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# One-pot synthesis of substituted imino- and imidazopyridines under catalyst-free conditions

F. N. Naghiyev, A. M. Maharramov, İ. M. Akhmedov, Kh. A. Asadov, A.N. Khalilov, A. V. Gurbanov, G. Z. Mammadova, A. R. Asgarova, E. Z. Guseynov, I. G. Mamedov*

*Faculty of Chemistry, Baku State University, Baku AZ1148, Azerbaijan*

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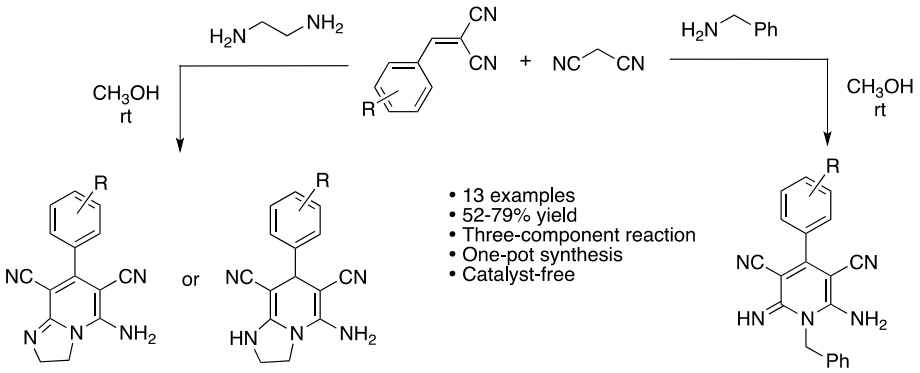
Substituted imino- and imidazopyridine derivatives were synthesized *via* a new one-pot, three-component reaction between benzylidenemalononitriles, malononitrile and amines under catalyst-free conditions at room temperature. When ethylenediamine was used as the amine component of the reaction, dihydro- and tetrahydroimidazopyridines were selectively obtained in good to high yields. On the other hand, the use of benzylamine led to the formation of 2-imino-1,2-dihydropyridine products. The reactions were found to tolerate the presence of electron-donating and withdrawing substituents on the benzylidenemalononitrile reactants. Products of these reactions are crystalline and can be isolated by a simple procedure at room temperature in good yields and with high purity.

**Keywords:** Benzylidenemalononitrile, Imidazopyridine, Iminodihydropyridine, X-ray analysis

GRAPHICAL ABSTRACT




## INTRODUCTION

Heterocyclic chemistry continues to be at the forefront of organic chemistry due to its importance across a variety of disciplines such as medicinal chemistry, agricultural chemistry and materials science [1,2]. Pyridine ring, a privileged structural core in heterocyclic chemistry, is present in many natural products such as nicotinic acid, nicotinamide and vitamin $B_6$ which play key roles in metabolism. In addition, functionalized pyridines have been shown to exhibit a broad range of biological activities including antimicrobial, antiulcer, anticancer, antipyretic and anti-inflammatory activities [3-7].

Due to all these attractive features of pyridine-containing compounds, numerous synthetic methods that enable the construction of substituted pyridines have been developed [8-10]. Recently, transition metal-catalyzed coupling reactions of enamides with alkynes, and TfOH-promoted reactions of enaminones with aldehydes were shown to be highly effective for the synthesis of substituted pyridines [11-13]. $Zn(NO_3)_2{\cdot}6H_2O$ was found to be a potent catalyst for the synthesis of unsymmetrical multisubstituted pyridines *via* the reaction of β-ketoesters with ketene *N,S*-acetals or ketene *N,N*-acetals [14]. Dong and co-workers reported in 2013 a copper-catalyzed, three-component reaction between sulfonyl azides, alkynes and 2-[(amino) methylene]malononitriles that gave rise to the formation of 4-amino- and 6-amino-2-iminopyridine derivatives [15]. An efficient one-pot methodology was reported by Ranu and co-workers in 2007 for the synthesis of substituted pyridines *via* the condensation of aldehydes, malononitrile and thiophenols promoted by the basic ionic liquid [bmIm]OH [16]. A multicomponent reaction of malononitrile and aldehydes with ammonium acetate catalyzed by $Et_3N$ was developed for the synthesis of aminopyridine derivatives [17]. In

* To whom all correspondence should be sent:
E-mail: bsu.nmrlab@mail.ru

addition to these methods, efficient protocols for the synthesis of highly substituted pyridines and imidazopyridines starting from 2-aminopyridines, 2-bromopyridines, 2-(1*H*-benzo[*d*]imidazol-2-yl)acetonitrile [31], 2-amino-1-(2-propenyl)pyridinium bromide salt, α,β-unsaturated ketones, 1,3-dienes, and *O*-acetylketoximes have been successfully developed [18-32].

