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Pseudo six-component stereoselective synthesis of 2,4,6-triaryl-3,3,5,5-tetracyanopiperidines

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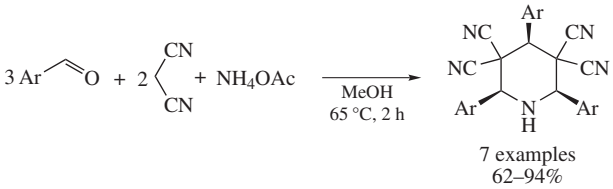
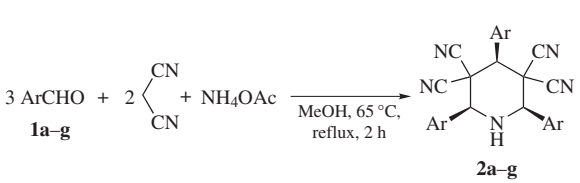
The Knövenagel–Michael–Mannich cascade reaction of aromatic aldehyde (3 equiv.), malononitrile (2 equiv.) and ammonium acetate or aqueous ammonia provides convenient stereoselective access to *cis*,*cis*-2,4,6-triaryl-3,3,5,5-tetracyanopiperidines in 62–94% yields. Six new bonds form as a result of the domino process, ammonium acetate serving as a nitrogen source.



In recent decades, the number of multicomponent studies permanently boosts since the methodology of multicomponent 'one-pot' reactions has serious advantages in comparison to an ordinary multi-step synthesis, such as minimization of the environmental loading, access to complicated molecules without isolation of intermediates, and decrease in labour expenses as well as costs for raw materials.[1,2] The dynamic development of multicomponent strategy allows one to obtain a wide range of structures for modern organic,[3,4] medicinal[5] and applied[6] chemistry.

The piperidine nucleus is a well-known heterocyclic component in a variety of natural compounds.[7] Compounds bearing the piperidine moiety possess a lot of biological actions, for example, anticonvulsant, antimicrobial, antihistamine, anti-inflammatory, antimalarial, anti-HIV, and anticancer activities.[8,9]

Recently Wang *et al.* proposed a new multicomponent approach to the synthesis of polysubstituted piperidines,[10] when ammonium acetate was used as nitrogen source for the piperidine cycle assembling from nitrostyrene, aromatic aldehydes, and C–H acids. Although these processes enable a wide variation of aryl substituents, they significantly suffer from moderate yields (no more 75%) and long reaction times. Furthermore, column chromatography was required for purification of the desired products.



a Ar = Ph, 85%
b Ar = 4-MeC_6H_4, 72%
c Ar = 2-FC_6H_4, 70%
d Ar = 4-FC_6H_4, 83%
e Ar = 3-BrC_6H_4, 94%
f Ar = 3-Py, 92%
g Ar = 4-Py, 62%

Scheme 1 *Reagents and conditions:* ArCHO **1** (9 mmol), $CH_2(CN)_2$ (6 mmol) and NH_4OAc (6 mmol), MeOH (5 ml), reflux, 2 h; for **2b** aqueous ammonia (25 wt%, 6 mmol) was used as nitrogen source, 25 °C, reaction time was 6 h.

As a part of our continuous interest in the development of new methodologies using malononitrile as essential building block for the synthesis of different type of cyclic (cyclopropanes,[11–13] cyclohexanes[14]) and heterocyclic (pyrrolines,[15] spiropyrimidines,[16] chromenes,[17,18] chromenopyridines,[19] pyranoquinolines,[20] polyheterocycles[21]) systems, we report herein a new effective multicomponent approach to polycyano-substituted piperidines from aromatic aldehydes, malononitrile and ammonium acetate without catalyst (Scheme 1, Table 1).

