



An Efficient Approach for the Synthesis of Pyrazolo [1,2,a] [1,2,4]Triazole-1,3-Diones Using an Electrochemical Cell

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ABSTRACT

A mild and efficient method was applied for the one-pot three-component synthesis of pyrazolo[1,2-a][1,2,4]triazole-1,3-diones from the condensation between arylaldehydes, malononitrile and 4-phenylurazole using electrolysis in an undivided cell in the presence of sodium bromide as an electrolyte. This procedure has many advantages such as : no need to catalyst, clean work-up, short reaction time and high yield. The products were obtained just with the simple filtration.

Keywords: Pyrazolo[1,2-a][1,2,4]triazole-1,3-dione; 4-phenylurazole; Malononitrile; Electrolysis.

INTRODUCTION

Many of heterocyclic compounds containing nitrogen have significant synthetic and biological importance, which act as polyfunctionalized fragments, agrochemicals, and pharmaceuticals¹⁻¹⁰. Pyrazolourazoles as their fused derivatives with diverse structures have attracted much interest because of their wide range of biological properties such as analgesic, antibacterial, anti-inflammatory, antidiabetic, and psychoanaleptic activities¹¹⁻¹⁶ (Figure 1). Many methods have been reported for their synthesis in recent years¹⁷⁻²⁶, and development

of new approaches for their synthesis seems to be interesting challenge.

For preparing biologically active compounds in organic, combinatorial, and medicinal chemistry the electrosynthetically multicomponent reactions (EMCRs) have been used widely²⁷. Due to the electron transfer between an electrode and the substrate molecules, the formation of highly reactive intermediates is achieved under mild conditions, avoiding reductive or oxidant agents as well as acids, bases and related waste by-products so that it can be one of the various fields in green chemistry²⁸.

In continue of our research on multi-component reactions²⁹⁻³², Herein, we report an efficient and green synthesis of pyrazolo[1,2-*a*][1,2,4]triazole-1,3-dione derivatives using an electrochemical cell (scheme 1).

MATERIALS AND METHOD

All reagents and solvents were obtained from Fluka and Merck and used without further purification. TLC was performed on Silica–gel Polygram SILG/UV 254 plates. Melting points and IR spectra were measured on an Electro thermal 9100 apparatus and a JASCO FT-IR-460 plus spectrometer. Controlled-current coulometer and preparative electrolysis were performed using a SAMA potentiostat/galvanostat (Zahedan, Iran), respectively. The ¹H NMR spectra were obtained on Bruker DRX-400 Advance instruments with DMSO.

General procedure for the synthesis of 7-amino-1,3-dioxo-2-phenyl-2,3-dihydro-1H,5H-pyrazolo(1,2-*a*)(1,2,4)triazole-6-carbonitrile

A mixture of arylaldehyde (1 mmol), malononitrile (1mmol), 4-phenylurazole (1mmol) and NaBr (0.05 g, 0.5 mmol) in EtOH (20 mL) was stirred with a magnetic stirrer and electrolyzed in an undivided cell equipped with a graphite anode, and an iron cathode at ambient temperature under a constant current density of 10mA/cm² (electrodes square 5 cm²), until the catalytic quantity of 0.1 F/mol of electricity was passed. After electrolysis process, the mixture was filtered, then it was rinsed twice with cold ethanol to obtained corresponding product.

Analytical data for the selected compounds

7-amino-5-(3-nitrophenyl)-1,3-dioxo-2-phenyl-2,3-dihydro-1H,5H-pyrazolo(1,2-*a*)(1,2,4)triazole-6-