In this work, we report the development of a one-pot, three-component reaction between benzylidenemalononitriles, malononitrile and amines that lead to the synthesis of substituted imino- and imidazopyridines under catalyst-free conditions. Our interest in these compound classes stems from the attractive biological activity profiles observed for various pyridobenzimidazole derivatives (Figure 1) [33,34]. In a study reported by Denny and co-workers in 2011, 1-amino-2,4-dicyanopyrido[1,2-*a*] analogues (**1**) were found to effectively inhibit the cellular function of the pore-forming protein perforin [33]. More recently, Huttunen and co-workers reported in 2016 the reversible inhibition of the L-type amino acid transporter 1 (LAT1) by the pyridobenzimidazole analogue **2** (Fig. 1) [34]. Among the few synthetic methods available for the preparation of such pyridobenzimidazole derivatives [35-38], the reaction between 1H-benzimidazole-2-carbonitrile and arylidenemalononitriles reported by Bogdanowicz-Szwed and Czarny has been the most commonly utilized method [35]. The one-pot, three-component reactions that we have developed in this study operate under mild conditions, and result in rapid generation of complexity that leads to formation of multisubstituted imino- and imidazopyridines in an effective manner.

## EXPERIMENTAL

All commercially available chemicals were obtained from Merck and Fluka companies and used without further purification. Melting points were measured on a Stuart SMP30 apparatus without correction. $^{1}H/^{13}C$ NMR spectra were recorded on a Bruker Avance 300-MHz spectrometer at 300 and 75 MHz, respectively (Figs. S1-13). X-Ray analyses were performed on a Bruker APEX equipment. Thin-layer chromatography (TLC) on commercial aluminum-backed plates of silica gel (60 F254) was used to monitor the purity of compounds and progress of reactions. Iodine vapor was used as a visualizing agent, eluent - 5:2 hexane/ethyl acetate.

### *General procedure for the synthesis of compounds **6a–f**, **9g-i***

Mixture of benzylidenemalononitriles (**3a-f**, **3g-i**) (5.1 mmol) and malononitrile (5.2 mmol) was dissolved in 25 mL of methyl alcohol and stirred for 5-7 min. Ethylenediamine (5.2 mmol) was added to the mixture under vigorous stirring. The progress of the reaction was monitored by TLC (EtOAc/n-hexane, 2:1). The reaction mixture was stirred for 48-72 h. When the solvent was evaporated, crystals precipitated. Crystals were filtered through filter paper and recrystallized from a mixture of ethanol-water.

### *General procedure for the synthesis of compounds* **13j-m**

Mixture of benzylidenemalononitriles (**10j-m**) (5.1 mmol) and malononitrile (5.2 mmol) was dissolved in 35 ml of methyl alcohol and stirred for 5-7 min. Benzylamine (5.2 mmol) was added to the mixture under vigorous stirring. The progress of the reaction was monitored by TLC (EtOAc/n-hexane, 2:1). The reaction mixture was stirred for 48-72 h. When the solvent was evaporated, crystals precipitated. Crystals were filtered through filter paper and recrystallized from a mixture of ethanol-water.

## RESULTS AND DISCUSSION

We initiated our studies by the investigation of the three-component reaction between benzylidene-malononitrile (**3a-f**), malononitrile (**4**) and ethylene-diamine (**5**) (Table 1). Gratifyingly, the reaction was observed to proceed smoothly at room temperature in a methanol solution in the absence of a catalyst, and the dihydroimidazopyridine product **6a** was obtained in 52% isolated yield (Table 1, entry 1). Afterwards, the effect of the electronic properties of the substituents on the benzylidene-malononitrile component was investigated. When benzylidenemalononitrile reactants (**3b-d**) with -$CH_3$, -$OCH_3$ and -$N(CH_3)_2$ groups as electron-donating substituents were tested, the targeted dihydroimidazopyridine products **6b**, **6c** and **6d** were obtained in 66, 66 and 72% yields, respectively (entries 2-4). In addition, electron-withdrawing -F and -Br substituents were also found to be tolerated in this three-component reaction affording the dihydroimidazopyridine products **6e** and **6f** in good yields (entries 5 and 6). Finally, it is worth mentioning that, by the use of microwave (MW) irradiation, the reaction time could be decreased down to 175 min, compared to 48-72 h at room temperature (yields were similar at room temperature).

