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Graphical Abstract

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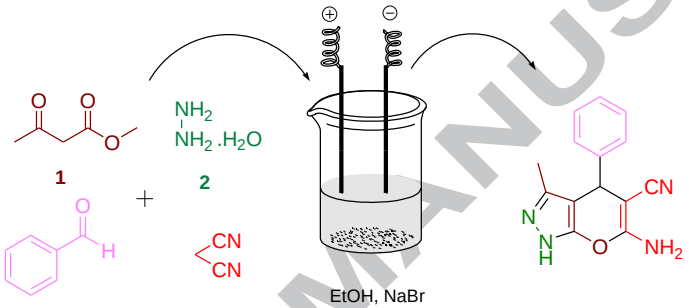

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ABSTRACT

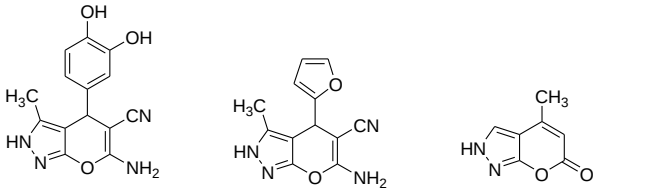
An efficient one pot, multicomponent-tandem synthesis of highly functionalized 1,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile is reported by electrochemically induced condensation of ethyl acetoacetate, hydrazine hydrate, malononitrile and various aromatic aldehydes. The reaction is carried out in an undivided cell, at a constant current in the presence of NaBr as a supporting electrolyte and ethanol as solvent.

In recent decades, the multicomponent reactions (MCRs) have been used extensively to prepare biologically active compounds and have become an important field of research in organic, combinatorial, and medicinal chemistry.[1] MCR strategy offers significant advantages over conventional linear-type synthesis due to its soft, convergent and atom efficient nature.[2] In recent years, the synthesis of combinatorial small-molecule heterocyclic libraries has emerged as a valuable tool in the searching of novel drugs or biologically active molecules. Thus, the success of combinatorial chemistry in drug discovery is considerably dependent on further advances in MCR methodology and, according to current synthetic demands, ecologically pure multicomponent procedures are particularly welcome.

1,4-dihydropyrano[2,3-c]-pyrazole moiety (Fig. 1) often appears as an important structural motif in biologically active compounds and show broad range of biological and pharmacological properties such as anticancer,[3] anti-HIV,[4] antimicrobial,[5] antiviral,[6] anti-inflammatory,[7] insecticidal, molluscicidal,[8] anticoagulant, diuretic, antianaphylactic,[9] antimalarial,[10] and anti-proliferative[11] agents. The biological properties of 1,4-dihydropyrano[2,3-c]-pyrazole have attracted many synthetic chemists to explore different methods suitable for their synthesis, though there are several methods reported in the literature for the formation of four component reaction such as by using nano TiO_2,[12] nano-CuI,[13] Fe_3O_4 nanoparticles,[14] DABCO,[15] DBU,[16] isonicotinic acid,[17] disulfonic acid imidazolium chloroaluminate,[18] piperidine and pyridine,[19] pyrrolidine,[20] iodine ,[21] cerium ammonium nitrate (CAN).[22] However, many 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.

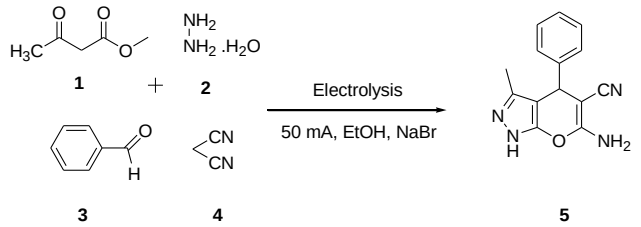
The electrochemical procedure is advantageous for a multicomponent reaction in utilizing simple equipment, an undivided cell that would be of value for a large-scale process due to its catalytic nature, and the use of cheap and environmentally friendly chemical reagent electricity. In electrochemistry electro-generated base (EGB) promotes reactions in good yields without use of acid, base or catalyst. Electrosynthesis have many advantages which include high atom economy, the use of mild reaction conditions, decreased energy requirements and reduced reaction times. These advantages prompted us to developed MCR strategy for synthesis of 1,4-dihydropyrano[2,3-c]-pyrazole.

