Monatshefte für Chemie - Chemical Monthly
https://doi.org/10.1007/s00706-018-2187-x

ORIGINAL PAPER

# Stereoselective one-pot synthesis of polycyanosubstituted piperidines

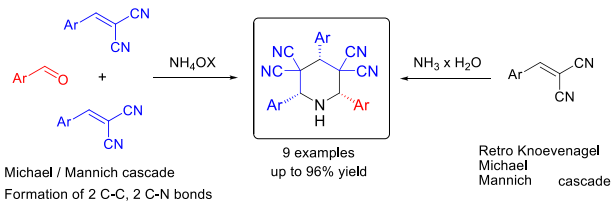
Anatoly N. Vereshchagin[1] · Kirill A. Karpenko[1] · Michail N. Elinson[1] · Sergey V. Gorbunov[1] · Alexandra M. Gordeeva[1] · Pavel I. Proshin[1] · Alexander S. Goloveshkin[2] · Mikhail P. Egorov[1]

Received: 22 January 2018 / Accepted: 14 March 2018


## Abstract

An effective and facile multicomponent method for the synthesis of polysubstituted piperidines is described. The Michael–Mannich type cascade of benzylidenemalononitriles with aromatic aldehydes and ammonium acetate or aqueous ammonia provides convenient access to the stereoselective synthesis of 3,3,5,5-tetracyano-2,4,6-triarylpiperidines in good to excellent yields in one-pot manner. Ammonium acetate or aqueous ammonia plays a role both as a catalyst and as a nitrogen source. It is established that the reaction proceeds via sequence of equilibriums and a competitive mechanisms are implemented.

## Graphical abstract




**Keywords** Multicomponent reaction · Polysubstituted piperidines · Aromatic aldehydes · Benzylidenemalononitriles · Stereoselectivity

## Introduction

In recent decades, the growing number of studies in the field of multicomponent processes is connected with the fact that methodology of multicomponent 'one-pot' reactions has serious advantages in comparison to an ordinary multi-step synthesis [1–6]. The first advantage is a significant time of process decrease and labor expenses as well as costs for raw materials, which is particularly important in large-scale drugs and natural products syntheses [7–10]. The second one is eco-friendly type of processes characterized by reducing the amount of waste, because it does not require isolation of intermediate products and their purification. Such dynamic development of multicomponent strategy allows to obtain a wide range of structures for modern organic [11–16], medicinal [17–21], applied [22, 23], and combinatorial [24–28] chemistry.

The piperidine nucleus is a well-known heterocyclic component in a variety of natural compounds [29–31]. The most important out of them are morphine, codeine, coniine, lobeline, piperidine, sedamine, etc. Compounds bearing the piperidine moiety possess anti-hypertensive, anticonvulsant, antimicrobial, antimycobacterial, antihistamine, anti-inflammatory, antimalarial, and anti-HIV activities [32–35]. The studies showed that some 3-spiroindole-2,4-

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00706-018-2187-x) contains supplementary material, which is available to authorized users.

✉ Anatoly N. Vereshchagin
vereshchagin@ioc.ac.ru

[1] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, Russian Federation

[2] A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow, Russian Federation

Published online: 04 September 2018

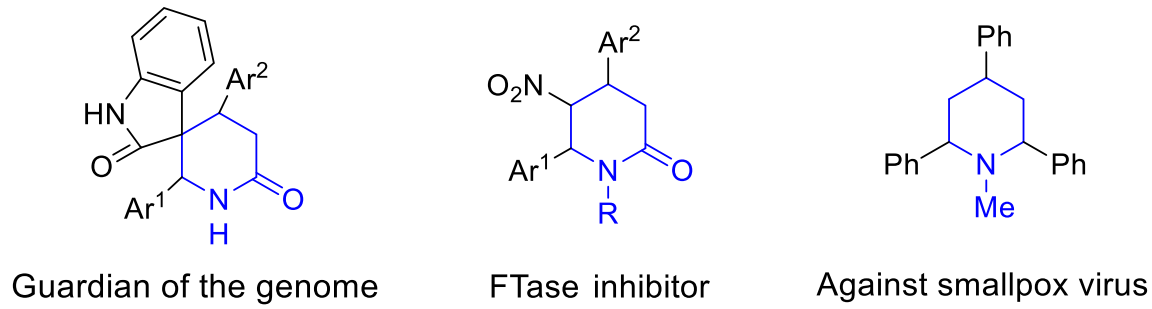


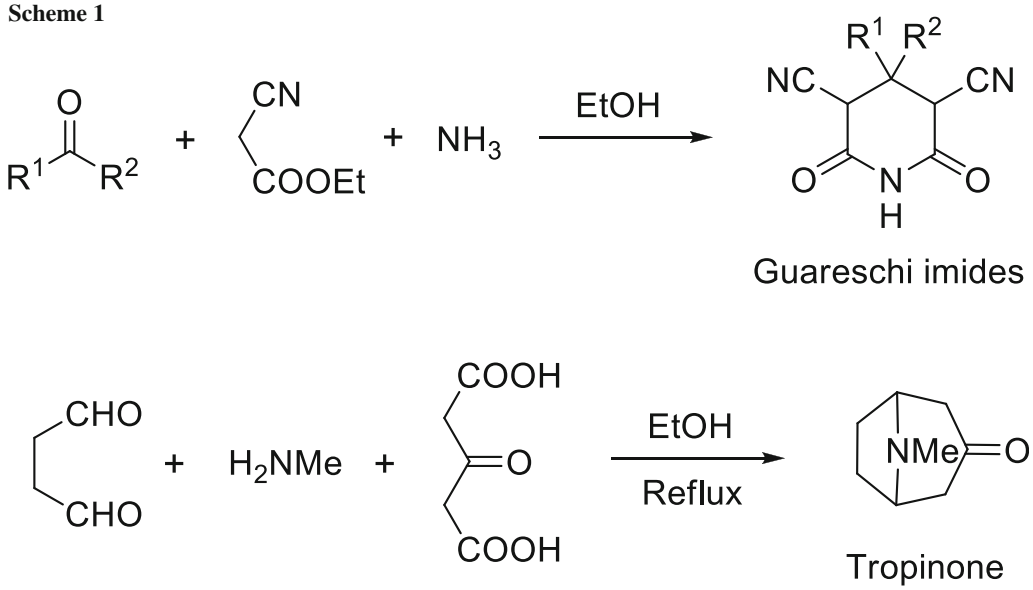

**Fig. 1** Pharmacological activity of products containing piperidine moety

diarylpiperidine-6-ones (Fig. 1) are noted with an inherent anti-cancer activity [36]. These compounds inhibit the protein binding between MDM2, produced by cancer cells, and p53 protein (the so-called "guardian of the genome") which is responsible for the normal functioning of cells. 5-Nitro-4,6-diaryl-2-piperidones act as inhibitors of farnesyltransferase (FTase) and induce a regression of cattle brain tumor without any toxicity [37]. Also, piperidines have been identified as antiviral [38] and herbicidal [39] agents. For instance, *N*-methyl-2,4,6-triphenylpiperidine (Fig. 1) demonstrates an efficiency against the smallpox virus [38].

