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MULTI-COMPONENT REACTION SYNTHESIS OF 1,6-DIAMINO-2-OXO-1,2,3,4-TETRAHYDROPYRIDINE-3,5-DICARBONITRILES USING ULTRASONICATION AND DMAP AS CATALYST

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Abstract. 4-(Dimethylamino)pyridine was found to be an efficient homogenous catalyst for one-pot multi-component reactions between hydrazine monohydrate, ethyl cyanoacetate, ketone, and malononitrile for the synthesis of 1,6-diamino-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile derivatives using ultrasonication at room temperature in ethanol solution within 35-50 min with yields of over 90%. This procedure offers various remarkable features such as short reaction times, clean reaction condition, excellent yields, and easy work-up methods.

Keywords: one-pot reaction, multi-component reaction, pyridine-2(1*H*)-one derivative, ultrasonication, 4-(dimethylamino)pyridine.

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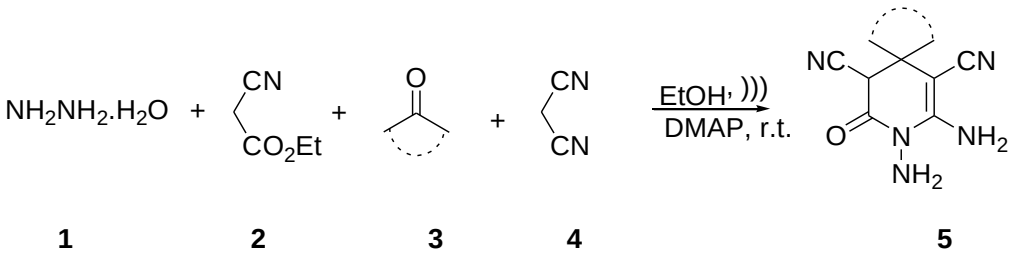
Introduction

Multi-component reactions (MCRs) are a suitable method for the obtaining of new chemical entities required by agrochemical and pharmaceutical industries [1,2]. Also, MCRs have been applied to synthesize active biological compounds, thus playing important role in medicinal research and organic chemistry [3]. There are one-pot procedures for synthesis of an individual product in the reaction between three or more available components, attained in a one-step without isolation of any intermediate [4]. The most notable advantages of MCRs are simple procedures, excellent yields, efficient and reducing reaction times [5-8]. Therefore, they are considered as one of the best tools for the facile approach to various heterocycles, drug design, drug discovery, and also the eco-friendly multi-component procedures [9,10].

Nitrogen-containing heterocyclic molecules in five- and six-membered rings such as pyridine and pyridinone rings compose a considerable part of chemical identities which are of predominant interest in medicinal chemistry due to industrial, pharmacological, biological activities such as anesthetic, antimalarial, antibacterial, antioxidant and antiparasitic properties [11-15]. The common method for the synthesis of pyridinones is ammonization of pyranone at high temperature or in sealed tube [16]. Recently, several improved methods for the synthesis of this heterocyclic system have been reported [17,18]. However, most of these methodologies have disadvantages such as inappropriate yields, long reaction times, multi-step procedures, and the use of organic solvents. By knowing these facts, we turned to more efficient methods for the preparation of this kind of compounds. Several methods have been reported for the synthesis of 1,6-diamino-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile derivatives [19,20]. Our proposed method, using an ultrasonication and a catalyst, led to higher yields than previously reported ones. 4-(Dimethylamino)pyridine (DMAP) has widely been used in the synthesis of various organic compounds as an advantageous nucleophilic basic catalyst, such as the application of DMAP that reported acylation reactions [21,22], Baylis-Hillman reactions [23], Michael additions [24] and esterification reactions in water [25].

In recent years, ultrasound irradiation has increasingly been used for performing a wide range of chemical reactions and processes, including water treatment, materials production, and chemical synthesis [26-28]. Also, ultrasonication has been widely used in organic reactions, for example, in the synthesis of interesting heterocyclic compounds [29-31].