At the optimization stage, benzaldehyde **1a** was selected as the model reactant (see Table 1). Initially, we tested the catalytic efficacy of different bases (entries 1–5). When triethylamine and piperidine were used as the bases, product **2a** was obtained in 78 and 65% yields, respectively (entries 1, 3). Aprotic acetonitrile as a solvent (entry 2) as well as inorganic bases (entries 4, 5) were ineffective for the synthesis of **2a**. We have found that the absence of a base catalyst did not affect the yield of **2a** (entry 6). The temperature played an important role in the Knoevenagel–Michael–Mannich cascade. Lowering it from 65 to 25 °C caused drop in the yield up to 15% (entry 7). The yield was not improved

Table 1 Multicomponent transformation of benzaldehyde **1a**, malononitrile and ammonium acetate into substituted piperidine **2a.**[a]

Entry	Base (50 mol%)	Solvent	*T*/°C	*t*/h	Yield of **2a** (%)
1	Et_3N	MeOH	65	1	78[b]
2	Et_3N	MeCN	81	1	15[c]
3	Piperidine	MeOH	65	1	65[b]
4	K_2CO_3	MeOH	65	1	not detected
5	NaOH	MeOH	65	1	not detected
6	–	MeOH	65	1	78[b]
7	–	MeOH	25	1	15[c]
8	–	EtOH	78	1	72[b]
9	–	MeOH	65	2	85[b]
10	–	MeOH	65	4	84[b]

[a] Benzaldehyde **1a** (9 mmol), malononitrile (6 mmol) and ammonium acetate (6 mmol) were stirred in solvent (5 ml). [b] Isolated yield. [c] NMR data.

when ethanol possessing higher boiling point was used (entry 8). Optimal duration of the process in refluxing methanol was 2 h (entries 9, 10).

Under optimal conditions thus found (see Table 1, entry 9), the similar reactions between various aromatic aldehydes **1a–g** (both with electron-withdrawing and electron-donating substituents), malononitrile and ammonium acetate were carried out to prepare the corresponding 2,4,6-triaryl-3,3,5,5-tetracyanopiperidines **2a–g** in 62–94% yields (see Scheme 1).† However, when we tried to synthesized tri-*p*-tolyl analogue **2b** from *p*-tolualdehyde **1b** under the same conditions, completely different results were obtained: (4-methylbenzylidene)malononitrile **3b** was isolated in 92% yield. It is known that olefins containing electron-donating groups have a low electrophilicity and hardly react with nucleophiles in the absence of catalyst.[22] Therefore, on moving to aqueous ammonia as a nitrogen source, the desired product **2b** was obtained in 72% yield (~20 °C, 6 h, MeOH) with full consumption of intermediate olefin **3b**.

Thus, the new multicomponent reaction provides tetracyanopiperidines **2a–g** in moderate to excellent yields in one step from cheap and available starting materials. Note that products were isolated by simple filtration of the reaction mixture. The synthesis of compounds **2a**,**b** had been reported earlier,[23] however, that method had significant disadvantages. First, they were produced from commercially unavailable 1-aryl-*N*,*N*-bis(arylmethylene) methanediamines by reaction with malononitrile and ammonium acetate in boiling ethanol in moderate yields (53% for **2a** and 60% for **2b**). Second, purification of **2a**,**b** by recrystallization from THF–methanol was needed. Moreover, no data on stereochemistry of piperidines **2a**,**b** was given.[23]

In the NMR spectra of compounds **2a–g** only a single set of signals was observed assuming formation of individual diastereoisomers. The X-ray diffraction data of single crystal of compound **2f** indicated that the aryl substituents are located in equatorial positions of the piperidine ring (Figure 1).‡

Taking into consideration the data obtained and results on domino reaction of nitrostyrenes, malonate, aromatic aldehydes and ammonium acetate giving substituted piperidin-2-ones,[10] the mechanism for the current transformation is proposed (Scheme 2).