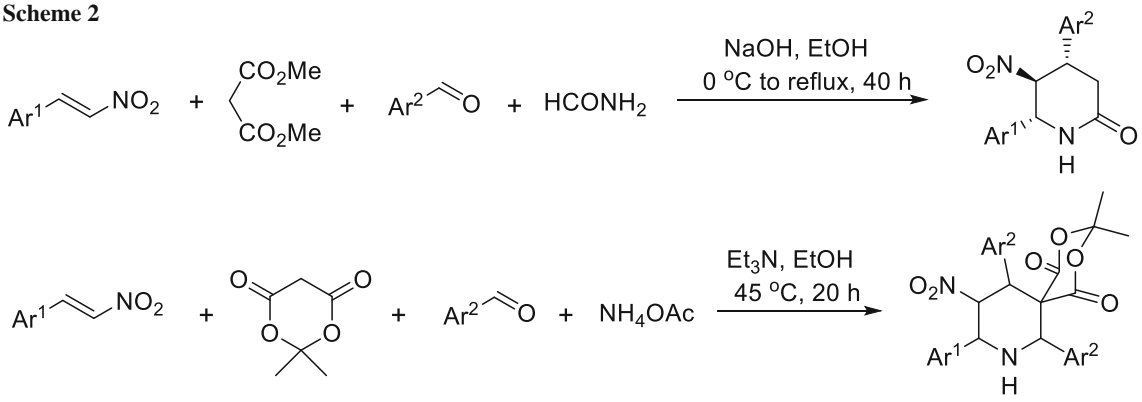
Guareschi's imides synthesis via condensation of ketones, ethyl cyanoacetate, and ammonia should be considered as the first multicomponent synthesis of substituted piperidine (Scheme 1) [40]. Another prominent multicomponent reaction for the preparation of piperidines is Robinson's [41] tropinone synthesis, which was modified by Schöpf [42] and known as the Robinson–Schöpf reaction. However, to date the multicomponent reactions are rather limited for the construction of structurally and stereochemically diverse polysubstituted piperidine derivatives. These methods have a number of drawbacks such as necessity for rigorous conditions (extra dry solvents, inert atmosphere and are limited to utilization of expensive reagents [43]).

Recently Wang et al. proposed a new multicomponent approach to the synthesis of polysubstituted piperidines (Scheme 2) [44–47]. In particular, formamide [44] or ammonium acetate [45–47] was used as nitrogen source for the piperidine cycle construction. Therefore, the multicomponent synthesis of nitro-substituted piperidines from nitrostyrene, aromatic aldehydes, C–H acid (malonic ester, cyanoacetic ester, Meldrum's acid), and ammonium acetate or formamide was implemented. Although these multicomponent processes provide a wide variation of aryl substituents, they significantly suffer from moderate yields (no more 75%) and long reaction times. Furthermore,

**Scheme 1**



**Scheme 2**




column chromatography is required for purification of the desired products.

As a part of our continuous interest directed toward the development of new methodologies using alkylidenmalononitriles as essential building blocks for the synthesis of different type of cyclic (cyclopropanes [48–51], cyclohexanes [52]) and heterocyclic (pyrrolines [53], pyrrolidinones [54], spiropyrimidines [55], spiropyrazolones [56]) systems, we report now effective multicomponent approach to polysubstituted piperidines from benzylidenemalononitriles, aromatic aldehydes and ammonium acetate or aqueous ammonia without catalyst under mild conditions.

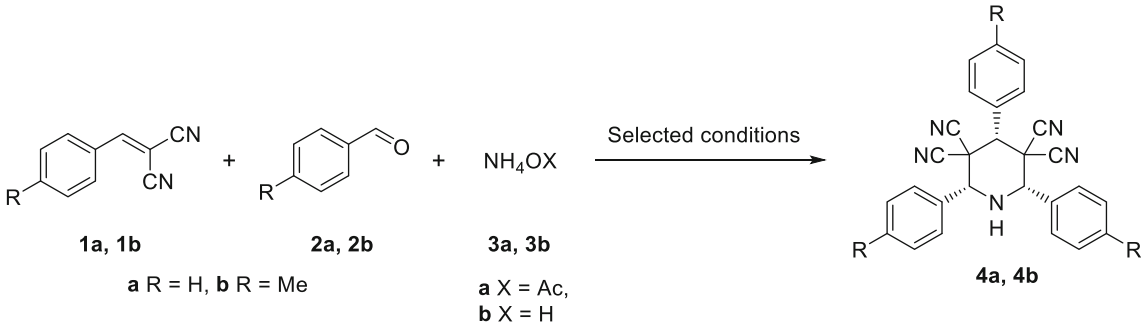
## Results and discussion

In the present study, we report our research on multicomponent synthesis of 2,4,6-triarylpiperidine-3,3,5,5-tetracarbonitriles. In order to find optimal conditions multicomponent transformations of benzylidenemalononitrile (**1a**) with benzaldehyde (**2a**) and ammonium acetate (**3a**) or aqueous ammonia (**3b**, 25% by weight in water, labeled as $NH_4OH$) were selected as model reactions (Table 1, entries 1–9, 23). There ammonium acetate was applied as "nitrogen source". Triethylamine was used as a base, because of its better catalytic activity for sequential Michael addition/aza-Mannich cascade between nitrostyrenes, Meldrum's acid, malonate, and ammonium acetate [49]. Surprisingly, it was found that the presence of a base did not affect the yield of **4a** (Table 1, entries 1–3). An increase in the temperature led to reduced reaction time and increased yield of **4a** (entry 4). The optimal amount of ammonium acetate was found to be 1.5 equivalent to benzaldehyde (entry 7). For instance, decrease up to 1 equiv. negatively affected the piperidine **4a** yield from 86 to 59% (entry 6). Heating at 78 or 40 °C in ethanol, analogous procedures resulted in piperidine **4a** in 70 and 63% product yields, respectively (entries 8, 9). However, when we tried to synthesized 2,4,6-tris(4-methylphenyl)piperidine-3,3,5,5-tetracarbonitrile (**4b**) at the same conditions, completely different results were obtained (Table 1, entries 10–22). Heating of (4-methylbenzylidene)malononitrile (**1b**), *p*-tolualdehyde (**2b**), and ammonium acetate at 65 °C in methanol for 4 h resulted in the formation of **4b** in trace amount (entry 10). Arguably, the cause for such a low performance is a result of **2b** poor solubility in alcohol. However, an increase in the solvent amount did not lead to any improvement in the process (entry 11). Next, we surveyed a numbers of bases for optimization of **4b** synthesis and found that the presence of base almost has no effect on yield (entries 12–18). Adapting the aqueous ammonia as a "nitrogen source" drastically changed the outcome. When two equivalents of (4-methylbenzylidene)malononitrile, *p*-tolualdehyde, and aqueous ammonia were mixed in methanol for 6 h, a 77% yield of **4b** was obtained, wherein full conversion of **1b** was achieved (entry 19). The optimal amount of ammonia was also 1.5 equiv. (entries 19–21). Temperature increase led to reducing yield of **4b** up to 62% (entry 22). The optimal conditions found (entry 19) were also effective for the synthesis of **4a** (entry 23).

With these reaction conditions identified, benzylidenemalononitriles **1a**–**1i**, aromatic aldehydes **2a**–**2j** (both with electron-withdrawing and electron-donating substituents), and ammonium acetate or aqueous ammonia were transformed into corresponding 2,4,6-triarylpiperidine-3,3,5,5-tetracarbonitriles **4a**–**4j** (Table 2).

