An efficient one pot three component synthesis of fused pyridines via electrochemical approach

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Graphical Abstract

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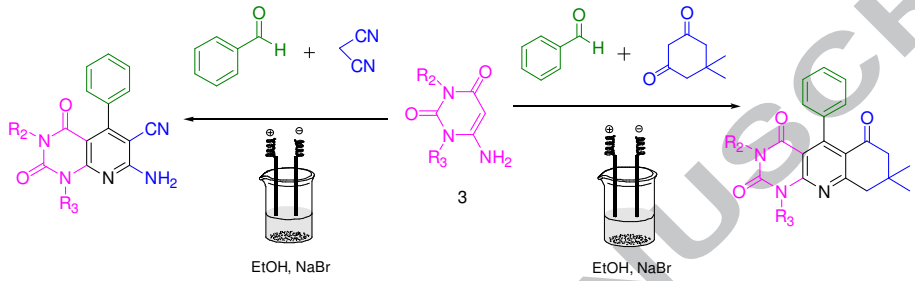

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An efficient one pot three component synthesis of fused pyridines via electrochemical approach

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ABSTRACT

A convenient and economical method is developed for the synthesis of pyrido[2,3-*d*]pyrimidine derivatives by electrochemically induced condensation of various aromatic aldehydes, dimedone or malononitrile and 6-amino uracil. The reaction is carried out in an undivided cell, at a constant current in the presence of NaBr as supporting electrolyte and ethanol as solvent.

Multicomponent reactions have been recently recognized as a powerful tool in synthetic organic chemistry. They allow one-pot reaction in which three or more reactants are combined together to form a new desired compound in sort duration. Multicomponent reactions (MCRs) play an important role in atom economy and green chemistry.[1] These reactions dramatically reduce the generation of chemical waste and the cost. MCR strategies offer significant advantages over conventional linear type synthesis.[2] It provide powerful dais to access diversity as well as complexity in few reaction steps. The conventional multi-step synthesis of compounds involve purification of compounds after each individual step,[3] which leads to two main disadvantages, synthetic inefficiency and the production of large amount of waste.

The derivatives of 6-amino uracil have received considerable attention over the last few years due to their vast range of biological and pharmacological properties such as, antimicrobial,[4] antibacterial,[5] antifungal,[6] antiallergic,[7] anti-inflammatory,[8] analgesic,[9] antihypertensive [10] and antitumor.[11] The synthesis of pyrido[2,3-*d*]pyrimidine derivatives has been explored extensively in recent years. Various methods such as using microwave,[12] magnesium oxide,[13] diammonium hydrogen phosphate (DAHP),[14] bismuth(III)-nitrate pentahydrate[15] and palladium-catalyzed oxidative coupling[16] have been reported. However, conventional methods for the synthesis of these products suffer from various drawbacks such as harsh reaction conditions, prolonged reaction time, low yield, use of toxic organic solvents, expensive reagents and catalysts. Therefore simple, efficient and environmentally benign approaches for synthesis of pyrido[2,3-*d*]pyrimidine are desirable.

In electrochemistry electron serve as sole reagent hence there is no need of acid, base or catalyst, electrogenerated base (EGB) promote reactions in good yields. Electrosynthesis have many advantages with atom economy, mild reaction conditions, decreased energy requirements and reduced waste production, and the ability to perform a wide range of precisely tuned oxidation and reduction reaction. As a part of our ongoing efforts towards synthesis of medicinally important compound,[17] we developed a convenient and environmentally friendly method for multicomponent synthesis of pyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives and 8,9-dihydro-1,3,8,8-tetramethyl 5-phenylpyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione derivatives by the electrochemical transformation using 6-aminouracil, various aromatic aldehydes, malononitrile or dimedone as starting material in an undivided cell at 40 °C under a constant current density.