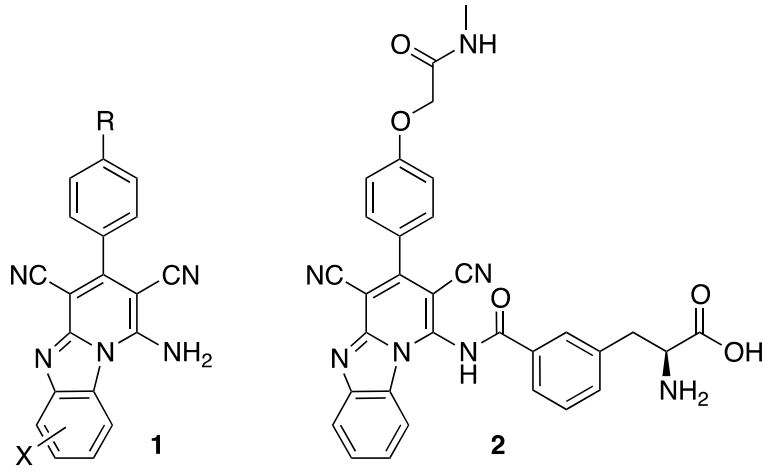
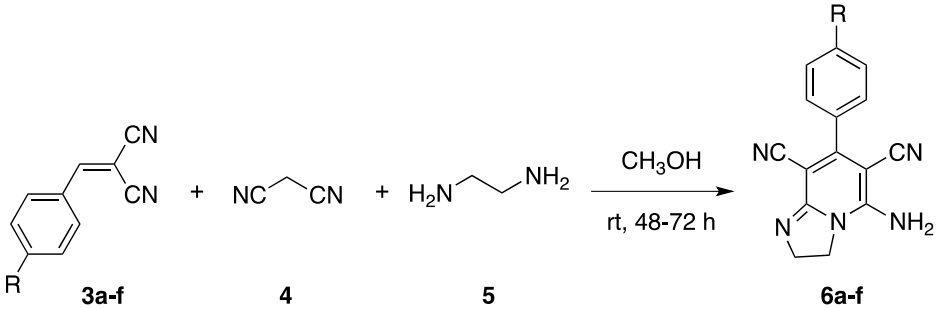



**Fig. 1.** Examples of biologically active pyridobenzimidazole analogues.

**Table 1.** Synthesis of dihydroimidazopyridine derivatives (**6a-f**) *via* three-component reaction between benzylidenemalononitriles, malononitrile and ethylenediamine.




**3a-f** **4** **5** **6a-f**

| Entry | R | Product | Yield (%) |
|---|---|---|---|
| 1 | H | 6a | 52 |
| 2 | $CH_3$ | 6b | 66 |
| 3 | $OCH_3$ | 6c | 66 |
| 4 | $N(CH_3)_2$ | 6d | 72 |
| 5 | F | 6e | 68 |
| 6 | Br | 6f | 62 |

The structures of the synthesized dihydroimdazopyridines were determined by NMR spectroscopy (Figs. S1-6). In addition, good quality crystals of three dihydroimidazopyridine products (**6b, 6c, 6e**) were obtained, and their structures were confirmed by single-crystal X-ray analysis (Fig. 2). Compound **6b** exhibits an intermolecular hydrogen bond in its crystal packing between one of the $NH_2$ hydrogens and the imine nitrogen of the dihydroimidazole moiety (Fig. 2a). On the other hand, compounds **6c** and **6e** were found to possess dimeric, hydrogen-bonded structures in which two intermolecular N-H···N≡C hydrogen bonds are present (Figs. 2b and 2c). This hydrogen bonding network is reminiscent of those previously observed for 2-cyanophenol derivatives [39,40]. Moreover, the crystal structure of **6e** revealed a F···F interaction with a distance of 2.77 Å between the two fluorine atoms [41]. The proposed reaction mechanism is shown in Scheme 1. Initially, ethylenediamine (**5**) is expected to act as a base and abstract one of the protons of malononitrile (**4**) to form the corresponding carbanion **7**. This carbanion could then undergo a Michael addition to benzylidenemalononitrile (**3a**) to give intermediate **8**. The incorporation of ethylenediamine (**5**) with separation of ammonia ($NH_3$) followed by a final oxidation would lead to the formation of the final dihydroimidazopyridine product **6a**. Surprisingly, when the three-component condensation of malononitrile and ethylenediamine with the dichloro-substituted benzylidenmalononitrile **3g** was tested, tetrahydroimidazopyridine product **9g** was obtained as the major product in 64% yield instead of the expected dihydroimidazopyridine compound (Table 2, entry 1). The generality of this outcome was examined with other dichloro-substituted benzylidenemalononitriles with –Cl substituents located at different positions (**3h** and **3i**). In accordance with our initial observation, these reactants afforded the tetrahydroimidazo-