As it is shown from Table 2, transformations of benzylidenemalononitriles **1b**, **1c** containing weak electron-donating methyl group were proceeded in the presence of more reactive aqueous ammonia as a nitrogen source (Table 2, entries 2, 3). Nevertheless, olefin **1d** containing strong electron-donating methoxy group did not react even

**Table 1** Optimization of reaction conditions in the synthesis of **4a** and **4b**




| Entry | R | X, equiv. | Solvent | Base, mmol | *T*/°C | Time/h | Product | Yield/%[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | H | Ac, 3 | MeOH | $Et_3N$, 1.5 | rt | 2 | **4a** | 76 |
| 2 | H | Ac, 3 | MeOH | $Et_3N$, 0.3 | rt | 2 | **4a** | 75 |
| 3 | H | Ac, 3 | MeOH | – | rt | 2.5 | **4a** | 76 |
| 4 | H | Ac, 3 | MeOH | – | 65 | 0.5 | **4a** | 86 |
| 5 | H | Ac, 2 | MeOH | – | 65 | 0.5 | **4a** | 86 |
| 6 | H | Ac, 1 | MeOH | – | 65 | 0.5 | **4a** | 59 |
| 7 | H | Ac, 1.5 | MeOH | – | 65 | 0.5 | **4a** | 86 |
| 8 | H | Ac, 1.5 | EtOH | – | 78 | 0.5 | **4a** | 70 |
| 9 | H | Ac, 1.5 | EtOH | – | 40 | 1 | **4a** | 63 |
| 10 | Me | Ac, 1.5 | MeOH | – | 65 | 4 | **4b** | Trace |
| 11 | Me | Ac, 1.5 | MeOH[b] | – | 65 | 4 | **4b** | Trace |
| 12 | Me | Ac, 1.5 | MeOH | $Et_3N$, 1.5 | 65 | 4 | **4b** | (15)[c] |
| 13 | Me | Ac, 1.5 | MeOH | $Et_3N$, 3.0 | 65 | 4 | **4b** | (17)[c] |
| 14 | Me | Ac, 1.5 | MeOH | $Et_3N$, 3.0 | 65 | 12 | **4b** | (10)[c] |
| 15 | Me | Ac, 1.5 | MeOH | Piperidine, 3.0 | 65 | 12 | **4b** | (15)[c] |
| 16 | Me | Ac, 1.5 | MeOH | NaOH, 3.0 | 65 | 4 | **4b** | (10)[c] |
| 17 | Me | Ac, 1.5 | MeOH | NaOH, 3.0 | 65 | 12 | **4b** | Trace |
| 18 | Me | Ac, 1.5 | MeCN | NaOH, 3.0 | 82 | 4 | **4b** | Trace |
| 19 | Me | H, 1.5 | MeOH | – | rt | 6 | **4b** | 77 |
| 20 | Me | H, 3 | MeOH | – | rt | 6 | **4b** | 64 |
| 21 | Me | H, 1 | MeOH | – | rt | 6 | **4b** | 52 |
| 22 | Me | H, 1.5 | MeOH | – | 40 | 4 | **4b** | 62 |
| 23 | H | H, 1.5 | MeOH | – | rt | 2 | **4a** | 82 |

Reaction conditions: benzylidenemalononitrile **1** (6 mmol), benzaldehyde **2** (3 mmol), and ammonium acetate or aqueous ammonia were stirred at selected conditions in 5 $cm^3$ of solvent until complete conversion of **1** was achieved (indicated by TLC)

[a]Isolated yields

[b]20 $cm^3$ of MeOH was used

[c]According to $^1H$ NMR data. There was a low conversion of **1b**

after 48 h stirring at rt or 6 h refluxing (entries 4, 5). Apparently, this is due to the fact that (4-methoxylbenzylidene)malononitrile (**1d**) has a low electrophilicity and hardly reacts with nucleophiles under catalyst-free conditions [57]. The olefins **1e**–**1j** which contain electron-withdrawing groups in aromatic ring are more electrophilic than **1b**, **1c** and reacted in the presence of ammonium acetate to form corresponding piperidines **4e**–**4j** (entries 6–10, 11–13). Moreover, reaction of highly electrophilic (4-nitrobenzylidene)malononitrile (**1i**) with 4-nitrobenzaldehyde (**2i**) and ammonium acetate at the same conditions resulted in oligomerization of the product (entry 11). Piperidine **4i** was obtained under milder conditions. **1i** full conversion and formation of **4i** in 70% yield were achieved at rt within 8 h stirring (entry 12).

The new multicomponent reaction allows to obtain tetracyanopiperidines **4** in moderate to excellent yields in one step from cheap and available starting materials. It

**Table 2** Multicomponent synthesis of piperidines **4**


**1** **2** **3** **4**

| Entry | Alkene | Aldehyde | Ar | X | *T*/°C | Time/h | Product | Yield/%[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | **2a** | Ph | Ac | 65 | 0.5 | **4a** | 86 |
| 2 | **1b** | **2b** | 4-$MeC_6H_4$ | H | rt | 6 | **4b** | 77 |
| 3 | **1c** | **2c** | 3-$MeC_6H_4$ | H | rt | 6 | **4c** | 69 |
| 4 | **1d** | **2d** | 4-$MeOC_6H_4$ | H | rt | 48 | **4d** | Not detected |
| 5 | **1d** | **2d** | 4-$MeOC_6H_4$ | H | 65 | 6 | **4d** | Not detected |
| 6 | **1e** | **2e** | 2-$FC_6H_4$ | Ac | 65 | 0.5 | **4e** | 72 |
| 7 | **1f** | **2f** | 3-$FC_6H_4$ | Ac | 65 | 0.5 | **4f** | 78 |
| 8 | **1g** | **2g** | 4-$FC_6H_4$ | Ac | 65 | 0.5 | **4g** | 82 |
| 9 | **1h** | **2h** | 3-$BrC_6H_4$ | Ac | 65 | 0.5 | **4h** | 96 |
| 10 | **1h** | **2h** | 3-$BrC_6H_4$ | Ac | rt | 36 | **4h** | 92 |
| 11 | **1i** | **2i** | 4-$NO_2C_6H_4$ | Ac | 65 | 0.5 | **4i** | Not detected |
| 12 | **1i** | **2i** | 4-$NO_2C_6H_4$ | Ac | rt | 8 | **4i** | 70 |
| 13 | **1j** | **2j** | 3-Py | Ac | 65 | 0.5 | **4j** | 94 |

Reaction conditions: benzylidenemalononitrile **1** (6 mmol), benzaldehyde **2** (3 mmol), and ammonium acetate or aqueous ammonia (4.5 mmol) were stirred at selected conditions in 5 $cm^3$ of methanol until complete conversion of **1** was achieved (indicated by TLC)

[a]Isolated yields

should be noted that products were isolated by simple filtration of the reaction mixture. The synthesis of **4a**, **4b** had been reported earlier [58]. However, the method of its preparation has significant disadvantages. Firstly, **4a**, **4b** were obtained from commercially unavailable 1-aryl-*N*,*N*-bis(arylmethylene)methanediamine by reaction with malononitrile and ammonium acetate in a boiling ethanol in moderate yields (53% for **4a** and 60% for **4b**). Secondly, purification of **4a**, **4b** was proceeded via recrystallization from THF/methanol. Moreover, no any information about stereochemistry of the piperidines **4a**, **4b** is contained in the paper [58].

In NMR spectra of **4a–4c**, **4e–4j,** only a single set of signals were identified assuming stereoselective formation of individual diastereoisomers. The X-ray crystal diffraction data indicated that the phenyl substituents are located in equatorial position of the piperidine ring (Fig. 2).

To evaluate the synthetic potential of the procedure, we proposed that the multicomponent transformation of benzylidenemalononitrile (**1a**, 2 equiv.), *p*-tolualdehyde (**2b**, 1 equiv.), and ammonium acetate (**3a**, 1.5 equiv.) in dry methanol has been carried out (Scheme 3).

A complete conversion of starting materials was observed with two products obtained in the reaction.