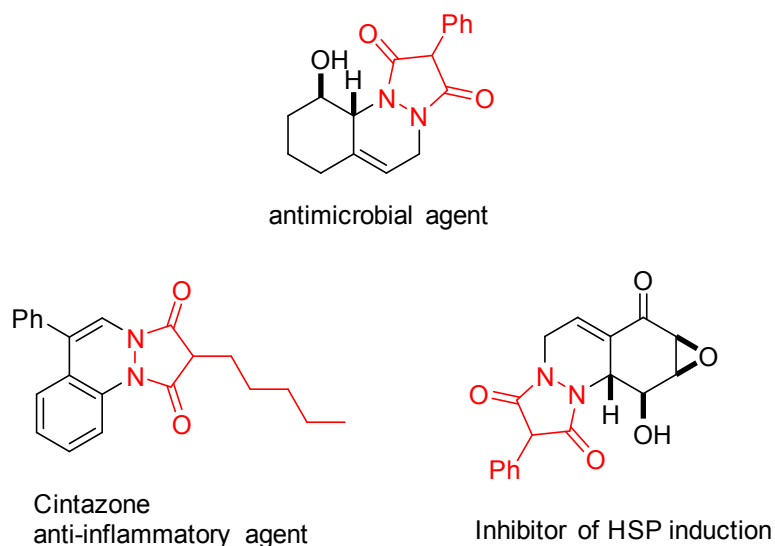
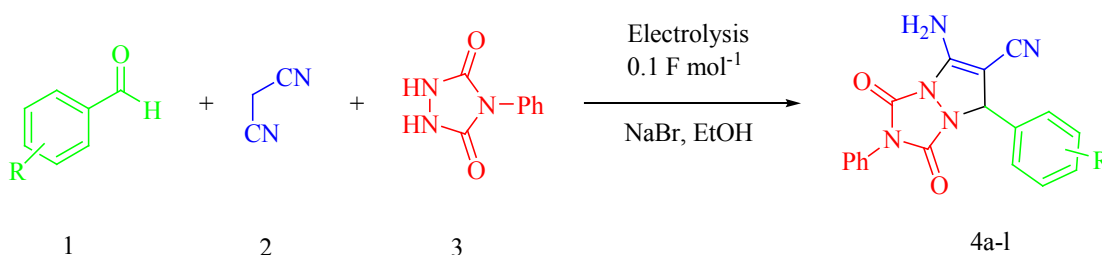


Fig. 1: pyrazolourazoles with diverse structures



Scheme 1: Synthesis of pyrazolo [1,2-*a*][1,2,4]triazole-1,3-dione derivatives with an electrochemical cell

carbonitrile (4b)

White powder, m.p.: (>300°C.); IR (KBr) (ν_{max}/cm^{-1}): 3430, 3314, 2189, 1766, 1715. ^1H NMR (400 MHz, DMSO- d_6) δ_{H} 6.094 (1H, s, CH), 7.47-8.37 (11H, m, H-Ar and NH_2).

7-amino-5-(3-chlorophenyl)-1,3-dioxo-2-phenyl-2,3-dihydro-1H,5H-pyrazolo(1,2-a)(1,2,4)triazole-6-carbonitrile (4c)

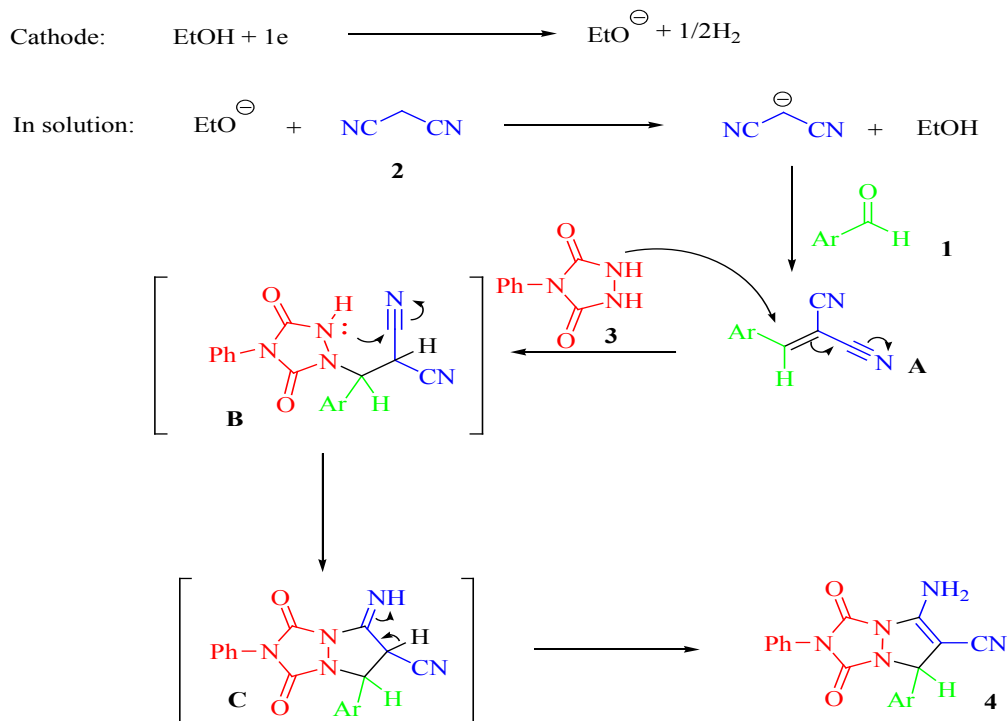
White powder, m.p.: (>300°C.); IR (KBr) (ν_{max}/cm^{-1}): 3450, 3338, 2200, 1778, 1715. ^1H NMR (400 MHz, DMSO- d_6) δ_{H} 6.09 (1H, s, CH), 7.47-8.37 (11H, m, H-Ar and NH_2)

