, (66), 9721.
<http://dx.doi.org/10.1016/j.tet.2010.10.041>
29. Liu, W. B.; Jiang, H. F.; Zhu, S. F.; Wang, W. *Tetrahedron* **2009**, (65), 7985.
<http://dx.doi.org/10.1016/j.tet.2009.07.046>
30. Rodriguez H.; Coro J.; Lam A.; Salfran E.; Rodriguez-Salarichs J.; Suarez M.; Albericio F.; Martin N. *Arkivoc* **2011**, (ix) 125.
<http://dx.doi.org/10.3998/ark.5550190.0012.909>