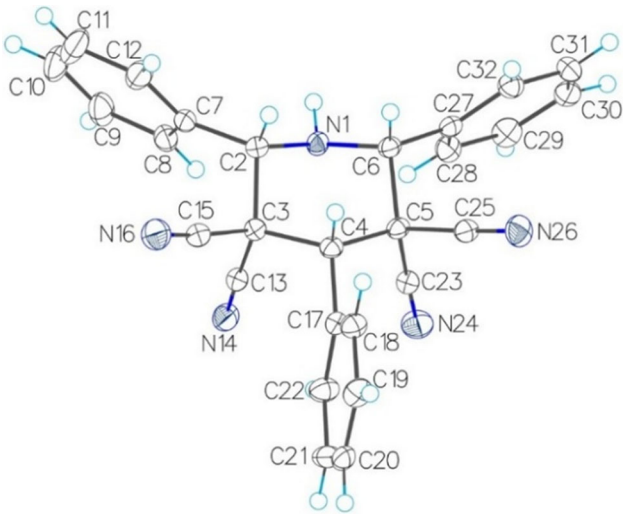
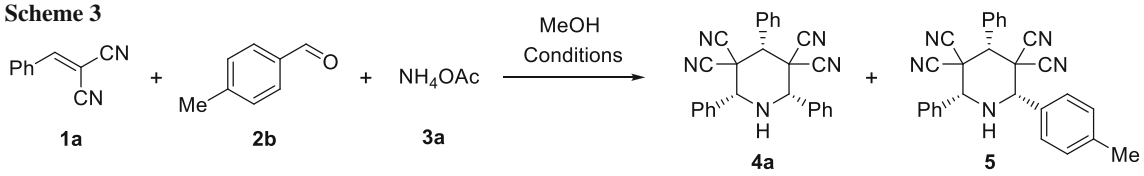



**Fig. 2** The general view of **4a** in crystal. Atoms are represented by thermal displacement ellipsoids ($p$ = 50%)

Surprisingly, it was found that the main product was 2,4,6-triphenylpiperidine-3,3,5,5-tetracarbonitrile (**4a**) and minor product was the expected 2-(4-methylphenyl)-4,6-diphenylpiperidine-3,3,5,5-tetracarbonitrile (**5**) in ratio 2:1 (by

**Scheme 3**




NMR). In case of water ammonia (**3b**, 1.5 equiv.) as a nitrogen source for the same reaction (stirring at rt for 6 h in methanol) afforded a similar mixture of **4a** and **5** in ratio 3:1. The chemical shifts difference of the donor- and acceptor-substituted piperidines is enough for structure elucidation. The characteristic signals of $^1$H NMR spectra of the piperidines **4a**, **4b**, **4i**, and **5** are represented in Fig. 3. For example, the NH proton of **4a** was registered on 4.83 ppm (Fig. 3a). Chemical shifts of NH and 4-CH protons of piperidines were confirmed by 2D NMR (see supplementary materials). The same proton signal of **4b** shifted into strong field on 4.64 ppm (Fig. 3b). In the case of strong acceptor like nitro-group NH proton noticeable shifted in downfield and was registered on 5.35 ppm (Fig. 3c). We postulate the formation of the piperidine **5** based on NMR data.

The NH signal of **5** slightly shifted into strong field in comparison with the same signal of the **4a** (Fig. 3d; 4.75 ppm for **5**, 4.83 ppm for **4a**). Apparently, this is due to the fact that NH group of new compound is surrounded by more donor substituents than the same NH in **4a**; however, in the same time it is surrounded by less acceptor substituents than the same NH in **4b**. We suppose that this is a middle option between **4a** and **4b** that corresponds to the structure **5**. Moreover, only one $CH_3$ signal on 2.36 ppm was registered in the $^1$H NMR spectra of the mixture of **4a** and **5**.

Taking into consideration the data obtained and results on domino reactions of benzylidenecyanoacetates with methanolic ammonia into functionalized 2-piperidones [59], we envisaged the following sequence of equilibriums to explain the formation of **4** and **5** (Scheme 4). We believe that parallel pathways should exist. The benzylidenemalononitriles **1** undergo Michael attack by one molecule of ammonia to result in the formation of the 2-[amino(aryl)methyl]malononitrile **A** which then is deprotonated by ammonia to form anion **B**. The derived anion triggers a second Michael addition at the $\beta$-position of another molecule of **1** to form the anion **C** (pathway 1). Further condensation of **C** with aldehyde **2** and cyclization affords the product **5** (when $Ar^1 = Ar^2$, product **5** is equal to **4**). Another competing pathway deals with imine **E** formation followed by retro-Knoevenagel with the formation of aldehyde **I** and anion of malononitrile **H** (pathway 2). Next, the Schiff base was afforded from the intermediate **C** and aromatic aldehyde **I**, finally by intramolecular nucleophilic addition of intermediate arylimine **J** to form the piperidine **4**.

The retro-Knoevenagel reactions are known and applicable in organic synthesis [60, 61]. In favor of pathway 2 stands the fact that the ratio between products **4a** and **5** changed when water ammonia was used as a nitrogen source for the assembling of benzylidenemalononitrile (**1a**) and *p*-tolualdehyde (**2b**) into piperidine cycle. Excess of the water caused a faster retro-Knoevenagel reaction and formation of aldehyde **I** and subsequently of product **4a**. The study of benzylidenemalononitrile behavior in methanolic ammonia can serve as an additional evidence of pathway 2 (Table 3).

We have found that piperidines **4** can be obtained directly from benzylidenemalononitriles **1** by aqueous ammonia action in moderate yields. This domino transformation considers the realization of both reaction pathways (Scheme 4).

## Conclusion

The new one-pot assembling of benzylidenmalononitriles, aromatic aldehydes, and ammonium acetate or aqueous ammonia as nitrogen source leads to the stereoselective formation of 3,3,5,5-tetracyano-2,4,6-triarylpiperidines in 69–96% yields. It is established that the reaction proceeds via sequence of equilibriums and competitive mechanisms are implemented. The process smoothly proceeds with olefins and aromatic aldehydes bearing both electron-donating and electron-withdrawing groups. Ammonium acetate or aqueous ammonia plays a role both as a catalyst and as a nitrogen source. Products were purified by simple filtration and column chromatography was avoided entirely.

## Experimental

All melting points were measured with a Gallenkamp melting point apparatus. $^1$H and $^{13}$C NMR were recorded with a Bruker AM300 at ambient temperature in DMSO-$d_6$