pyridine products **9h** and **9i** in 73 and 79% yields, respectively (entries 2 and 3). In addition to the NMR spectroscopic analyses of the newly synthesized tetrahydroimidazopyridines (Figs. S7-9), the structure of product **9h** was further confirmed by single-crystal X-ray analysis (Fig. 3). In this crystal structure, molecules of **9h** form a hydrogen-bonded network by intermolecular hydrogen bonds with water molecules in addition to H···Cl interactions.

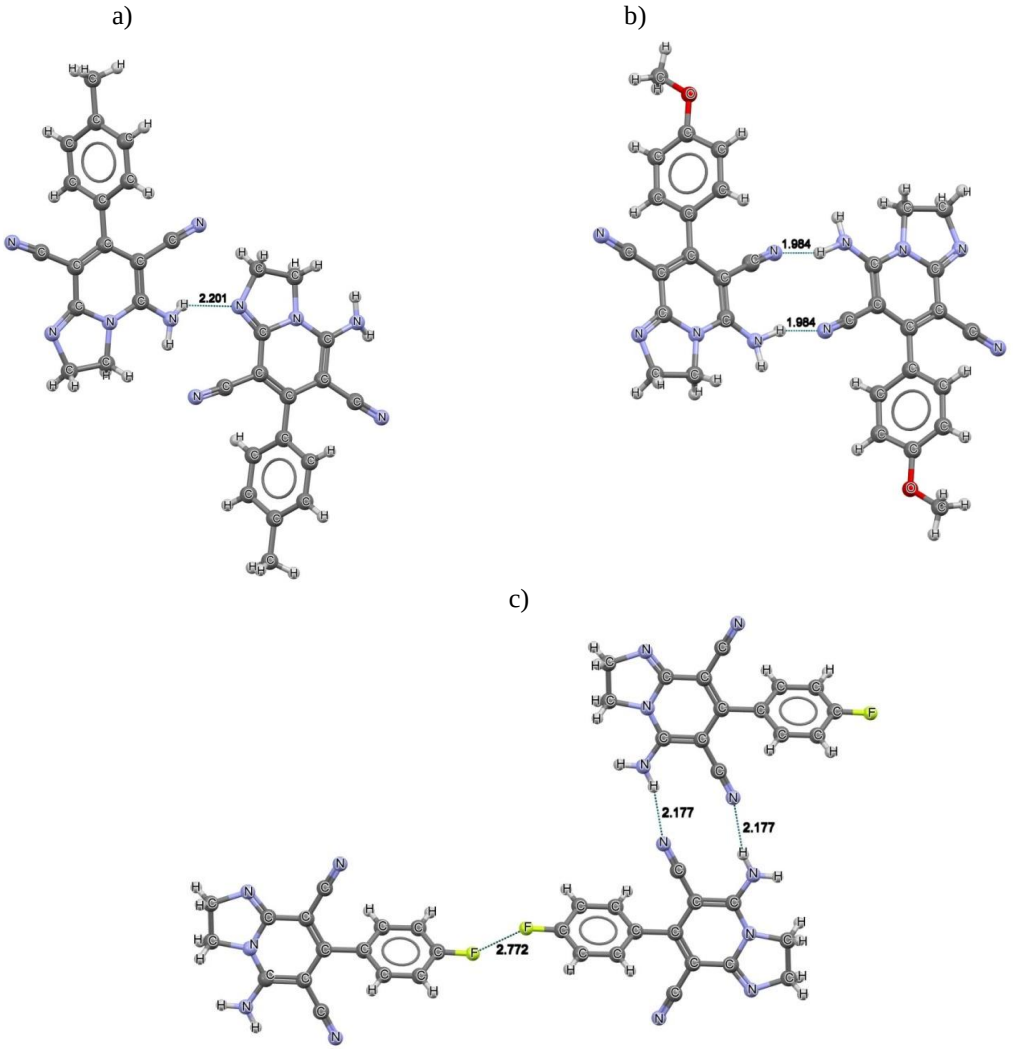
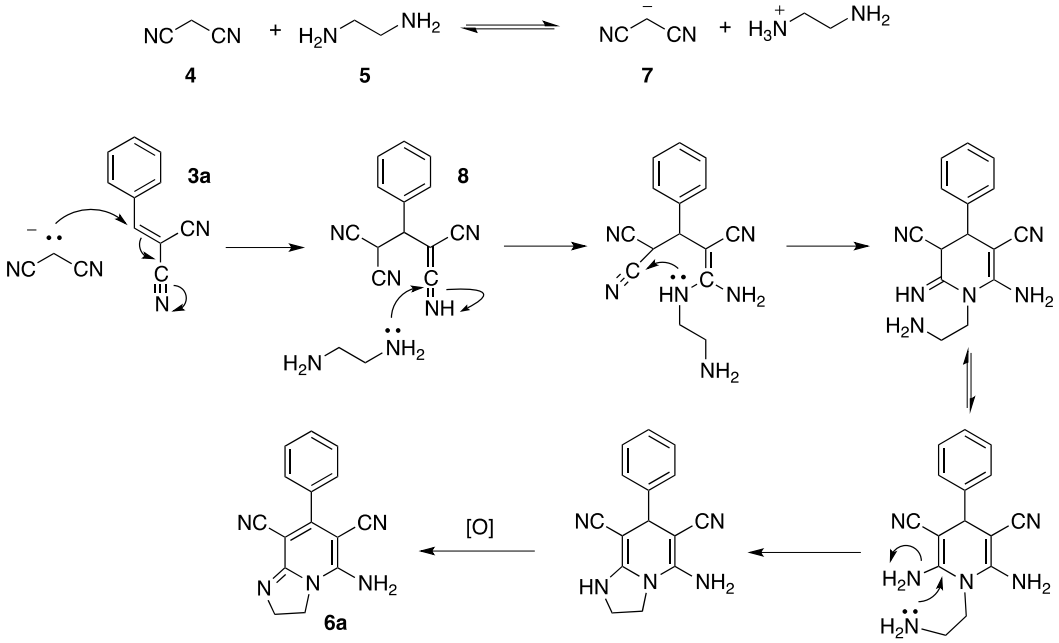
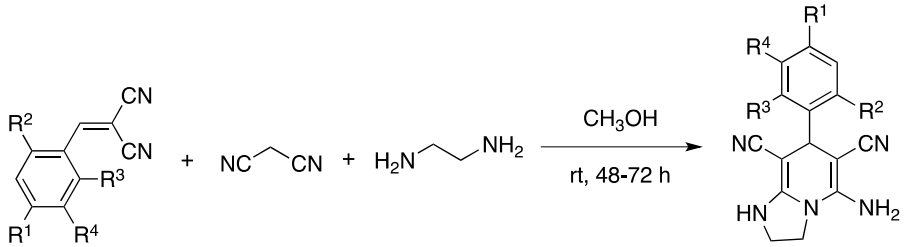