Scheme 1. Synthesis of 1,6-diamino-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile derivatives.

As a continuation of our research on multi-component reactions [32-46], herein we present the operational synthesis of pyridine-2(1H)-one derivatives *via* one-pot multi-component reactions between hydrazine monohydrate, ethyl cyanoacetate, ketones and malononitrile (Scheme 1).

Experimental

Generalities

All *melting point* values were determined on an Electrothermal 9100 apparatus. IR spectra were recorded on a JASCO FT-IR-460 plus spectrometer in KBr with absorptions in cm^{-1}. *Thin-layer chromatography* (TLC) was carried out on silica-gel plates Polygram SILG/UV 254. ^1H and ^{13}C *NMR spectra* were recorded using a Bruker Advance DPX 300 (300 and 75 MHz), spectra are provided as Supplementary material file. The spectra were measured in DMSO-d_6 relative to tetramethylsilane. Mass spectra were recorded on an Agilent Technology (HP) 5973 mass spectrometer operating at an ionization potential of 70 eV. *Ultrasonication* was performed in a KQ-250E medical ultrasound cleaner with a frequency of 40 kHz, and output power of 250 W.

All reagents were purchased from Merck or Aldrich and were used without further purification.

General procedure for the synthesis of pyridine-2(1H)-one derivatives

A solution of hydrazine monohydrate **1** (1.0 mmol), ethyl cyanoacetate **2** (1.0 mmol), ketone **3** (1.0 mmol), malononitrile **4** (1.0 mmol) and 4-(dimethylamino)pyridine (20 mol%, 0.2 mmol) in ethanol (10 mL) was charged. The mixture was sonicated in the water bath at 25–30°C. After the completion of the reaction (followed by TLC), the reaction mixture was filtered and the precipitate was recrystallized from ethanol to obtain the pure products **5** derivatives.

1,6-diamino-4,4-dimethyl-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile ***5a***, white solid, 96% yield, m.p. 207-209°C. IR (KBr, cm^{-1}): *v* 3415, 3346, 3307, 2175, 1700, 1638, 1570, 1428, 1329, 1218, 918, 858; ^1H NMR: δ 1.12 (3H, s, CH_3), 1.28 (3H, s, CH_3), 4.59 (1H, s, CH), 5.22 (2H, s, NH_2), 6.69 (2H, s, NH_2).

1,6-diamino-4-cyclopropyl-4-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile ***5b***, grey solid, 95% yield, m.p. 183-186°C. IR (KBr, cm^{-1}): *v* 3624, 3399, 2880, 2177, 1708, 1632, 1578, 1427, 1338, 1291, 1227, 1166, 940, 836.

2,3-diamino-4-oxo-3-azaspiro[5.5]undec-1-ene-1,5-dicarbonitrile ***5c***, white solid, 97% yield, m.p. 172-174°C. IR (KBr, cm^{-1}): *v* 3465, 3356, 2936, 2184, 1699, 1625, 1565, 1424, 1328, 1285, 914, 864, 681; ^1H NMR (300 MHz, DMSO-d_6): δ 1.33-1.71 (10H, m, 5 CH_2), 4.53 (1H, s, CH), 5.27 (2H, s, NH_2), 6.71 (2H, s, NH_2).

2,3-diamino-9-methyl-4-oxo-3-azaspiro [5.5]undec-1-ene-1,5-dicarbonitrile ***5d***, white solid, 95% yield, m.p. 175-177°C. IR (KBr, cm^{-1}): *v* 3465, 3356, 2184, 1699, 1625, 1565, 1424, 1328, 1148,902, 836, 687; ^1H NMR (300 MHz, DMSO-d_6): δ 0.89 (3H, d, *J*= 6.3 Hz, CH_3), 1.14-1.22 (1H, m, CH), 1.26-1.41 (2H, m, CH_2), 1.45-1.61 (4H, m, 2 CH_2), 1.64-1.77 (2H, m, CH_2), 4.51 (1H, s, CH), 5.23 (2H, s, NH_2), 6.68 (2H, s, NH_2).