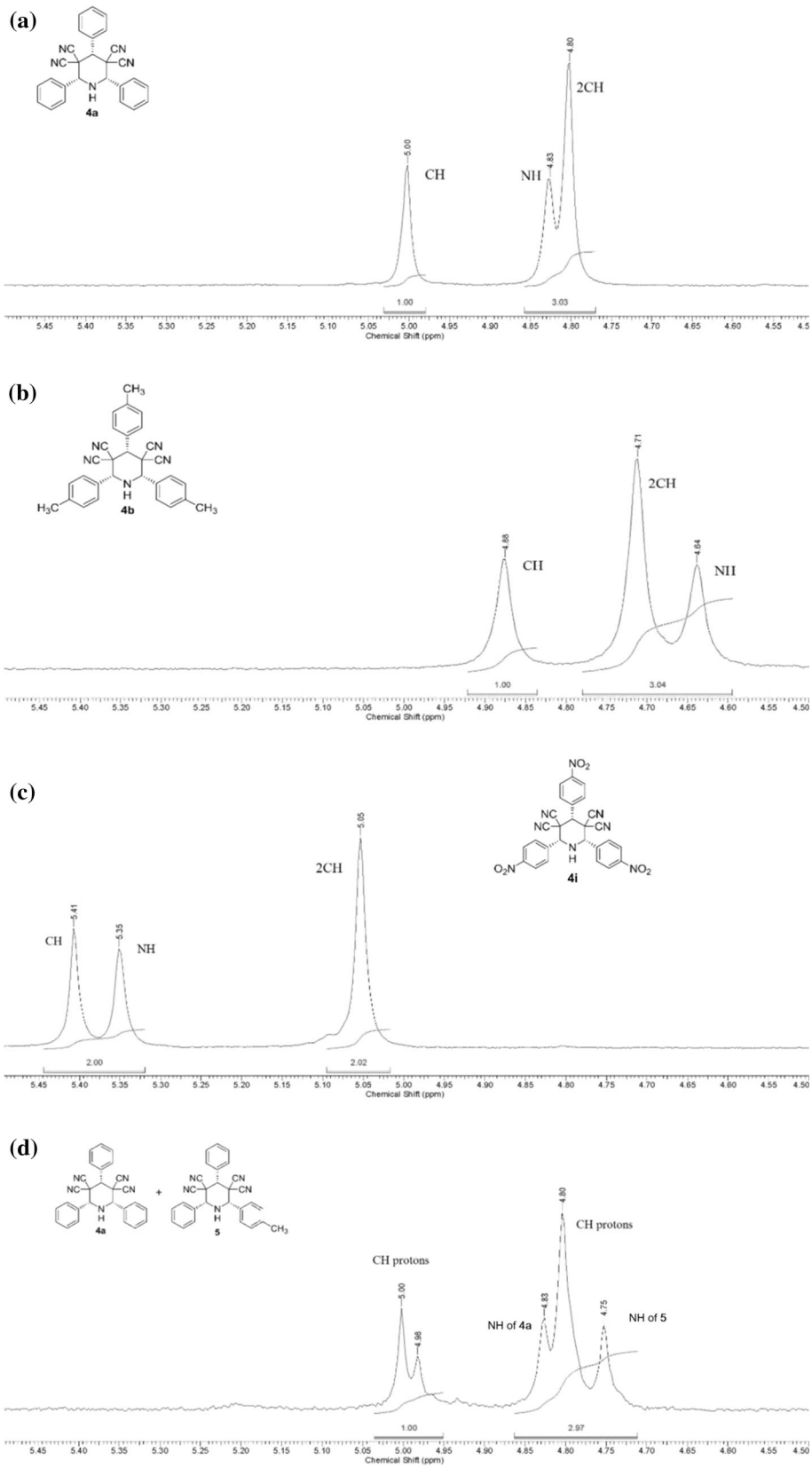



**Fig. 3** Characteristic proton signals of: **a**, **4a**; **b**, **4b**; **c**, **4i**; **d**, mixture of **4a** and **5**

**Scheme 4**

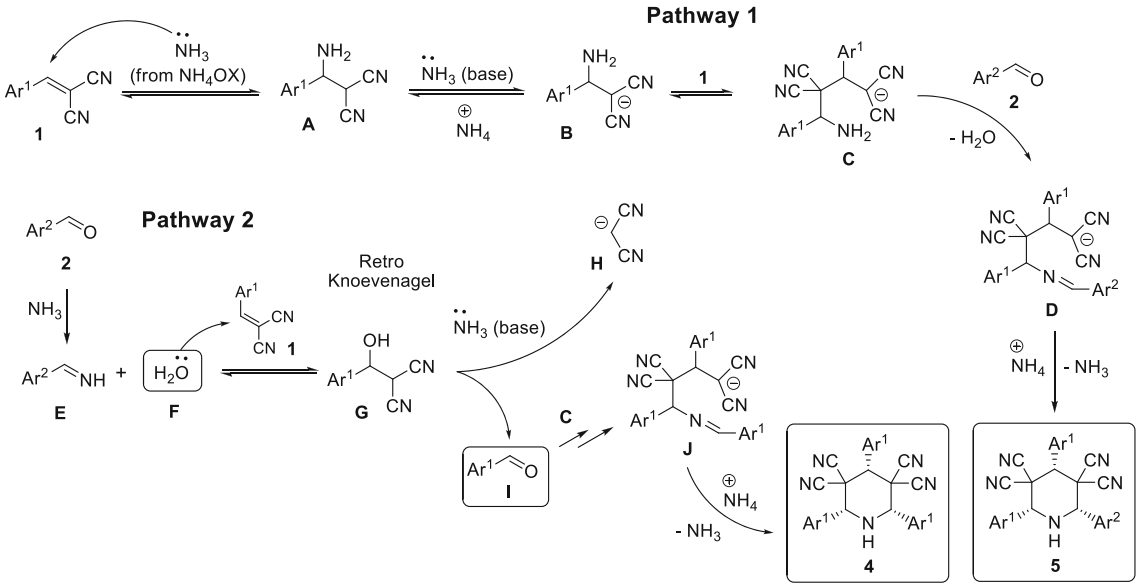
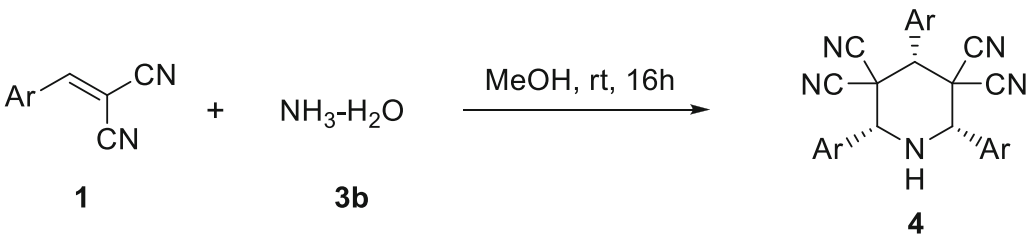



**Table 3** Direct synthesis of piperidines **4** from benzylidenemalononitriles **1** by aqueous ammonia action




| Entry | Alkene | Ar | Product | Yield/%[a] |
|---|---|---|---|---|
| 1 | **1a** | Ph | **4a** | 41 |
| 2 | **1b** | 4-$MeC_6H_4$ | **4b** | 35 |
| 3 | **1e** | 3-$FC_6H_4$ | **4e** | 37 |
| 4 | **1f** | 4-$FC_6H_4$ | **4f** | 37 |
| 5 | **1g** | 3-$BrC_6H_4$ | **4g** | 42 |
| 6 | **1i** | 3-Py | **4i** | 44 |

Reaction conditions: benzylidenemalononitrile **1** (3 mmol), ammonia (in water, 25% by weight, 3 mmol) in 5 $cm^3$ of methanol were stirred at rt for 16 h

[a]Isolated yields

solutions. Chemical shifts values are given in $\delta$ scale relative to $Me_4Si$. IR spectra were recorded with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. Mass spectra (EI = 70 eV) were recorded with a Finningan MAT INCOS 50 spectrometer. Thin-layer chromatography (TLC) was performed using silica gel GF254 precoated plates (0.20 mm thickness). Visualization on TLC was achieved by UV light (254 nm). Benzaldehydes **2** were obtained from commercial sources and used without further purification. Benzylidenemalononitriles **1** were obtained from benzaldehydes **2** and malononitrile by Knoevenagel condensation using sodium acetate as a catalyst [62, 63].