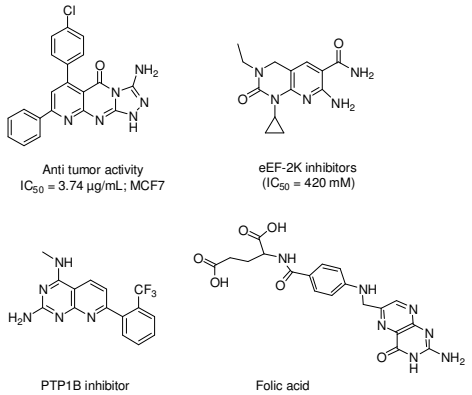
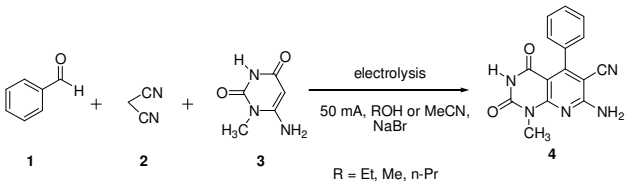
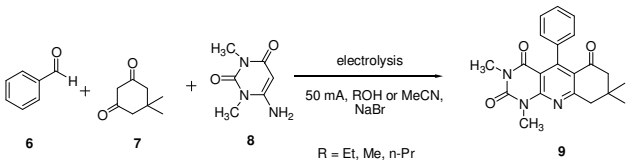


Figure 1. Several biologically active pyrido[2,3-*d*]pyrimidine compounds.



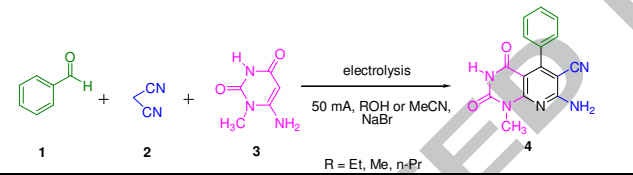
Scheme 1. Synthesis of 7-amino-1,2,3,4-tetrahydro-1methyl-2,4-dioxo-5-phenylpyrido[2,3-d]pyrimidine-6-carbonitrile.



Scheme 2. Synthesis of 8,9-dihydro-1,3,8,8-tetramethyl-5-phenylpyrimido[4,5-b]quinoline-2,4,6-(1H, 3H, 7H)-trione.

Three component compounds related to scheme 1 and 2 were prepared by several methods,[19] which require large amounts of oxidants. In situ purification produce large amounts of undesired waste so developing greener and efficient procedure is still an important need. Our investigation is based on the electrochemically induced transformation of aryl aldehydes, malononitrile or dimedone and 6-aminouracil into Pyrido[2,3-d]pyrimidines under optimum reaction conditions (current density 10 mA/cm^2, 0.77 F/mol passed electricity, 40^{o}C, EtOH) by electrolysis in an undivided cell. The synthetic pathway is shown in Scheme 1 and 2.

Table 1[a] Optimization of reaction conditions for synthesis of pyrido[2,3-*d*]pyrimidine 40^{o}C.[a]