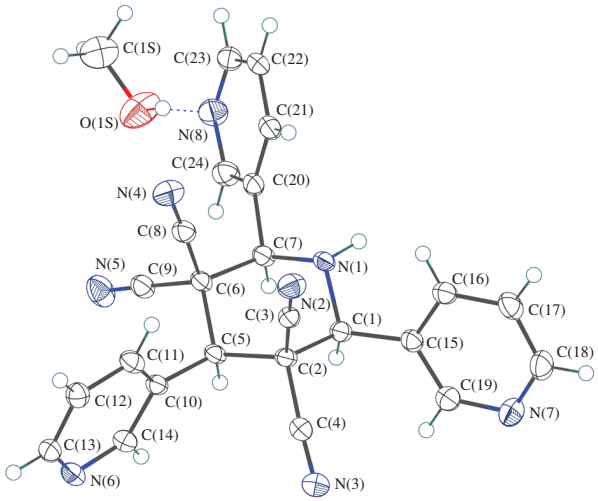
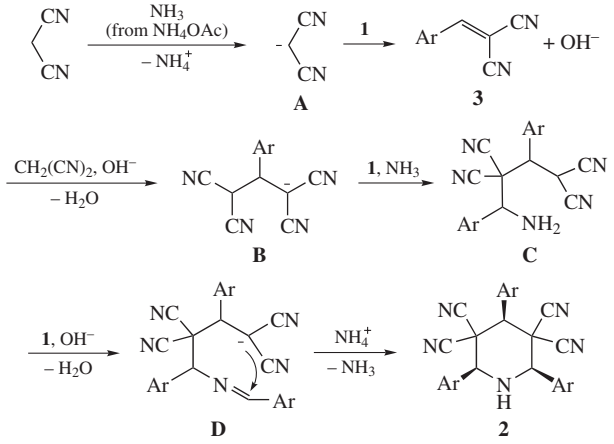


Figure 1 The general view of **2f** in a crystal. Atoms are represented by thermal displacement ellipsoids (p = 50%).

† *General procedure*. A mixture of aromatic aldehyde **1** (9 mmol), malononitrile (396 mg, 6 mmol) and ammonium acetate or aqueous ammonia (25 wt%, 6 mmol) was stirred in methanol (5 ml) at 65 °C for 2 h. Then the mixture was cooled to –10 °C for 15 min. The solid precipitate was filtered and dried to afford pure products **2a–g**.

For characteristics of compounds **2a–g**, see Online Supplementary Materials.



Scheme 2

The NH_4OAc-catalyzed Knoevenagel condensation of malononitrile with aromatic aldehyde results in benzylidenemalononitrile **3**, which then undergoes the Michael attack by the second molecule of malononitrile to give 1,1,3,3-tetracyanopropane anion **B**. Species **B** exists in alcohol solution in the equilibrium with the molecule of benzylidenemalononitrile **3** and the anion of malononitrile **A**.[24] The Mannich reaction of aldehyde **1**, ammonia (formed *in situ* from NH_4OAc) and **B** leads to tetracyanoamine **C**. Next, Schiff base **D** is formed from intermediate **C** and the second molecule of aldehyde **1**. Finally, cyclization of intermediate **D** affords sterically less hindered cyclic amine **2** as *cis*,*cis*-isomer.

In conclusion, the new pseudo-six-component reaction has been developed, which allows one to obtain 2,4,6-triaryl-3,3,5,5-tetracyanopiperidines in high yields as single diastereomers in one step from cheap and available starting materials. Six new bonds form as a result of the Knoevenagel–Michael addition–Mannich cascade. The process smoothly occurs with aromatic aldehydes bearing both electron-donating and electron-withdrawing groups. Ammonium acetate or aqueous ammonia serve both as catalysts and as nitrogen sources. Products were purified by simple filtration, no column chromatography was needed.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.07.014.

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‡ *Crystal data for* **2f**. $C_{25}H_{20}N_8O$ (M = 448.49), monoclinic, space group $P2_1/n$ (no. 14), a = 12.3233(10), b = 11.3955(10) and c = 16.8451(14) Å, β = 108.574(2)°, V = 2242.3(3) Å^3, Z = 4, T = 120 K, μ(MoKα) = = 0.087 mm^{-1}, d_{calc} = 1.328 g cm^{-3}. Total of 30317 reflections measured (4.4° ⩽ 2θ ⩽ 61.02°), 6843 unique (R_{int} = 0.0792, R_σ = 0.0688) which were used in all calculations. The final R_1 = 0.0517 [$I > 2\sigma(I)$] and wR_2 = = 0.1285 (all data).

CCDC 1812779 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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