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Electro-Organic Synthesis: An Efficient Method for the Preparation of Nanosized Particles of Phthalazine Derivatives *via* One-Pot Multicomponent Reactions

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Aza heterocyclic compounds are major interest for organic chemists because of their mainly pharmacological activities and clinical applications such as antianxiety, antitumor, anticonvulsant, cardiotonic and vasorelaxant. This contribution describes an electrochemical approach for the preparation of nanosized particles of phthalazine in high yields and very short reaction time. The method is based on the one-pot multicomponent reaction (MCRs) of phthalhydrazide, malononitrile and aldehydes in propanol employing undivided cell in the presence of NaBr as an electrolyte. The product was characterized, after purification, using IR, ^{1}H NMR, ^{13}C NMR, MS and SEM. This procedure provides a method by which nanoparticles are synthesized directly from phthalhydrazide, malononitrile and aldehydes insides of a routine protocol for the synthesis of nano particles of organic compounds in which the synthesized organic compound is transformed into nanosized particles using modern high technology, for example ultrahighpressure rapid expansion of supercritical solution, and supercritical antisolvent with enhanced mass transfer. Size reduction is a fundamental unit operation having important applications in pharmacy. It helps to improve solubility and bioavailability, reduce toxicity, enhance release, and provide better formulation opportunities for drugs.

Keywords: Phthalhydrazide, Malononitrile, Aldehydes, Nanosized particles, Multicomponent

NTRODUCTION

The development of new efficient methods for synthesizing structurally diverse aza heterocyclic is of major interest for organic chemists. Among a large variety of nitrogen-containing heterocycles, derivatives whit a bridgehead phthalazine are common and these moieties are continually receiving much attention from organic and medicinal chemists, mainly due to its the pharmacological activities and clinical applications such as antianxiety [1], antitumor [2], anticonvulsant [3], cardiotonic [4] and vasorelaxant [5]. Albeit, there are methods available for the synthesis of different phthalazine derivatives [6-9] but the significant synthetic potential of these methods is often limited on account of their technical complexity, generally use of expensive catalyst or toxic organic solvents [10,11 strong acidic conditions [12,13] and harsh reaction], conditions [12-14].

Multicomponent reactions have gained significant importance as a tool for the synthesis of a wide variety of useful compounds in view of the fact that products are formed in a single step, and the diversity can be readily achieved, simply by varying the reacting components [15]. Electro synthesis, as a synthetic methodology to facilitate preparation of organic compounds, is a focal point of research activities in the fields of modern organic, bioorganic and medicinal chemistry [16,17], Most recently we reported the preparation of indenoquinoxaline [18], indeno imidazole [19], indeno quinolone [20] *via* multi-component reactions, and pyrans [21] and oxindoles [22] by using mentioned electro-catalytic technique.

EXPERIMENTAL

Apparatus and Reagents

Controlled-current coulometry and preparative electrolysis were performed using a SAMA potentiostate/

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galvanostate (Isfahan, Iran). The working electrodes were on an iron cathode (5 cm^2) and a magnesium anode (5 cm^2). The IR spectra were recorded on a Bruker IFS-66 FT-IR spectrophotometer. Mass spectra were obtained using a QP-1100 EX Shimadzu GC-MS (EI at 70 eV) and Agilent Technologies 5937 mass selective detector. Scanning electron microscopy (SEM) was run with axl30 scanning electron microanalyzer (Philips, Netherlands) at an acceleration voltage of 20.0 kV. The melting point of the product was obtained using an electrothermal melting point apparatus (U.K.), model 9200. All compounds were commercially available, obtained from Merck and used without further purification.