In continuation of our ongoing efforts towards synthesis of medicinally important compound,[23] we developed a convenient and environmentally friendly method for multicomponent synthesis of 1,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile derivatives by the electrochemical transformation using acetoacetate, hydrazine hydrate, malononitrile and various aromatic aldehydes as starting material in an undivided cell (Scheme 1) at 40°C under a constant current density.



Chk1 kinase inhibitors | Molluscicidal agent | antiinflammatory agents

Figure 1. biologically active compounds bearing a 1,4-dihydropyrano[2,3-c]-pyrazole core.



Scheme 1. Synthesis of 1,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile.

The synthesis of 1,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile generally requires large amounts of oxidants, expensive catalyst and in situ purification along with produce large amounts of undesired waste so developing greener and efficient procedure is still an important need. Our study is based on the electrochemically induced transformation of ethyl acetoacetate, hydrazine hydrate, malononitrile and aromatic aldehydes to 1,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile under optimum reaction conditions (current density 10 mA/cm^2, 0.93 F/mol passed electricity, 40^{o}C, EtOH) by electrolysis in an undivided cell. The synthetic pathway is shown in Scheme 1.

In the present protocol product formed in good yield at room temperature in short time using small amount of electricity as energy, electro-generated base (EGB) induces the reaction. While conventional heating method[18] requires more energy and time with expensive catalyst in harsh reaction condition.

Table 1[a] Electrode optimization for the synthesis of 1,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile.

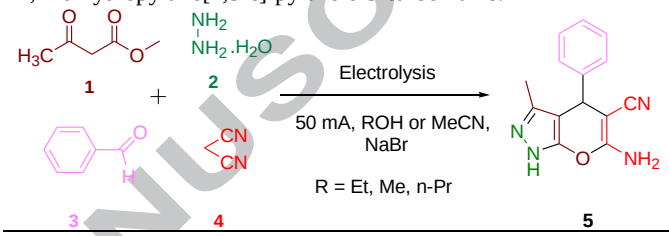
Entry	Anode/ Cathode	Solvent/ Electrolyte	Current density (mA/cm^2)	Yield[b] (%)
1	graphite/iron	EtOH/NaBr	1.0	45
2	graphite/iron	EtOH/NaBr	5.0	80
3	graphite/iron	EtOH/NaBr	10.0	90
4	graphite/graphite	EtOH/NaBr	10.0	40
5	Platinum/graphite	EtOH/NaBr	10.0	45
6	Platinum/graphite	EtOH/NaBr	5.0	20
7	RVC/graphite	EtOH/NaBr	N/A	25
8	RVC/graphite	EtOH/NaBr	N/A	30

[a]General procedure: Ethyl acetoacetate (1 mmol), hydrazine hydrate (1.5 mmol), aromatic aldehydes (1 mmol), and malononitrile (1 mmol) electrolyte (0.5 mmol), EtOH (25 mL).
[b]Yield of isolated product.

The nature of the electrode system was the most important factor in MCR reactions. To study the effect of electrode, we performed the reaction using various electrode combinations such as graphite-iron, graphite-graphite, platinum-graphite, RVC-graphite respectively as anode and cathode at constant current density. Current density proved to be the most important characteristic of the electrode. This refers to the amount of current applied per unit area of electrode surface. As the current density increased for a given electrode, the yield of the product increases significantly (Table 1, entries 1-3). Surprisingly, electrodes that have a high surface area and a low current density such as reticulated vitreous carbon[24] (RVC) were inferior to typical graphite electrodes. On screening different electrode combination at constant current density, we find that the yield was excellent with graphite-iron electrode combination. Hence graphite-iron electrode was chosen as preferred electrode combination.

