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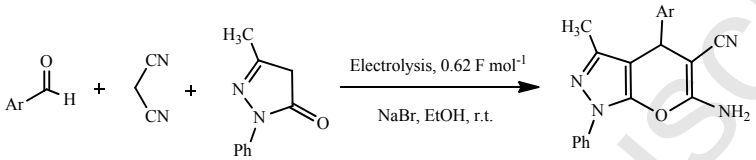
Graphical Abstract

Electro-catalyzed multicomponent transformation of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one to 1,4-dihydropyrano[2,3-c]pyrazole derivatives in green medium

Zahra Vafajoo*[,a], Nourallah Hazeri*[,a], Malek Taher Maghsoodlou [a], Hojat Veisi [b]



An efficient and convenient synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivatives is described, using the electrogenerated anion of ethanol as the base in the presence of sodium bromide as an supporting electrolyte in a one-pot, three component condensation of malononitrile, aromatic aldehydes and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one.

Original article

Electro-catalyzed multicomponent transformation of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one to 1,4-dihydropyrano[2,3-c]pyrazole derivatives in green medium

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ABSTRACT

An efficient and convenient synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivatives is described, using the electrogenerated anion of ethanol as the base in the presence of sodium bromide as an supporting electrolyte in a one-pot, three component condensation of malononitrile, aromatic aldehydes and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one. The reaction is carried out in an undivided cell containing an iron electrode as the cathode and a graphite electrode as the anode, at a constant current at room temperature.

1. Introduction

Multi-component reactions (MCRs) constitute an especially attractive synthetic strategy for rapid and efficient library generation due to the fact that the diversity can be achieved simply by varying the reacting components. To promote the mentioned reactions, various catalytic systems have been used [1-3]. Recently, the development and application of electrodes as catalyst in organic chemistry, have received considerable attention. Also, electrochemical synthesis as unique technique is valuable for large-scale processes because electricity is a cheap and environmentally responsible chemical reagent and its interest behavior to produce initial base as catalyst can be used at ambient temperature and pressure [4]. According to this information, many chemical transformations such as MCRs to prepare various suitable compounds can be performed.

1,4-Dihydropyrano[2,3-c]pyrazole derivatives are a class of important heterocycles with a wide range of biological and pharmacological properties such as antimicrobial [5], insecticidal and molluscicidal activities [6], anticancer, anticoagulant, diuretic, spasmolytic and antianaphylactic agents [7]. Many methods with different conditions have been reported. Some of these compounds have been already prepared in the presence of CuO – CeO_2 [7], triethylammonium acetate (TEAA) [6], imidazole [8], L-proline or KF-alumina [9], Silica bonded *n*-propyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride (SB-DABCO) [10] and $H_{14}[NaP_5W_{30}O_{110}]$ [11].

However, some of these protocols require long reaction times, multi-step reactions and complex synthetic pathways and afford products with only modest yields. Therefore, the introduction of milder, faster and more ecofriendly methods, accompanied with higher yields are needed.

In continuation of previous work [12] to develop efficient and environmentally benign procedures, we report the successful synthesis of 4-dihydropyrano[2,3-c]pyrazole derivatives *via* direct addition of various aromatic aldehydes, malononitrile and 3-methyl-1-phenyl-

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1*H*-pyrazol-5(4*H*)-one in an undivided cell at room temperature under a constant current density and without base or any additive catalyst in green media.

2. Experimental

The structural evaluation studies of compounds were performed with various experimental techniques such as IR, elemental analysis, ^{1}H NMR and ^{13}C NMR spectroscopies. Complete relevant spectra (^{1}H NMR, ^{13}C NMR and IR) for the products are available in the supporting information.

2.1 Typical experimental procedure for electrocatalytic synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivatives

A mixture of aryl aldehyde (2 mmol), malononitrile (3 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (2 mmol), and NaBr (0.05 g, 0.5 mmol) in EtOH (20 mL) was electrolyzed in an undivided cell equipped with a magnetic stirrer, a graphite anode, and an iron cathode at 25 °C under a constant current density of 10 mA/cm^2 [electrodes square 5 cm^2] until the catalytic quantity of 0.62 F/mol of electricity was passed. After the electrolysis was finished, the precipitated products were separated by filtration which was then twice rinsed with an ice-cold ethanol/water solution (9:1, 5 mL), and dried under reduced pressure.