7-amino-5-(2-chlorophenyl)-1,3-dioxo-2-phenyl-2,3-dihydro-1H,5H-pyrazolo(1,2-a)(1,2,4)triazole-6-carbonitrile (4l)

White powder, m.p.: (>300°C.); IR (KBr) (ν_{max}/cm^{-1}):

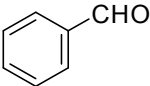
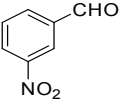
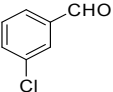
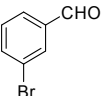
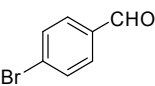
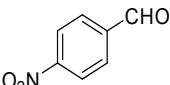
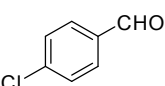
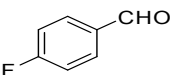
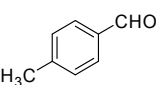
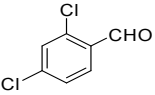
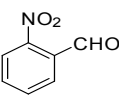
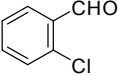
Table 1: Optimization of Reaction Conditions for the Synthesis of 7-Amino-1,2,3,5-Tetrahydro-1,3-Dioxo-2,5-Diphenylpyrazolo[1,2-a][1,2,4]Triazole-6-Carbonitrile

Entry	I (mA)	Current density (mA/cm ²)	Time (min)	catalyst passed (F/mol)	Electricity (%)	Yields
1	5	1	250	-	0.1	50
2	10	2	160	-	0.1	65
3	20	4	50	-	0.1	80
4	50	10	33	-	0.1	93
5	75	15	23	-	0.1	80



Scheme 2: Proposed mechanism for the synthesis of pyrazolo[1,2-a][1,2,4]triazole-1,3-dione derivatives using electrolysis in the presence of sodium bromide as an electrolyte

Table 2: Synthesis Of Pyrazolo[1,2-A][1,2,4]Triazole-1,3-Dione Derivatives

Entry	Aldehyde	Product	Yield(%)	m.p(°C)	Reference [24]
1		4a	93	>300	>300
2		4b	93	>300	>300
3		4c	85	>300	>300
4		4d	90	>300	>300
5		4e	85	>300	>300
6		4f	90	>300	>300
7		4g	90	>300	>300
8		4h	89	>300	>300
9		4i	83	>300	>300
10		4j	87	>300	>300
11		4k	90	>300	>300
12		4l	93	>300	>300

3400, 3319, 1778, 1725. $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ_{H} 6.27 (1H, s, CH), 7.44-7.69 (11H, m, H-Ar and NH_2).

RESULTS AND DISCUSSION

To optimized the reaction conditions, the condensation between benzaldehyde, malononitrile and 4-phenylurazole was chosen as model reaction. The reactive mixture was stirred at room temperature, and this progress was monitored by TLC. The reaction is performed in alcoholic solvents in the presence of sodium bromide as an electrolyte. Various current quantities were applied under the mentioned conditions. As can be seen in Table 1, excellent conversions of the starting materials were obtained under 10 mA/cm² current densities after 0.1 F/mol of electricity had passed. The current density of 10 mA/cm², $I = 50$ mA, electrode surface Scheme 1.

Using mentioned optimized reaction, the reaction were explored for the synthesis of a wide variety of pyrazolo[1,2-*a*][1,2,4]triazole-1,3-diones using aromatic aldehydes, malononitriles and 4-phenylurazol. The results are summarized in Table 2. As shown in Table 2, the products were obtained in excellent yields.

We proposed mechanism for the preparation of pyrazolo[1,2-*a*][1,2,4]triazole-1,3-dione derivatives. First, deprotonation of an alcohol

at the cathode leads to the formation of the alkoxide anion³³. It's subsequent reaction in solution with malononitrile gives rise to the malononitrile anion. Then, Knoevenagel condensation of aldehyde **1**, with the malononitrile anion takes place in the solution with the elimination of water and the formation of the corresponding α -cyanocinnamo-nitrile derivatives **A**. The subsequent hydroxide-promoted Michael addition of 4-phenylurazole **3** to the electron-deficient Knoevenagel adduct **A** followed by intramolecular cyclization results in the corresponding products **4**, with regeneration of the alkoxide anion as the last step, which continues the catalytic chain process by the interaction with the next molecule of malononitrile.

CONCLUSION

The pyrazolo[1,2-*a*][1,2,4]triazole-1,3-dione derivatives were synthesised in the presence of sodium bromide as an electrolyte under neutral and mild conditions. The main advantages of this method are the very short reaction time, high yields, simple work-up, use of non- hazardous organic solvent and catalyst.

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