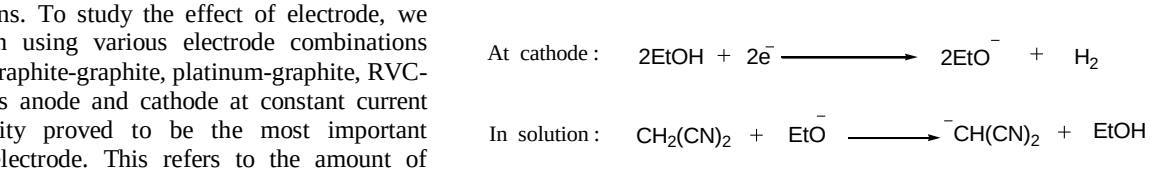
For solvent optimization, the reaction performed under various solvents and found that ethanol solvent at current density of 10 mA/cm^2 (I = 50 mA, electrode surface = 5 cm^2) promote the reaction. Ethyl acetoacetate, hydrazine hydrate, malononitrile and aromatic aldehydes yields 1,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile efficiently at 40^{o}C. We applied different amount of current for the same reaction and found that at 10 mA/cm^2 current densities (when 0.93 F/mol of electricity had been passed), the yield of reaction was excellent (Table 2, entry 7). Finally, to explore the scope and generality of the reaction, we extended our work under optimized reaction conditions to various substituted aryl aldehyde and notice that there was no considerable effect of substituent (electron withdrawing group or electron donating groups) on yields of reaction. In all cases, rapid synthesis of the products occurred in good yields under optimum reaction condition and the results are summarized in Table 3.

Table 2[a] Optimization of reaction conditions for synthesis of 1, 4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile.[a]



Solvent	I (mA)	Current density (mA/cm^2)	Time (min)	Electricity Passed (F/mol)	Temp (^{o}C)	Yield[b] (%)
EtOH	15	03	240	02.23	25	15
EtOH	50	10	240	07.46	25	25
EtOH	100	20	240	14.92	25	36
EtOH	05	01	120	00.37	40	45
EtOH	15	03	120	01.11	40	65
EtOH	25	05	90	01.39	40	80
EtOH	50	10	30	00.93	40	90
MeOH	50	10	35	01.08	40	80
n-PrOH	50	10	40	01.24	40	65
MeCN	50	10	45	01.39	40	60

[a]General procedure: Ethyl acetoacetate (1 mmol), hydrazine hydrate (1.5 mmol), aromatic aldehydes (1 mmol), and malononitrile (1 mmol) electrolyte (0.5 mmol), EtOH (25 mL), iron cathode (5 cm^2), graphite anode (5 cm^2).
[b]Yield of isolated product.

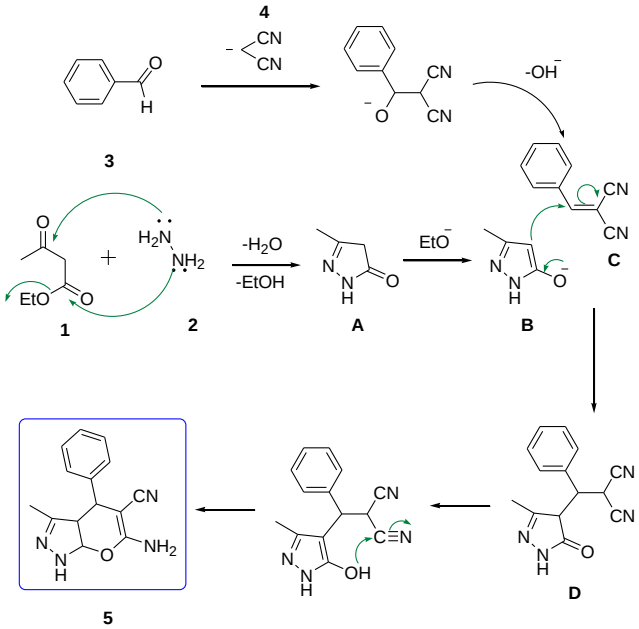


Scheme 2. Synthesis of malanonitrile anion in alcohol.

A possible mechanism is outlined in Scheme 3. In initiation step, the deprotonation of alcohol at cathode leads to the formation of alkoxide anion. The reaction between alkoxide anion and malononitrile in solution gives rise to malononitrile anion (Scheme 2).

The Knoevenagel condensation of malononitrile anion **4** with aromatic aldehyde **3** gives corresponding arylidenemalononitrile **C** with elimination of hydroxide anion. On the other hand compound **A** was synthesized by the reaction of ethyl acetoacetate **1** and hydrazine hydrate **2**, which enolised in the

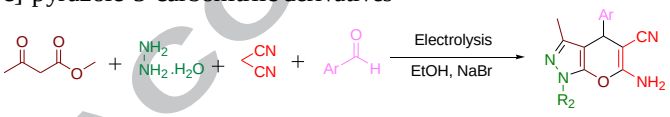
presence of ethoxide ion to form compound **B**. Subsequently, the enolizable compound **B** condensed with the Knoevenagel adducts **C** via Michael addition to give intermediate **D**. Intermediate product **D** by intramolecular cyclization converted in to final product **5**.