**Fig. 2.** X-ray structures of dihydroimidazopyridine products (a) **6b**; (b) **6c**; and (c) **6e**.



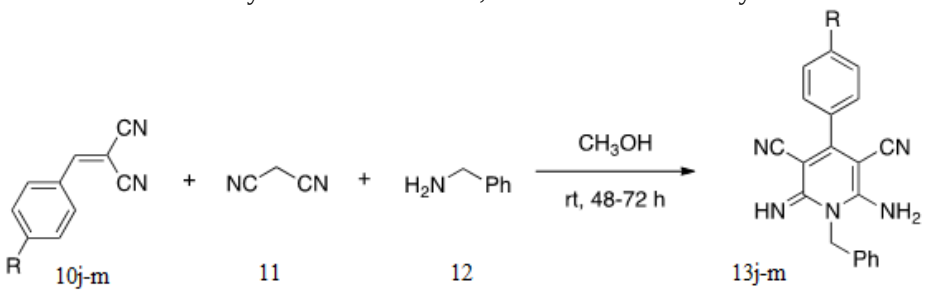
**Scheme 1.** Proposed reaction mechanism

**Table 2.** Synthesis of tetrahydroimidazopyridine derivatives (**9g-i**) *via* three-component reaction between dichloro-substituted benzylidenemalononitriles, malononitrile and ethylenediamine.



| Entry | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Product | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | Cl | Cl | H | H | 9g | 64 |
| 2 | H | Cl | Cl | H | 9h | 73 |
| 3 | H | H | Cl | Cl | 9i | 79 |