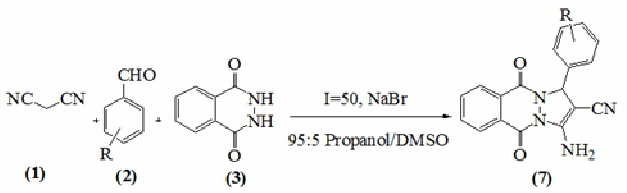
General Electro-Synthesis Procedure for Preparation of Phtalazine Derivatives

A mixture of malononitrile 1 (0.066 g, 1 mmol), aldehyde 2 (1 mmol), and phthalhydrazide 3 (1 mmol), NaBr (0.05 g, 0.5 mmol) in *n*-PrOH/DMSO (95/5%) (25 ml) was stirred and electrolyzed in an undivided cell equipped with iron cathode (5 cm^2), magnesium anode (5 cm^2) at r.t. under constant current density 10 mA cm^{-2} (I = 50 mA). After completion of the reaction (monitored by TLC, ethyl acetate/*n*-hexane 1/1), the solvent was evaporated under reduced pressure and then 20 ml ethanol (80% + 1 ml DMSO) was added to the reaction mixture. The resulting solid was separated by centrifugation.

Selected Data

3-Amino-1-(4-bromophenyl)-5,10-dioxo-5,10-dihydro-1Hpyrazolo[1,2-b]phthalazine-2-carbonitrile (7b). Yellow powder; m.p.: 151 °C. IR (KBr): ν (cm^{-1}) 3431, 1663, 2195. ^{1}H NMR (300 MHz, DMSO-d_6) δH 6.11 (1H, s, CH), 7.40-8.26 (10H, m, H-Ar and NH_2). ^{13}C NMR (300 MHz, DMSO-d_6) δC 61.4, 63.1, 116.7, 122.3, 127.2, 127.6, 129.2, 129.4, 129.7, 131.8, 133.9, 134.8, 138.4, 151.3, 154.2, 156.9. MS (m/z, %): 396 (M^++2), 394 (M^+). Anal. Calcd. for $C_{18}H_{11}BrN_4O_2$: C, 54.70; H, 2.81; N, 14.18%. Found: C, 54.60; H, 2.73; N, 14.10.

3-Amino-1-(4-fluorophenyl)-5,10-dioxo-5,10-dihydro-1Hpyrazolo[1,2-b]phthalazine-2-carbonitrile (7c). Yellow powder; m.p.: 245 °C. IR (KBr): ν (cm^{-1}) 3420, 1657, 2191. ^{1}H NMR (300 MHz, DMSO-d_6) δH 6.13 (1H, s, CH), 7.11-8.28 (10H, m, H-Ar and NH_2). ^{13}C NMR (300 MHz, DMSO-d_6) δC 61.4, 62.8, 115.3, 116.3, 116.1, 127.5, 127.9, 129.2, 129.5, 129.7, 129.9, 134.5, 134.9, 151.5, 154.2, 157.6, 160.9, 164.3. MS (m/z, %): 334 (M^+). Anal. Calcd. for $C_{18}H_{11}FN_4O_2$: C, 64.67; H, 3.32; N, 16.76%. Found: C, 64.60; H, 3.23; N, 16.67.



Scheme 1. Formation of phthalazines

3-Amino-1-(4-chlorophenyl)-5,10-dihydro-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (7d). Yellow powder; m.p.: 268 °C. IR (KBr): ν (cm^{-1}) 3420, 1650, 2193c. ^{1}H NMR (300 MHz, DMSO-d_6) d = 6.13 (1H, s, CH), 7.44-7.58 (4H, m, ArH), 7.90-8.39 (4H, m, ArH), 8.23 (2H, s, NH_2). ^{13}C NMR (300 MHz, DMSO-d_6) δC 61.6, 62.5, 116.7, 127.3, 127.8, 129.1, 129.6, 133.8, 135.0, 135.3, 137.2, 152.3, 154.6, 157.4 ppm MS (m/z, %): 350 (8) (M^+), 335 (27), 239 (100). Anal. Calcd. for $C_{18}H_{11}ClN_4O_2$: C, 61.64; H, 3.16; N, 15.97. Found: C, 61.54; H, 3.07; N, 15.89.