2,3-diamino-4-oxo-3-azaspiro[5.6]dodec-1-ene-1,5-dicarbonitrile ***5e***, gray solid, 95% yield, m.p. 203-207°C. IR (KBr, cm^{-1}): *v* 3356, 3189, 2179, 1708, 1630, 1562, 1429, 1256, 1141, 988, 852,701; ^1H NMR: δ 1.43-1.88 (12H, m, 6 CH_2), 4.47 (1H, s, CH), 5.24 (2H, s, NH_2), 6.67 (2H, s, NH_2).

7,8-diamino-9-oxo-8-azaspiro[4.5]dec-6-ene-6,10-dicarbonitrile ***5f***, white solid, 90% yield, m.p. 182-185°C; IR (KBr cm^{-1}): *v* 3387, 3345-3288, 2961, 2899, 2181, 1704, 1631, 1575, 1428, 1345, 1220, 952.

2,3-diamino-8,8,10-trimethyl-4-oxo-3-azaspiro [5.5]undec-1-ene-1,5-dicarbonitrile ***5g***, white solid, 88% yield; m.p.: 255-257°C. IR (KBr, cm^{-1}): *v* 3471, 3364, 2299, 2955, 2911, 2868, 2175, 1705, 1615, 1557, 1461, 1430, 1299, 1148, 902, 836, 687; ^1H NMR: δ 0.87 (3H, s, CH_3), 0.91 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.05 - 2.24 (7H, m, 1

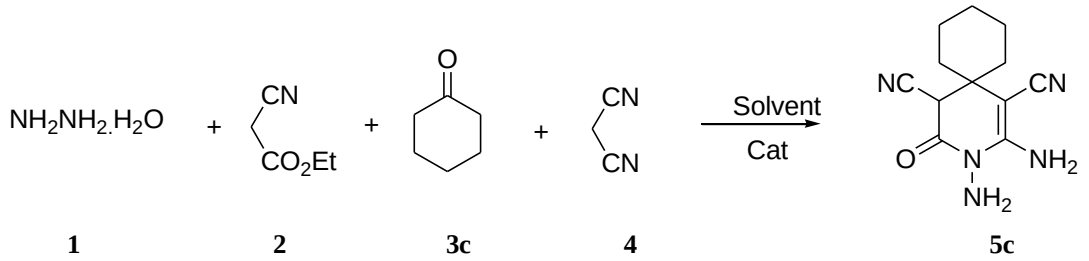
CH, 2 CH_2), 4.63 (1H, s, CH), 5.22 (2H, s, NH_2), 6.63 (2H, s, NH_2); ^{13}C NMR: δ 22.9, 24.6, 26.3, 31.3, 34.4, 35.9, 42.5, 43.4, 47.4, 50.8, 61.9, 115.9, 121.3, 154.9, 163.7; MS (EI, 70 eV) m/z (%): 287.5 (M^+, 84.77).

1,6-diamino-4-benzyl-4-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile ***5h***, gray solid, 90% yield, m.p. 216-218°C. IR (KBr, cm^{-1}): *v* 3420, 3311, 2974, 2936, 2875, 2176, 1715, 1634, 1620, 1564, 1429, 1338, 1237, 1166, 934, 839, 705, 686; ^{1}H NMR: δ 1.26 (3H, s, CH_3), 2.59 (1H, d, *J*= 12.9 Hz, CH), 2.75 (1H, d, *J*= 12.6 Hz, CH), 4.77 (1H, s, CH), 4.90 (2H, s, NH_2), 6.66 (2H, s, NH_2), 7.10-7.30 (5H, m, $CH_{aromatic}$); ^{13}C NMR: δ 25.1, 37.1, 42.7, 47.8, 59.8, 115.8, 119.82, 127.3, 128.2, 130.8, 136.3, 154.2, 162.7; MS (EI, 70 eV) m/z (%): 282.5 (M^+, 0.6).