**Table 3.** Synthesis of 2-imino-1,2-dihydropyridine derivatives (**13j-m**) *via* three-component reaction between para-substituted benzylidenemalononitriles, malononitrile and benzylamine



| Entry | R | Product | Yield% |
|---|---|---|---|
| 1 | H | 13j | 63 |
| 2 | $OCH_3$ | 13k | 75 |
| 3 | Br | 13l | 61 |
| 4 | $CF_3$ | 13m | 69 |

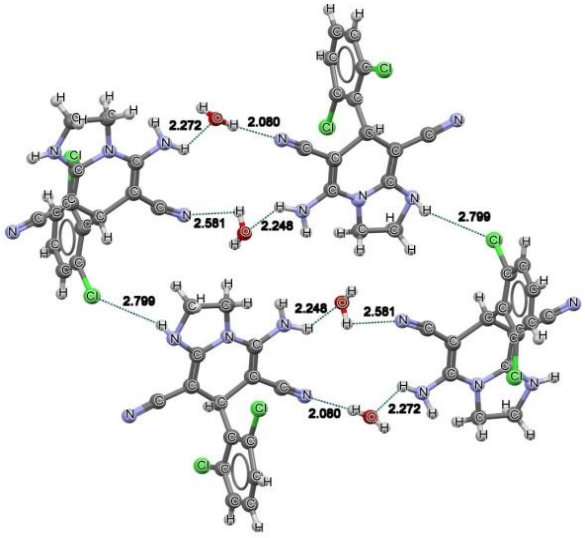



**Fig. 3.** X-ray structure of the tetrahydroimidazopyridine product **9h**.

Finally, the newly developed three-component reaction was tested using benzylamine (**12**) as the amine reactant in place of ethylenediamine (**5**). Fortunately, the reaction of benzylidenemalononitrile (**3a**) with malononitrile (**4**) and benzylamine (**12**) in methanol afforded the corresponding 2-imino-1,2-dihydropyridine product **13j** in 63% isolated yield (Table 3, entry 1, Figs. S10-13). The reaction was found to tolerate the presence of electron-donating (-$OCH_3$) and electron-withdrawing (-Br and -$CF_3$) groups on the phenyl ring, and the corresponding iminodihydropyridine products were obtained in good yields (75, 61 and 69% yields, respectively, entries 2-4).

## CONCLUSION

We have developed an effective one-pot, three-component reaction for the synthesis of multisubstituted imino- and imidazopyridine starting from benzylidenemalononitriles, malononitrile and amines. The reactions are operationally simple, work at room temperature and under catalyst-free conditions. While dihydro- and tetrahydroimidazopyridines were obtained in a selective manner as the major products when ethylenediamine was used as the amine reactant, the use of benzylamine gave rise to the formation of 2-imino-1,2-dihydropyridine products. Investigation of the substrate scopes of the developed methodology indicated that the reactions tolerate a variety of benzylidene-malononitriles having electron-donating and withdrawing substituents, and the targeted products were obtained in good to high yields (52-79%).

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## ЕДНОСТАДИЕН СИНТЕЗ НА ЗАМЕСТЕНИ ИМИНО- И ИМИДАЗОПИРИДИНИ В ОТСЪСТВИЕ НА КАТАЛИЗАТОР

Ф. Н. Нагиев, А. М. Магеррамов, И. М. Ахмедов, Х. А. Асадов, А. Н. Халилов, А. В. Гурбанов, Г. З. Мамедова, А. Р. Асгарова, Е.З. Гусейнов, И. Г. Мамедов*

*Факултет по химия, Държавен университет в Баку, Баку, AZ1148, Азербайджан*

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(Резюме)

Заместени производни на имино- и имидазопиридини са синтезирани чрез нова едностадийна трикомпонентна реакция между бензилиденмалононитрили, малононитрил и амини в отсъствие на катализатор при стайна температура. При използване на етилендиамин като аминния компонент на реакцията се получават селективно дихидро- и тетрахидроимидазопиридини с добър до висок добив. Използването на бензиламин води до образуване на 2-имино-1,2-дихидропиридинови продукти. Установено е, че реакциите толерират присъствието на електрон-отдаващи и електрон-изтеглящи заместители върху бензилиденмалононитриловите реагенти. Продуктите на тези реакции са кристални и могат да се изолират с добър добив и висока чистота чрез лесна процедура при стайна температура.