2.2 Analytical data for selected compounds

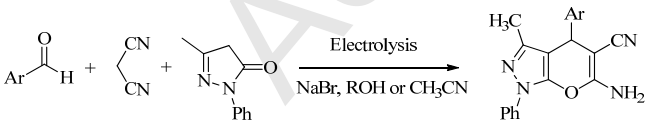
6-Amino-4-(3-ethoxy-4-hydroxyphenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4o**): mp: 189-171 ^{o}C; IR (KBr, cm^{-1}): ν_{max} 2195 (C≡N);3329-3420 (NH_2), ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.29-1.33 (t, 3H, *J*= 7.2 HzCH_3), 1.83 (s, 3H, CH_3), 3.96-4 (q, 2H, *J*= 7.2 Hz CH_2), 4.58 (s, 1H, CH), 6.60- 7.82 (m, NH_2 and Ar), 8.85 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13 (CH_3), 15 (CH_3), 36.7 (CH), 59 (CN), 64 (CH_2), 99.4, 114, 116, 120.3, 120.6, 120.65, 126.5, 130, 135, 138. 144, 145.9, 146, 146.3, 146.8, 146.9, 159.6, 159.7; Anal. Calcd. for $C_{22}H_{20}N_4O_3$: C, 68.03; H, 5.19; N, 14.42%. Found: C, 68.12; H, 5.21; N, 14.38.

4,4'-(1,4-Phenylene)bis(6-amino-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile) (**4p**): mp: 236-238 ^{o}C; IR (KBr, cm^{-1}): ν_{max} 2191 (C≡N);3329-3366 (NH_2), ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.79 (s, 3H, CH_3), 4.80 (s, 1H, CH), 7.3 -8.6 (m, NH_2 and Ar); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13 (CH_3), 34.7 (CH), 57.7, 98.2, 120.4, 120.6, 124.4, 126.7, 129.8, 136, 137.9, 139.4, 144.5, 145.5, 149, 149.5,160, 160.1, Anal. Calcd. for $C_{34}H_{26}N_8O_2$: C, 70.58; H, 4.53; N, 19.37% Found: C, 70.33; H, 4.53; N, 19.59.

6-Amino-4-(biphenyl-4-yl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4q**): mp: 193-194^{o}C; IR (KBr, cm^{-1}): ν_{max} 2196 (C≡N);3328-3471(NH_2), ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.77 (s, 3H, CH_3), 4.88 (s, 1H, CH), 7.31-7.95 (m, NH_2 and Ar); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.4 (CH_3), 37 (CH), 58, 99, 120.4, 120.6, 126.6, 127, 127.3, 127.8, 129, 129.8, 138, 139, 140, 143,144, 145.8, 159.95, 160 , Anal. Calcd. for $C_{26}H_{20}N_4O$: C, 77.21; H, 4.98; N, 13.85%. Found: C, 77.14; H, 4.99; N, 14.01.

3. Results and discussion

Our investigations on the electrocatalytic multicomponent chain transformation of aryl aldehydes, 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one and malononitrile into 6-amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles under neutral and mild conditions by electrolysis in an undivided cell, began with the optimization of the reaction conditions. The synthetic pathway is shown in Scheme 1.



1-17 **2** **3** R= Me, Et, *n*-Pr **4a-q**

Scheme 1. Synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivatives catalyzed by an electrogenerated base.

Table 1 illustrates the obtained data for the synthesis of 6-amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile **4a** under various experimental conditions. The reaction is performed in alcohols or acetonitrile as solvent in the presence of an electrolyte at room temperature. The reaction progress was monitored with TLC.