2,3-diamino-4-oxo-3-azaspiro[5,11]heptadec-1-ene-1,5-dicarbonitrile ***5k***, white solid, 94% yield, m.p. 182-185°C. IR (KBr cm^{-1}): *v* 3432, 3336, 3280, 2933, 2863, 2250, 2178, 1707, 1622, 1579, 1470, 1425, 1329, 1244, 799; ^{1}H NMR: δ 1.36-1.75 (22H, m, 11 CH_2), 4.18 (1H, s, CH), 5.22 (2H, s, NH_2), 6.72 (2H, s, NH_2); ^{13}C NMR: δ 18.3, 19.9, 21.9, 22.1, 22.4, 22.4, 22.5, 26.0, 26.3, 26.4, 30.9, 37.6, 44.3, 60.0, 116.0, 120.7, 153.7, 162.0; MS (EI, 70 eV) m/z (%): 330.2 (M^+, 18).

Results and discussion

At first, the four-component reaction was carried out between hydrazine monohydrate **1**, ethyl cyanoacetate **2**, cyclohexanone **3c** and malononitrile **4** as an instant reaction in variant solvents with the appropriate catalysts to optimize the reaction conditions for the synthesis of pyridine-2(1H)-one derivatives (Scheme 2), and the results are summarized in Tables 1 and 2. Initially, the effect of various amount of piperidine, 1,4-diazabicyclo[2,2,2]-octane (DABCO) and DMAP as the catalyst, different temperature values, and various solvents as EtOH, H_2O, MeOH, H_2O/EtOH, and $(Me)_2CHOH$ was examined, the results are summarized in Table 1.



1 **2** **3c** **4** **5c**

Scheme 2. Synthesis of pyridine-2(1*H*)-one derivative.

Table 1

Optimization of reaction conditions [a].

Entry	*Catalyst, mol%*	*Solvent*	*Temperature, °C*	*Ultrasonication[b]*	*Time, min*	*Isolated yield, %*
1	-	EtOH	r.t	-	600	trace
2	Piperidine (10%)	EtOH	r.t	-	180	65
3	Piperidine (10%)	EtOH	r.t	✓	45	90
4	DABCO (10%)	EtOH	r.t	-	180	42
5	DABCO (20%)	EtOH	r.t	-	120	50
6	DABCO (20%)	EtOH	r.t	✓	45	84
7	DMAP (10%)	EtOH	r.t	-	180	50
8	DMAP (20%)	EtOH	r.t	-	120	83
9	**DMAP (20%)**	**EtOH**	**r.t**	✓	**45**	**97**
10	DMAP (25%)	EtOH	r.t	-	120	82
11	DMAP (25%)	EtOH	r.t	✓	45	97
12	DMAP (20%)	EtOH	40	-	120	76
13	DMAP (20%)	EtOH	60	-	120	75
14	DMAP (20%)	MeOH	r.t	-	180	76
15	DMAP (20%)	H_2O	r.t	-	240	55
16	DMAP (20%)	H_2O	r.t	✓	45	72
17	DMAP (20%)	H_2O/EtOH	r.t	-	240	65
18	DMAP (20%)	H_2O/EtOH	r.t	✓	45	77
19	DMAP (20%)	$(CH_3)_2COH$	r.t	-	360	51

[a]Reaction conditions: hydrazine monohydrate (1.0 mmol), ethyl cyanoacetate (1.0 mmol), malononitrile 1.0 mmol), cyclohexanone (1.0 mmol) in solvent (10 mL).
[b]Ultrasonic wave was set at 150 W and irradiation frequency at 40 kHz.