## General procedure for multicomponent synthesis of 2,4,6-triarylpiperidine-3,3,5,5-tetracarbonitriles 4

To a stirred solution of benzylidenemalononitrile **1** (6 mmol) and aromatic aldehyde **2** (3 mmol) in 5 $cm^3$ of methanol, 0.35 g ammonium acetate (**3a**, 4.5 mmol) or aqueous ammonia (**3b**, 25% by weight, 4.5 mmol) was added. The resultant mixture was stirred at the temperature and time indicated in Table 2. The reaction was completed as indicated by TLC. The reaction mixture was cooled to − 10 °C for 1 h. The precipitate solid was filtered and dried to afford pure product **4**.

## General procedure for multicomponent synthesis of 2,4,6-triarylpiperidine-3,3,5,5-tetracarbonitriles 4 directly from benzylidenemalononitriles 1

To a stirred methanolic solution of benzylidenemalononitrile **1** (3 mmol in 5 $cm^3$ of MeOH) aqueous ammonia (**3b**, 25% by weight, 3 mmol) was added. The resultant mixture was stirred at the room temperature for 16 h. The reaction mixture was cooled to − 10 °C for 1 h. The precipitate solid was filtered and dried to afford pure product **4**.

**2,4,6-Triphenylpiperidine-3,3,5,5-tetracarbonitrile (4a)** White solid; yield 1.07 g (86%); m.p.: 191–192 °C (lit. m.p.: 178–179 °C [58]). Single crystals of $C_{27}H_{19}N_5$ were grown from methanol. A suitable crystal was selected and placed on a Bruker Apex II CCD diffractometer. The crystal was kept at 120 K during data collection. Using Olex2 [64], the structure was solved with the XS [65] structure solution program using Direct Methods and refined with the XL [65] refinement package using least squares minimization.

Crystal data for **4a** ($C_{27}H_{19}N_5$, $M$ = 413.47 g/mol): monoclinic, space group $P2_1/c$ (no. 14), $a$ = 11.482(2) Å, $b$ = 15.755(3) Å, $c$ = 12.458(3) Å, $\beta$ = 03.71(3)°, $V$ = 2189.4(8) $Å^3$, $Z$ = 4, $T$ = 296.15 K, μ(CuKα) = 0.604 $mm^{-1}$, $Dcalc$ = 1.254 g/$cm^3$; 12423 reflections measured (7.926° ≤ 2Θ ≤ 135.282°), 3847 unique ($R_{int}$ = 0.0483, $R_{sigma}$ = 0.0437) which were used in all calculations. The final $R_1$ was 0.0411 ($I > 2\sigma(I)$) and $wR_2$ was 0.1014 (all data). Obtained crystal structure was deposited in CCDC (CCDC 1563837).

**2,4,6-Tris(4-methylphenyl)piperidine-3,3,5,5-tetracarbonitrile (4b)** White solid; yield 1.05 g (77%); m.p.: 161–162 °C (lit. m.p.: 159–160 °C [58]).

**2,4,6-Tris(3-methylphenyl)piperidine-3,3,5,5-tetracarbonitrile (4c, $C_{30}H_{25}N_5$)** White solid; yield 0.94 g (69%); m.p.: 136–137 °C; IR: $\bar{\nu}$ = 3333, 2923, 2840, 1609, 1491, 1459, 1362, 1279, 1135, 779 $cm^{-1}$; MS: *m/z* (%) = [$M^+$] (29), 364 (16), 289 (49), 263 (46), 220 (49), 199 (100), 185 (50), 130 (99), 89 (51); $^1$H NMR (300.13 MHz, DMSO-$d_6$): $\delta$ = 2.40 (s, 9H, 3 $CH_3$), 4.73 (s, 3H, 2 CH + NH), 4.90 (s, 1H, CH), 7.27–7.79 (m, 12H, Ar) ppm; $^{13}$C NMR (75.47 MHz, DMSO-$d_6$): $\delta$ = 20.8 (2C), 21.1, 44.8, 49.1, 66.2 (2C), 112.1 (2C), 112.9 (2C), 125.6, 126.0, 128.3, 128.7, 129.5, 130.0, 130.5, 131.3, 132.5, 135.0, 137.6, 138.8 ppm.

**2,4,6-Tris(2-fluorophenyl)piperidine-3,3,5,5-tetracarbonitrile (4e, $C_{27}H_{16}F_3N_5$)** White solid; yield 1.01 g (72%); m.p.: 175–176 °C; IR: $\bar{\nu}$ = 3333, 2968, 1617, 1589, 1494, 1461, 1378, 1283, 1241, 813 $cm^{-1}$; MS: *m/z* (%) = [$M^+$] (1), 230 (86), 201 (7), 183 (21), 172 (44), 145 (47), 124 (24), 123 (100), 122 (75); $^1$H NMR (300.13 MHz, DMSO-$d_6$): $\delta$ = 4.81 (s, 1H, CH), 5.56 (s, 1H, NH), 5.61 (s, 2H, CH), 7.28–7.59 (m, 9H, Ar), 8.01 (t, $J$ = 7.3 Hz, 2H, Ar), 8.29 (t, $J$ = 7.3 Hz, 1H, Ar) ppm; $^{13}$C NMR (75.47 MHz, DMSO-$d_6$): $\delta$ = 43.5, 57.4 (2C), 58.1 (2C), 112.0 (2C), 112.1 (2C), 115.1 (d, $J^4_{C\text{-}F}$ = 4.4 Hz, 2C), 115.7 (d, $J^4_{C\text{-}F}$ = 4.4 Hz), 116.1 (d, $J^3_{C\text{-}F}$ = 8.8 Hz, 2C), 116.3 (d, $J^3_{C\text{-}F}$ = 7.7 Hz), 127.7 (d, $J^3_{C\text{-}F}$ = 21.0 Hz, 2C), 129.1 (d, $J^2_{C\text{-}F}$ = 28.9 Hz), 129.2 (d, $J^2_{C\text{-}F}$ = 26.5 Hz, 2C), 129.3 (d, $J^2_{C\text{-}F}$ = 24.8 Hz), 131.1 (d, $J^2_{C\text{-}F}$ = 8.9 Hz, 2C), 131.8 (d, $J^2_{C\text{-}F}$ = 7.7 Hz), 159.3 (d, $J^1_{C\text{-}F}$ = 247.7 Hz, 2C), 159.5 (d, $J^1_{C\text{-}F}$ = 245.5 Hz) ppm.

**2,4,6-Tris(3-fluorophenyl)piperidine-3,3,5,5-tetracarbonitrile (4f, $C_{27}H_{16}F_3N_5$)** White solid; yield 1.09 g (78%); m.p.: 177–178 °C; IR: $\bar{\nu}$ = 3335, 3077, 1616, 1594, 1491, 1455, 1276, 1243, 1162, 1152 $cm^{-1}$; MS: *m/z* (%) = [$M^+$] (1), 231 (16), 230 (100), 201 (7), 172 (48), 145 (34), 123 (68), 122 (42), 96 (11); $^1$H NMR (300.13 MHz, DMSO-$d_6$): $\delta$ = 4.85 (s, 2H, CH), 5.06 (s, 1H, NH), 5.12 (s, 1H, CH), 7.38 (t, $J$ = 8.3 Hz, 2H, Ar), 7.52–7.60 (m, 7H, Ar), 7.68 (d, $J$ = 9.6 Hz), 8.77 (t, $J$ = 5.3 Hz, 2H, Ar) ppm; $^{13}$C NMR (75.47 MHz, DMSO-$d_6$): $\delta$ = 44.3, 48.1 (2C), 65.3 (2C), 111.7 (2C), 112.4 (2C), 114.2 ($J^2_{C\text{-}F}$ = 21.8 Hz), 115.3 (d, $J^2_{C\text{-}F}$ = 23.2 Hz), 116.7 (d, $J^2_{C\text{-}F}$ = 23.2 Hz), 116.8 (d, $J^2_{C\text{-}F}$ = 21.0 Hz), 117.9 (d, $J^4_{C\text{-}F}$ = 3.3 Hz), 118.2 (d, $J^4_{C\text{-}F}$ = 3.3 Hz), 130.6 (d, $J^3_{C\text{-}F}$ = 7.7 Hz), 131.6 (d, $J^3_{C\text{-}F}$ = 7.7 Hz), 134.6 (d, $J^3_{C\text{-}F}$ = 7.7 Hz), 139.4 (d, $J^3_{C\text{-}F}$ = 7.7 Hz), 161.9 (d, $J^1_{C\text{-}F}$ = 244.4 Hz), 162.0 ($J^1_{C\text{-}F}$ = 243.3 Hz) ppm.