Table 1
Optimization of reaction conditions for synthesis of 6-amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile at room temperature.[a]

Entry	Electrolyte	I (mA)	Current density (mA/ cm^2)	Time (min)	Catalyst	Solvent	Electricity passed (F mol^{-1})	Yield (%)[b]
1	NaBr	5	1	200	-	EtOH	0.62	70
2	NaBr	10	2	120	-	EtOH	0.74	75
3	NaBr	20	4	60	-	EtOH	0.74	80
4	NaBr	50	10	20	-	EtOH	0.62	90
5	NaBr	75	15	20	-	EtOH	0.93	75
6	NaBr	50	10	20	-	CH_3CN	0.48	94
7	NaBr	50	10	20	-	MeOH	0.62	80
8	NaBr	50	10	20	-	n-PrOH	0.62	70
9	-	-	-	20	Na	EtOH	-	<5
10	KBr	50	10	20	-	EtOH	0.62	40
11	KI	50	10	20	-	EtOH	0.62	45
12	Bu_4NBr	50	10	20	-	CH_3CN	0.48	95
13	Bu_4NBr	50	10	20	-	EtOH	0.62	95

[a] General procedure: Aldehyde (2 mmol), malononitrile (3 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (2 mmol), and electrolyte (0.5 mmol), solvent (20 mL), iron cathode (5 cm^2), and graphite anode (5 cm^2)
[b] Isolated Yield.

Various amounts of current were applied under the mentioned conditions. Excellent conversions of the starting materials were obtained under 10 mA/cm^2 current densities after 0.48 F/mol of electricity had been passed and I=50 mA, electrodes surface (5 cm^2) was found to be optimal for the electrochemically induced chain process and allowed for the highest yield of **4a** in solvent of CH_3CN and electrolyte of tetrabutyl ammonium bromide.

As seen in Table 1, acetonitrile as solvent can be useful and the related yield is excellent especially when combined with tetrabutylammonium bromide (Bu_4NBr) but this solvent is more expensive rather than an alcohol such as ethanol. Also, Acetonitrile has a modest toxicity in small doses. It can be metabolized to produce hydrogen cyanide, which is the source of the observed toxic effects [13, 14]. Meanwhile, Bu_4NBr commonly used as a phase transfer catalyst. We applied this compound as electrolyte in acetonitrile and ethanol. The results were shown Bu_4NBr can be effective and the product was formed in excellent yield even when EtOH was used as solvent. However, as mentioned in acetonitrile, Bu_4NBr is more expensive and very hazardous.

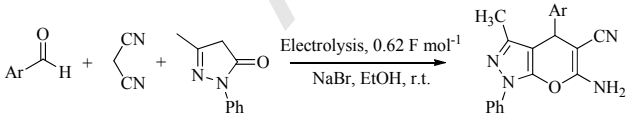
Under these conditions, conversions of the starting materials were allowed for the excellent yield of **4a** in ethanol as a solvent and sodium bromide was used as an electrolyte.

An increase in the current density up to 15 mA/cm^2 (I=75 mA) resulted in a slight decrease in the reaction yield, and may be a result of the activation of the undesired direct electrochemical processes that lead to oligomerization of the starting material.

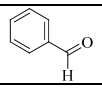
In comparison of electrocatalytic method with chemical method, we used sodium metal as catalyst (10 mol%) for preparation of **4a**, but desired product was obtained in low yields. So it seem this method hasn't preferable for certainly economical advantages. Regarding to Table 1, electrocatalytic method in comparison with other chemical methods has some advantages that it is green and environmentally friendship and catalyst is produced and consumed in reaction media.

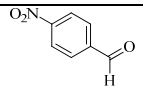
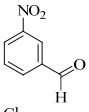
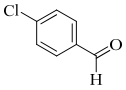
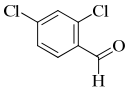
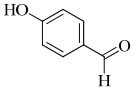
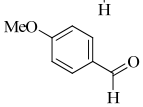
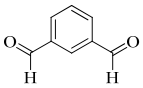
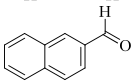
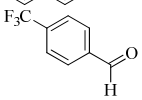
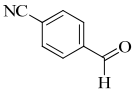
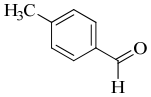
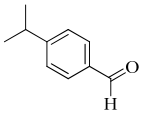
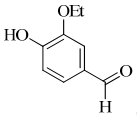
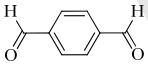
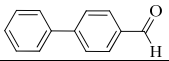
Using the optimized conditions, we also probed the scope and generality of the reaction of several aryl aldehydes with malononitrile and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one for synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivatives (Table 2, **4a-q**).