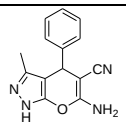
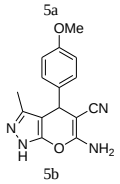
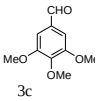
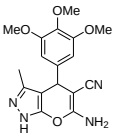
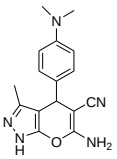
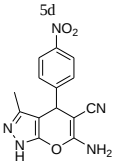
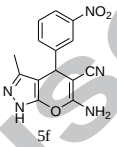
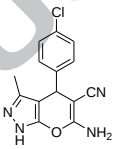
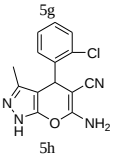
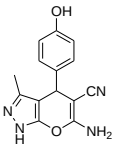
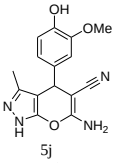
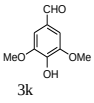
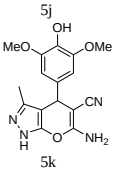
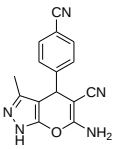
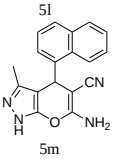
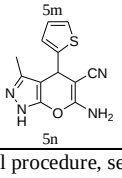
Scheme 3. A plausible mechanism for the formation of 1,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile **5** compounds.

In the present studies we conducted a four component reaction using hydrazine hydrate (1.5 mmol), ethyl acetoacetate (1 mmol), malononitrile (1 mmol) and aromatic aldehydes (1 mmol) in solution of NaBr (0.5 M) in ethanol (25 mL). The electrolysis was carried out in an undivided cell equipped with graphite rods (5 cm^2) as anode and Fe (5 cm^2) as cathode at 40 °C under constant current density 10 mA/cm^2 (I = 50 mA). The progress of the reaction was monitored by thin-layer chromatography. After the electrolysis was complete (30 min), the mixture was filtered and the solvent was evaporated under vacuum. The residue was purified by recrystallization from EtOH to furnish the desired product.

Table 3 Electrochemical synthesis of 1,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile derivatives [a b]



1 2 4 3a- 3n 5a - 5n

Entry	Aryl	Product	Time (min.)	Yield[c] (%)	mp (^{0}C)
1	 3a	 5a	30	90	243-246
2	 3b	 5b	30	85	210–212
3	 3c	 5c	35	85	208-210
4	 3d	 5d	35	86	168–170
5	 3e	 5e	25	90	251–252
6	 3f	 5f	25	88	194–196
7	 3g	 5g	25	90	234–236
8	 3h	 5h	30	90	146-148
9	 3i	 5i	35	76	224–226
10	 3j	 5j	35	76	232-234
11	 3k	 5k	35	80	198–200
12	 3l	 5l	30	90	196–198
13	 3m	 5m	25	80	200-201
14	 3n	 5n	30	86	244-246

[a] For the experimental procedure, see supporting information.
[b] All compounds are known and were characterized by comparison of their spectral data with those reported in the literature.[17, 25, 26]
[c] Yields of isolated pure compounds **5a**–**5n.**

In summary, we have developed a simple, efficient, economical, method for the synthesis of 1,4 -dihydropyrano[2,3-c]-pyrazole carbonitrile derivatives, by one-pot four-component reaction in ethanol in an undivided cell, in the presence of NaBr as an electrolyte. The use of cheap and environmental friendly chemical reagent electricity, low cast starting materials, non-hazardous reaction conditions, high yields and ease of separation of products through simple filtration thereby avoiding the need of column chromatography are some significance of proposed protocol.

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Highlights

- One pot four-component electro-synthesis of 1,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile derivatives
- Electro-induced condensation of ethyl acetoacetate, hydrazine hydrate, malononitrile and aromatic aldehydes.
- EGB promotes reaction in presence of NaBr as supporting electrolyte and ethanol as solvent.
- Small amount of current was used as energy source in the place of conventional heating.