**2,4,6-Tris(4-fluorophenyl)piperidine-3,3,5,5-tetracarbonitrile (4g, $C_{27}H_{16}F_3N_5$)** White solid; yield 1.15 g (82%); m.p.: 187–188 °C; IR: $\bar{\nu}$ = 3569, 3338, 2255, 2232, 1608, 1512, 1431, 1239, 1162, 842 $cm^{-1}$; MS: *m/z* (%) = [$M^+$-CN] (0.2), 414 (0.3), 295 (99), 231 (27), 230 (99), 183 (33), 173 (21), 172 (100), 145 (49), 123 (98), 122 (72); $^1$H NMR (300.13 MHz, DMSO-$d_6$): $\delta$ = 4.80 (s, 2H, CH), 4.91 (s, 1H, NH), 5.08 (s, 1H, CH), 7.39 (t, $J$ = 8.7 Hz, 4H, Ar),

7.53 (t, $J$ = 8.7 Hz, 2H, Ar), 7.75–7.82 (m, 4H, Ar), 7.94–8.12 (m, 2H, Ar) ppm; $^{13}$C NMR (75.47 MHz, DMSO-$d_6$): $\delta$ = 44.8, 47.9 (2C), 65.2 (2C), 111.8 (2C), 112.6 (2C), 115.7 (d, $J^2_{C\text{-}F}$ = 21.7 Hz, 4C), 116.9 (d, $J^2_{C\text{-}F}$ = 21.9 Hz, 2C), 128.7 (d, $J^4_{C\text{-}F}$ = 3.2 Hz, 2C), 130.5 (d, $J^3_{C\text{-}F}$ = 8.6 Hz, 4C), 131.1 (d, $J^4_{C\text{-}F}$ = 2.9 Hz), 131.4 (d, $J^3_{C\text{-}F}$ = 8.7 Hz, 2C), 161.3 (d, $J^1_{C\text{-}F}$ = 25.4 Hz, 2C), 164.7 (d, $J^1_{C\text{-}F}$ = 27.6 Hz) ppm.

**2,4,6-Tris(3-bromophenyl)piperidine-3,3,5,5-tetracarbonitrile (4h, $C_{27}H_{16}Br_3N_5$)** White solid; yield 1.87 g (96%); m.p.: 180–181 °C; IR: $\bar{\nu}$ = 3340, 2253, 1720, 1572, 1476, 1436, 1021, 1075, 783, 691 cm$^{-1}$; MS: *m/z* (%) = [M$^+$-$C_{10}H_5BrN_2$] 354 (11), 352 (23), 234 (51), 232 (55), 185 (32), 183 (40), 153 (100), 126 (39), 75 (37); $^1$H NMR (300.13 MHz, DMSO-$d_6$): $\delta$ = 3.75 (d, $J$ = 5.0 Hz, 3H, $CH_3$ from methanol), 4.10 (q, $J$ = 5.5 Hz, 1H, OH from methanol), 4.78 (s, 2H, CH), 5.06 (s, 1H, CH), 5.12 (s, 1H, NH), 7.51 (m, 2H, Ar), 7.70 (m, 6H, Ar), 7.91 (m, 3H, Ar), 8.04 (s, 1H, Ar) ppm; $^{13}$C NMR (75.47 MHz, DMSO-$d_6$): $\delta$ = 30.6, 44.2 (2C), 47.9 (2C), 65.2 (2C), 111.6 (2C), 112.3 (2C), 121.6 (2C), 122.5 (2C), 127.8 (2C), 127.9 (2C), 130.7, 130.8, 132.1 (2C), 132.9 (2C), 133.9, 134.5, 136.9 (2C) ppm.

**2,4,6-Tris(4-nitrophenyl)piperidine-3,3,5,5-tetracarbonitrile (4i, $C_{27}H_{16}N_8O_6$)** White solid; yield 1.15 g (70%); m.p.: 219–220 °C; IR: $\bar{\nu}$ = 3300, 3086, 2257, 2215, 1609, 1526, 1357, 1110, 858, 712 cm$^{-1}$; MS: *m/z* (%) = [M$^+$-$C_{10}H_5N_3O_2$] (2), 284 (31), 199 (100), 169 (25), 153 (61), 150 (30), 141 (47), 126 (62), 114 (21), 99 (18); $^1$H NMR (300.13 MHz, DMSO-$d_6$): $\delta$ = 5.04 (s, 2H, CH), 5.35 (s, 1H, NH), 5.40 (s, 1H, CH), 8.035 (d, $J$ = 8.6 Hz, 4H, Ar), 8.17 (d, $J$ = 8.6 Hz, 2H, Ar), 8.44 (d, $J$ = 8.5 Hz, 4H, Ar), 8.56 (d, $J$ = 8.5 Hz, 2H, Ar) ppm; $^{13}$C NMR (75.47 MHz, DMSO-$d_6$): $\delta$ = 43.6, 47.9 (2C), 65.0 (2C), 111.2 (2C), 111.9 (2C), 123.7 (4C), 125.0 (2C), 130.0 (4C), 130.8 (2C), 138.3, 141.0 (2C), 148.6 (2C), 149.1 ppm.

**2,4,6-Tris(3-pyridyl)piperidine-3,3,5,5-tetracarbonitrile (4j, $C_{24}H_{16}N_8$)** White solid; yield 1.17 g (94%); m.p.: 174–175.5 °C; IR: $\bar{\nu}$ = 3310, 3150, 2929, 2251, 1578, 1485, 1434, 1150, 1029, 722 cm$^{-1}$; MS: *m/z* (%) = [M$^+$-$C_{12}H_5N_5$] (49), 155 (100), 128 (44), 106 (29), 105 (20), 104 (76), 101 (39), 100 (20), 75 (47); $^1$H NMR (300.13 MHz, DMSO-$d_6$): $\delta$ = 4.94 (s, 2H, CH), 5.23 (s, 1H, NH), 5.26 (s, 1H, CH), 7.60 (d, $J$ = 4.4 Hz, 2H, Ar), 7.74 (d, $J$ = 4.4 Hz, 1H, Ar), 8.18 (d, $J$ = 7.7 Hz, 2H, Ar), 8.39 (d, $J$ = 8.5 Hz, 1H, Ar), 8.72 (d, $J$ = 4.4 Hz, 2H, Ar), 8.84 (d, $J$ = 4.4 Hz, 1H, Ar), 8.88 (s, 2H, Ar), 8.99 (s, 1H, Ar) ppm; $^{13}$C NMR (75.47 MHz, DMSO-$d_6$): $\delta$ = 44.3 (2C), 46.3, 48.6 (2C), 111.6 (2C), 112.3 (2C), 123.7 (2C), 124.8, 128.2, 130.3 (2C), 135.8, 136.2 (2C), 149.3 (2C), 150.3, 151.3 (2C), 152.2 ppm.