Table 2
Electrocatalytic multicomponent synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivative under optimized conditions.[a]



1-17 **4a-q**

Entry	Aldehyde	Time (min)	Product	Yield (%)[b]	M.p (°C) Ref
1		20	**4a**	90	168-170 169-171 [15]

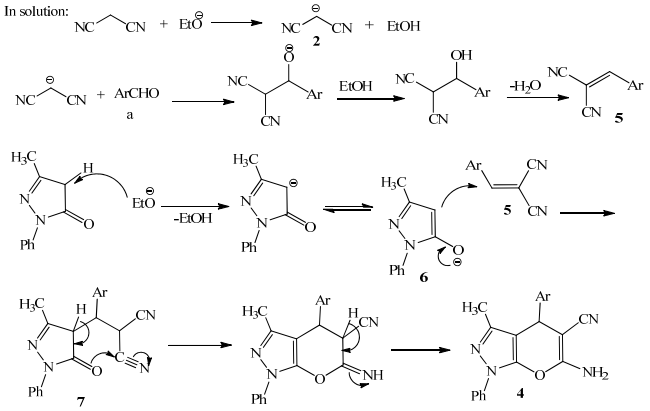
2		20	**4b**	95	196-198 195-197 [15]
3		20	**4c**	95	190-192 190-192 [7]
4		20	**4d**	90	174-176 173-175 [7]
5		20	**4e**	90	145-146 143-145[7]
6		20	**4f**	90	180-182 181-183 [7]
7		20	**4g**	85	211-213 210-212 [15]
8		20	**4h**	85	172-174 171-173 [7]
9		20	**4i**	80	198-200 198-200 [7]
10		20	**4j**	85	158-160 157-159 [7]
11		20	**4k**	95	182-184 182-184 [10]
12		20	**4l**	95	215-217 217-219 [10]
13		20	**4m**	85	172-173 173-175 [7]
14		20	**4n**	85	156-158 158–160 [10]
15		20	**4o**	80	189-171 -
16		20	**4p**	80	236-238 -
17		20	**4q**	75	193-194 -

[a] General procedure: Aldehyde (2 mmol), malononitrile (3 mmol), 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (2 mmol), and NaBr (0.05 g, 0.5 mmol), EtOH (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2), current density 10 mA/cm^2, at room temperature.
[b] Yield

As shown in Table 2, products were obtained in excellent yields. It was found that aromatic aldehydes both with electron withdrawing and donating groups in reaction with other starting material have excellent isolated yield. Notably, in examining their synthetic performance, it has been shown that this method is capable of promoting organic synthesis of 1,4-dihydropyrano[2,3-

c]pyrazole derivatives in an environmentally friendly condition. A catalytic amount of an electrogenerated base can efficiently induce the catalytic chain transformation of organic compounds. All these qualities agree well with the rules of green chemistry [4].

The proposed mechanism for the preparation of related products is depicted in Scheme 2. The initial formation of bromine on the anode is a well-known process and the corresponding halogen color was observed at the anode when the electrolysis was conducted without stirring the reaction mixture[10]. Deprotonation of an alcohol at the cathode leads to formation of alkoxide anion [16-19]. Its subsequent reaction in solution with malononitrile gives rise to malononitrile anion.



Scheme 2. The proposed mechanism for the formation of 1,4-dihydropyrano[2,3-c]pyrazole derivatives.

Then Knoevenagel condensation of aldehyde with malononitrile anion takes place in the solution with the elimination of water and formation of the corresponding α-cyanocinnamonitrile derivatives **5**.

We perform a control experiment to detect of intermediate **5**. The reaction was take placed in presence of benzaldehyde and malononitrile at mentioned conditions (room temperature, I = 50 mA, EtOH and NaBr) and the intermediate **5** was formed at 5 min in excellent yield (96%). Michael addition between **5** and **6** furnished **7**, which upon intramolecular cyclization and isomerization gave rise to product **4**.

Anode: $2Br^{\ominus} - 2e \longrightarrow Br_2$

Catode: $2\,EtOH + 2e \longrightarrow 2\,EtO^{\ominus} + H_2$

4. Conclusion

In conclusion, we have developed an efficient green procedure for the one-pot synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivatives in excellent yields under neutral and mild conditions in the presence of sodium bromide as an electrolyte. The very short reaction time, high yields, simple workup the non-chromatographic purification of products will make the present method an important addition to the available methodologies for synthesis of the products.

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