RESULTS AND DISCUSSION

In an extension of the method to confirm the proposed pathway we carried out the three-component reaction using malononitrile (**1**), aldehyds (**2**) and phthalhydrazide (**3**) for the one-pot, electro-synthesis of phthalazines (**7**) (Scheme 1).

In order to optimize the condition, we used aldehydes, malononitrile and phthalhydrazide to test various current densities and solvents. The results are summarized in Table 1.

The synthesis of phthalazine derivatives was achieved by the three-component condensation of aromatic aldehydes, malononitrile and phthalhydrazide in the presence of dry propanol and dimethylsolfoxide (95:5, PrOH/DMSO). The reaction was done at a current density of 10 mA cm^{-2} (I = 50 mA, electrode surface = 5 cm^2) stirred at room temperature in the presence of NaBr as an electrolyte. The reaction was completed within 1 h and the workup of the reaction

Table 1. Comparison of Effect of Different Solvent and Current on the Reaction of Malononitrile (1), 3-Nitrobenzaldehyd (2f) and Phthalhydrazide (3) to Afford the 3-Amino-5,10-dihydro-1-(3-nitrophenyl)-5,10-dioxo-1*H*-pyrazolo[1,2-b]phthalazine-2-carbonitrile (7a)

Entry[a]	I (mA)	Solvent	Electricity passed (F/mol)	T (min)	Yield (%)[b]
1	20	*n*-PrOH	3.0	240	48
2	50	*n*-PrOH	1.9	90	52
3	20	*n*-PrOH/DMSO 95/5%	3.0	240	90
4	50	*n*-PrOH/DMSO 95/5%	1.9	90	95

[a]For all reactions, 0.5 mmol of NaBr, iron cathode (5 cm^2), magnesium anode (5 cm^2) and room temperature were used. [b]Isolated yields based on phtalhydrazide.

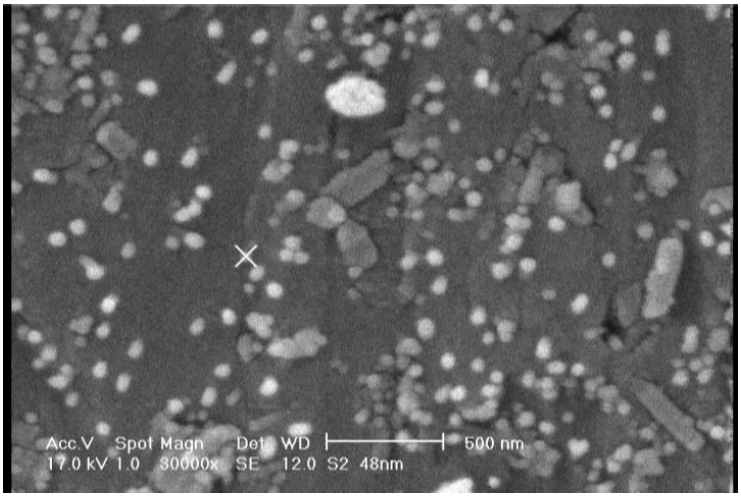


Fig. 1. Images of nano-sized particles of 3-amino-5,10-dihydro-1-(3-nitrophenyl)-5,10-dioxo-1*H*-pyrazolo[1,2-b]phthalazine-2-carbonitrile.

mixture showed that phthalhydrazide has been prepared efficiently.

It was found that this product is composed of nano-sized particles. An SEM micrograph of the template-synthesized nano-sized particles, obtained by powder, is shown in Fig. 1.

The average particle size, DSEM, is < 100 nm. The size and the form of the aggregates dependupon the conditions of sample preparation.

Although we do not know exactly the nanoparticle formation mechanism, we think existence of the Mg^{2+} in the solution might prevent the aggregation of the products [23,24].