**Acknowledgements** This work was supported by the Russian Science Foundation (RSF Grant 17-73-20260).

## References


1. Zhu J, Wang Q, Wang M (2015) Multicomponent reactions in organic synthesis. Wiley-VCH, Weinheim
2. Graaff C, Ruijter E, Orru RVA (2012) Chem Soc Rev 41:3969
3. Marson CM (2012) Chem Soc Rev 41:7712
4. Rotstein BH, Zaretsky S, Rai V, Yudin AK (2014) Chem Rev 114:8323
5. Dömling A (2015) Chem Rec 15:981
6. Elinson MN, Vereshchagin AN, Ryzhkov FV (2016) Chem Rec 16:1950
7. Gamez-Montano R, Zhu J (2002) Chem Commun 20:2248
8. Touré BB, Hall DG (2009) Chem Rev 109:4439
9. Ruijter E, Orru RVA (2013) Drug Discov Today 10:e15
10. Zarganes T, Dömling A (2014) Org Chem Front 1:834
11. Ganem B (2009) Acc Chem Res 42:463
12. Ruijter E, Scheffelaar R, Orru RVA (2011) Angew Chem Int Ed 50:6234
13. Shiri M (2012) Chem Rev 112:3508
14. Brauch S, van Berkel SS, Westermann B (2013) Chem Soc Rev 42:4948
15. Allais C, Grassot JM, Rodriguez J, Constantieux T (2014) Chem Rev 114:10829
16. Vereshchagin AN (2017) Russ Chem Bull 66:1765
17. Weber L (2002) Curr Med Chem 9:2085
18. Weber L (2002) Drug Discov Today 7:143
19. Slobbe P, Ruijter E, Orru RVA (2012) MedChemCommun 3:1189
20. Dömling A, Wang W, Wang K (2012) Chem Rev 112:3083
21. Koszytkowska-Stawińska M, Buchowicz W (2014) Beilstein J Org Chem 10:1706
22. Dömling A (2006) Chem Rev 106:17
23. Levi L, Müller TJJ (2016) Chem Soc Rev 45:2825
24. Bienayme H, Bouzid K (1998) Angew Chem Int Ed 37:2234
25. Ugi I, Heck S (2001) Comb Chem High Throughput Screen 4:1
26. Gerencsér J, Dormán G, Darvas F (2006) QSAR Comb Sci 25:439
27. Martin KS, Di Maso MJ, Fettinger JC, Shaw JT (2013) ACS Comb Sci 15:356
28. Rani GU, Kumar SV, Bharkavi C, Menéndez JC, Perumal S (2016) ACS Comb Sci 18:337
29. Elbein DA, Molyneux R (1987) In: Palletier SW (ed) Alkaloids: chemical and biological perspectives, vol 57. Wiley, New York
30. Pinder AR (1992) Nat Prod Rep 9:17
31. Felpin FX, Lebreton J (2004) Tetrahedron 60:10127
32. Ho B, Crider AM, Stables JP (2001) Eur J Med Chem 36:265
33. Maier CA, Wunsch B (2002) J Med Chem 45:438
34. Weis R, Schweiger K, Faist J, Rajkovic E, Kungl AJ, Fabian WMF, Schunack W, Seebacher W (2008) Bioorg Med Chem 16:10326
35. Misra M, Pandey SK, Pandey VP, Pandey J, Tripathi R, Tripathi RP (2009) Bioorg Med Chem 17:625
36. Wang W, Hu Y (2012) Med Res Rev 32:1159
37. Tanaka R, Rubio A, Harn NK, Gernert D, Grese TA, Eishima J, Hara M, Yoda N, Ohashi R, Kuwabara T, Soga S, Akinaga S, Nara S, Kanda Y (2007) Bioorg Med Chem 5:1363
38. Reshetov PV, Kriven'ko AP, Boreko EI, Vladyko GV, Korobchenko LV (1990) Pharm Chem J 24:889
39. Kudou T, Tanima D, Masuzawa Y, Yano T (2011) Ortho-substituted haloalkylsulfonanilide derivatives as herbicides. Eur Patent 2336104, 22 June 2011; (2010) Chem Abstr 152:357881

40. Guareschi L, Grande E (1898) Chem Zentralbl 69:544
41. Robinson R (1917) J Chem Soc 111:762
42. Schöpf C (1937) Angew Chem 50:779
43. Zhu W, Mena M, Jnoff E, Sun N, Pasau P, Ghosez L (2009) Angew Chem Int Ed 48:5880
44. Zhou Z, Liu H, Sun Q, Li Y, Yang J, Liu J, Yan P, Wang C (2005) Synlett 23:2255
45. Liu H, Zhou Z, Sun Q, Li Y, Li Y, Liu J, Yan P, Wang D, Wang C (2012) ACS Comb Sci 14:366
46. Li Y, Sun Q, Zhou Z, Liu J, Yang J, Wang C (2013) Monatsh Chem 144:1031
47. Li Y, Xue Z, Ye W, Liu J, Yao J, Wang C (2014) ACS Comb Sci 16:113
48. Elinson MN, Feducovich SK, Vereshchagin AN, Dorofeev AS, Dmitriev DE, Nikishin GI (2003) Russ Chem Bull Int Ed 52:2235
49. Elinson MN, Feducovich SK, Zaimovskaya TA, Vereshchagin AN, Gorbunov SV, Nikishin GI (2005) Russ Chem Bull Int Ed 54:1593
50. Vereshchagin AN, Elinson MN, Stepanov NO, Nikishin GI (2009) Mendeleev Commun 19:324
51. Elinson MN, Vereshchagin AN, Stepanov NO, Ilovaisky AI, Vorontsov AY, Nikishin GI (2009) Tetrahedron 65:6057
52. Elinson MN, Vereshchagin AN, Feducovich SK, Zaimovskaya TA, Starikova ZA, Belyakov PA, Nikishin GI (2007) Tetrahedron Lett 48:6614
53. Elinson MN, Feducovich SK, Zaimovskaya TA, Vereshchagin AN, Nikishin GI (2003) Russ Chem Bull Int Ed 52:2241
54. Vereshchagin AN, Elinson MN, Zaimovskaya TA, Nikishin GI (2008) Tetrahedron 64:9766
55. Vereshchagin AN, Elinson MN, Dorofeeva EO, Stepanov NO, Zaimovskaya TA, Nikishin GI (2013) Tetrahedron 69:1945
56. Elinson MN, Dorofeeva EO, Vereshchagin AN, Korshunov AD, Egorov MP (2016) Res Chem Intermed 42:2191
57. Lemek T, Mayr H (2003) J Org Chem 68:6880
58. Takajo T, Kambe S (1980) Synthesis 1980:833
59. Chakrabarty M, Karmakar S, Arima S, Harigaya Y (2007) Heterocycles 73:795
60. Geissler G, Hippius M, Tomaschewski G (1982) J Prakt Chem 324:910
61. Rajasekaran K, Sarathi A, Ramalakshmi S (2008) J Chem Sci 120:475
62. Elinson MN, Feducovich SK, Zaimovskaya TA, Vereshchagin AN, Nikishin GI (2005) Russ Chem Bull Int Ed 54:673
63. Vereshchagin AN, Elinson MN, Egorov MP (2015) RSC Adv 5:98522
64. Dolomanov OV, Bourhis LJ, Gildea RJ, Howard JAK, Puschmann HJ (2009) Appl Cryst 42:339
65. Sheldrick GM (2008) Acta Crystallogr A64:112