The best result was achieved by carrying out the reaction with 20 mol% of DMAP as a catalyst in EtOH as solvent at room temperature (Table 1, entry 8). Next, the effect of ultrasonication was investigated with various catalysts and solvents, the best result was obtained with 20 mol% DMAP as catalysis and EtOH as solvent under ultrasonication at room temperature (Table 1). Also, according to Table 2, the most suitable power for the ultrasonication device for the reaction is 150 W (Table 2, entry 4). As shown in Table 1, it was found that no product was discovered when the reaction was performed without any catalyst (Table 1, entry 1). To study the feasibility of this process, a variety of ketones **3** (1.0 mmol) including aliphatic chain and cyclic ketones were reacted with hydrazine monohydrate **1** (1.0 mmol), ethyl cyanoacetate **2** (1.0 mmol), and malononitrile **4** (1.0 mmol) under the optimized reaction conditions and lead to final products in acceptable yields, as presented in Table 3. Using the optimal conditions, synthesis of pyridine-2(*1H*)-one derivatives was attained.

6-Diamino-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile was produced according to the instruction [19], as presented in Scheme 3. First, a concentration of hydrazine monohydrate **1** with ethyl cyanoacetate **2** gave the intermediate **A**. The Knoevenagel condensation of ketone **3** with malonitrile **4** formed the intermediate **B**. Michael addition of intermediate **A** to **B** tolerates give intermediate **C**, which tolerates intramolecular cyclization to give intermediate **D**. Eventually, the intermediate **D** is tautomerized and organized the favourable product **5** (Scheme 3).

Table 2

The optimization of reaction condition under ultrasonication[a].

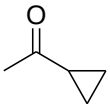
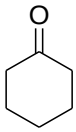
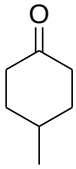
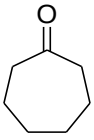
Entry	*Power, W*	*Time, min*	*Yield, %[b]*
1	100	30	52
2	100	60	81
3	150	30	76
4	**150**	**45**	**97**
5	200	45	97

[a]Reaction conditions: hydrazine monohydrate (1.0 mmol), ethyl cyanoacetate (1.0 mmol), malononitrile (1.0 mmol), cyclohexanone (1.0 mmol), DMAP (0.2 mmol) in solvent (10 mL) under ultrasonic waves and irradiation frequency at 40 kHz.

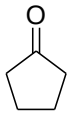
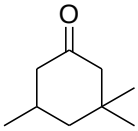
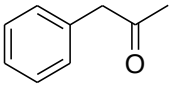
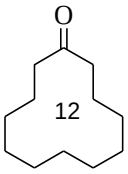
[b]Isolated yield.

Table 3

Synthesis of pyridine-2(*1H*)-one derivatives 5 under optimized conditions[a].