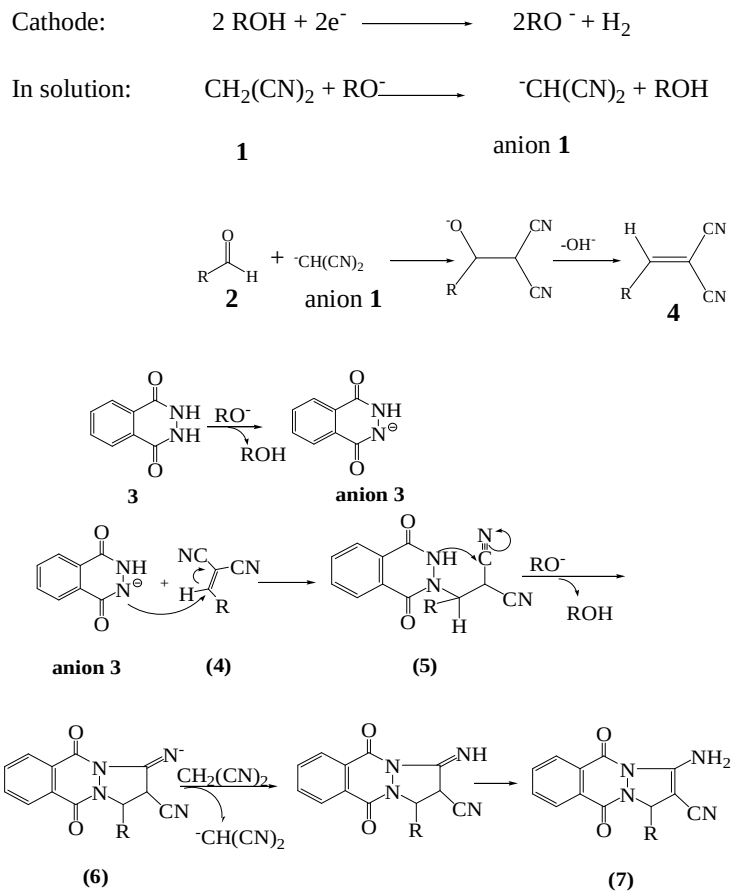
An attempt was made to prepare nano-sized particles of phthalazine derivatives from aromatic aldehydes, malononitrile and phthalhydrazide to extend the scope of the reaction. Hence, a number of nano-sized particles of phthalazine derivatives were participated with good yields [7-9]. The optimized results are summarized in Table 2.

Strong literature review shows, there are many articles that support the proposed mechanism as follow [25-28]: Alcohol deprotonation at the cathode led to the formation of an alkoxide anion. A subsequent reaction between the alkoxide anion and phtalhydrazide gives rise to a

Table 2. Results Obtained in the Reaction of a Series of Aldehydes (2a-f) with Malononitrile and Phtalhydrazide[a]

Entry	R	M. p. (°C)	Lit. M.p. (°C)[a]	Yield (%)[b]
7a	3-$NO_2C_6H_4$	260	269-271[7]	92
7b	4-BrC_6H_4	151	265-267[8]	80
7c	4-FC_6H_4	245	263-265[8]	75
7d	4-ClC_6H_4	268	270-272[9]	90
7e	4-$MeOC_6H_4$	238	270 (dec.)[9]	85
7f	3-$MeOC_6H_4$	111	264-266[9]	88

[a]For all reactions, 0.5 mmol of NaBr, iron cathode (5 cm^2), magnesium anode (5 cm^2) and room temperature were used. [b]Isolated yields based on phthalhydrazide.



Scheme 2. The formation of the products 7

phthalhydrazide anion. The condensation of anion 1 with aldehyde **2** yields intermediate **4**. Finally, product **7** is formed by the condensation of anion **3** and intermediate **4** (Scheme 2).

CONCLOSIONS

We have earlier reported electrosynthesis of nanoparticles of oxindoles and 2-amino-pyranes in a novel, practically convenient, easy and ecologically safe method, and now we have developed this method for the synthesis of nano-sized particles of pthalazine using a green chemical protocol. The use of electricity as a green catalyst not only gives high yield of nano particles but also provides a procedure by which nanoparticles are synthesized directly from phthalhydrazide, malononitrile and aldehydes.

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