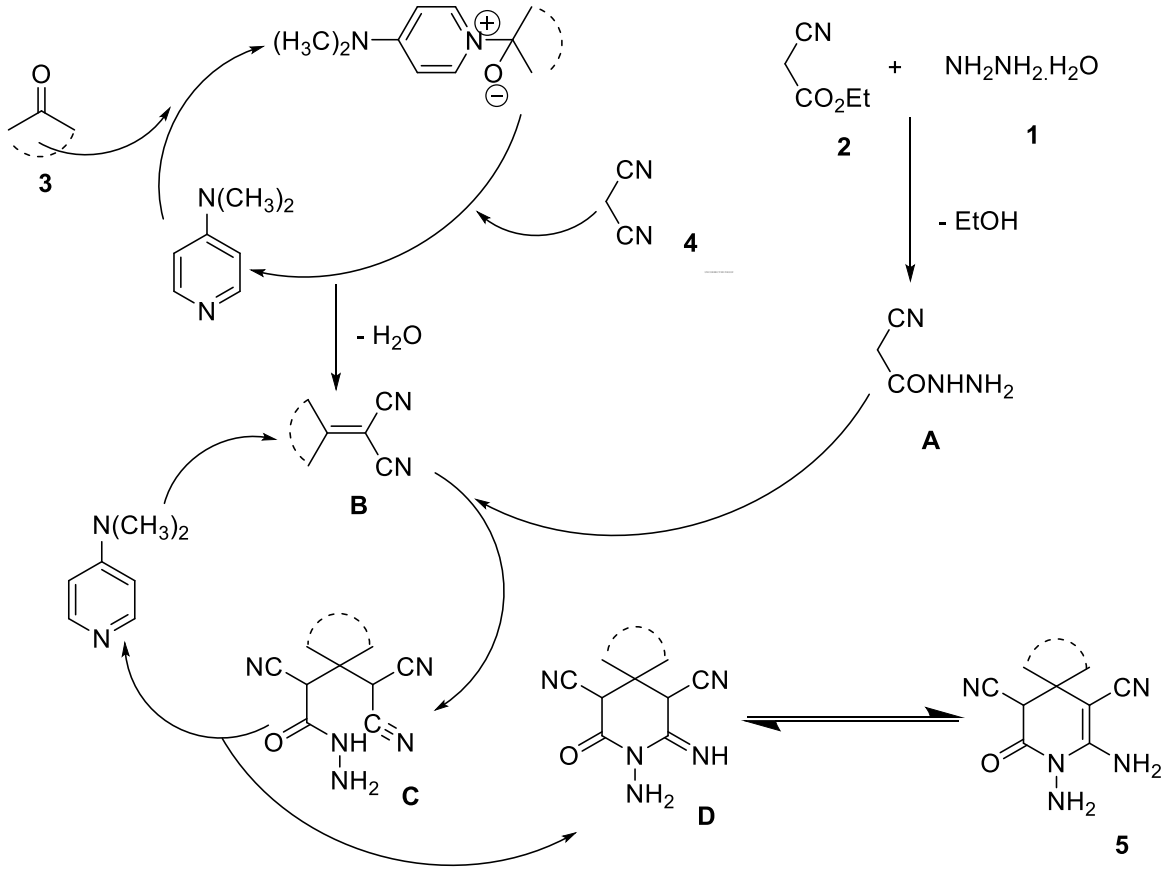
Entry	*Substrate*	*Product*	*Time, min*	*Yield, %[b]*	*M.p., °C*	
					This work	*Literature*
1		**5a**	35	96	207-209	198-200 [19]
2		**5b**	40	95	183-186	181-182 [19]
3		**5c**	45	97	172-174	170-172 [20]
4		**5d**	40	95	175-177	175-176 [19]
5		**5e**	45	95	205-207	210-212 [20]

Continuation of Table 3

Entry	*Substrate*	*Product*	*Time, min*	*Yield, %*[b]	*M.p., °C*	
					This work	*Literature*
6		**5f**	45	90	182-185	176-180 [20]
7		**5g**	50	88	255-257	-
8		**5h**	50	90	216-218	-
9		**5k**	50	94	182-185	-

[a]*Reaction conditions: hydrazine monohydrate (1.0 mmol), ethyl cyanoacetate (1.0 mmol), malononitrile (1.0 mmol), ketone derivatives (1.0 mmol), DMAP (0.2 mmol) in EtOH (10 mL) under ultrasound irradiation at room temperature.*

[b]*Isolated yield.*



Scheme 3. The suggested mechanism for synthesis of 6-diamino-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile.

Conclusions

In this study, an efficient method is presented for the one-pot multi-component synthesis of substituted pyridine-2(1*H*)-ones by applying 4-(dimethylamino)pyridine as an efficient catalyst under ultrasonication at room temperature *via* condensation of hydrazine monohydrate, ethyl cyanoacetate, malononitrile and ketone in ethanol solution within 35-50 min with yields of over 90%. In contrast to other, common procedures, the strong points of the developed method are the simple experimental procedure, shorter reaction times, acceptable yields, and an easy work-up procedure.

Supplementary information

Supplementary data are available free of charge at http://cjm.asm.md as PDF file.

Acknowledgments

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