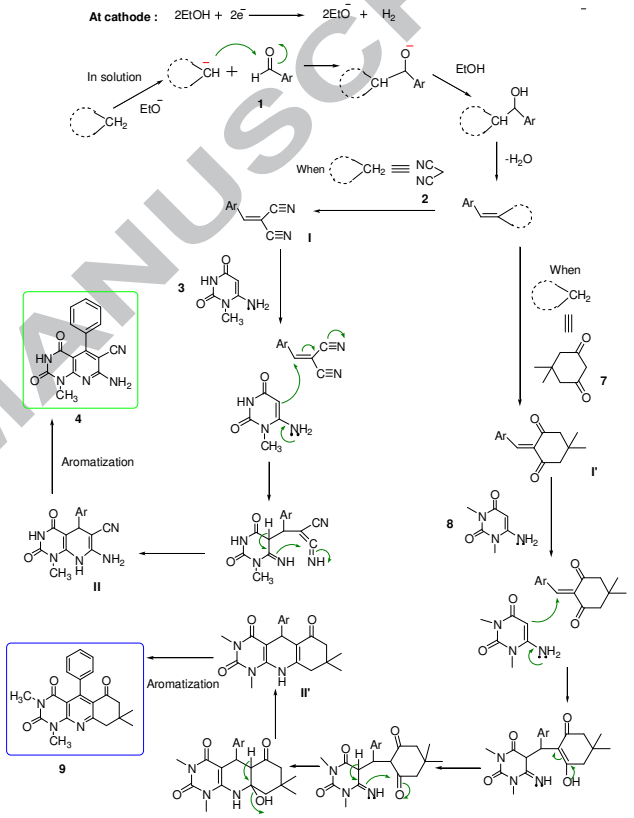


Electro-lyte	Solv-ent	I (mA)	Current density (mA/cm^2)	Time (min)	Electricit-y Passed (F/mol)	Yield[b] (%)
NaBr	EtOH	5	1	210	0.65	60
NaBr	EtOH	15	3	150	1.39	65
NaBr	EtOH	25	5	80	1.24	70
NaBr	EtOH	50	10	25	0.77	90
NaBr	MeOH	75	15	25	1.16	70
NaBr	MeOH	50	10	25	0.77	80
NaBr	n-PrOH	50	10	25	0.77	75
NaBr	MeCN	50	10	25	0.52	92
KBr	EtOH	50	10	25	0.77	40
KI	EtOH	50	10	25	0.77	42
Bu_4NClO_4	EtOH	50	10	25	0.77	90
Bu_4NClO_4	MeCN	50	10	25	0.52	92

[a]General procedure: 6-amino uracil (2 mmol), benzaldehyde (2 mmol), malononitrile (2.4 mmol), electrolyte (0.5 mmol), EtOH (30 mL), iron cathode (5 cm^2), graphite anode (5 cm^2).

[b]Yield of isolated product.

During the course of reaction we screen several 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 of benzaldehyde, malononitrile or dimedone and 6-aminouracil to pyrido[2,3-d]pyrimidine or pyrimido[4,5-b]quinoline 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 0.77 F/mol of electricity had been passed), the yield of reaction was excellent. Combination of Acetonitrile and tetrabutylammonium perchlorate (Bu_4NClO_4) show maximum yield. Acetonitrile is more expensive rather than ethanol and has a modest toxicity in small doses. It can be metabolized to produce hydrogen cyanide, which has toxic effects.[20] In general Bu_4NClO_4 is commonly used as PTC (phase transfer catalyst). When we used Bu_4NClO_4 as an electrolyte, we found excellent yield



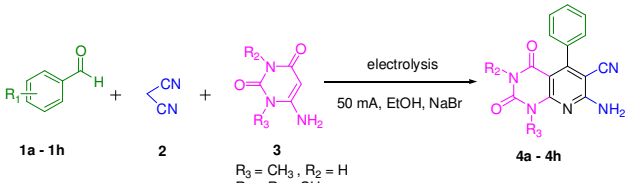
Scheme 3. A plausible mechanism for the formation of pyrido[2,3-d] pyrimidine **4** and pyrimido[4,5-b]quinoline **9** compounds.

The proposed mechanism is depicted in Scheme 3. Alcohol deprotonation at the cathode leads to the formation of an alkoxide anion. Subsequent reaction between the alkoxide anion and malononitrile gives rise to a malononitrile anion. The aldehyde reacts with malononitrile anion or with 5,5-dimethyl-1,3-cyclohexanedione anion followed by elimination of water to afford intermediate **I** or **I'**. The olefin intermediate undergoes Michael addition with 6-amino-1-methyluracil followed by intramolecular cyclization to give corresponding intermediate **II** or **II'**. This intermediate undergoes oxidation to give final product **4** or **9**.

The electrolysis performed under the optimum conditions (current density 10 mA/cm^2, 0.77 F/mol electricity passed at 40^{o}C, EtOH) for 30 min and results are summarized in Table 2. It was observed that aromatic aldehydes having electron withdrawing or donating groups reacts with malononitrile to give product in excellent yield.

In our studies we performed a three component reaction using aromatic aldehyde (2 mmol), malononitrile or dimedone (2.4 mmol) and 6-aminouracil (2 mmol), NaBr (0.5 M) in ethanol (25mL). 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 electrolysis (30 min), the mixture was filtered and solvent was evaporated under vacuum. The residue was purified by recrystallization from EtOH to furnish the desired product. In this protocol we use graphite as anode and iron as cathode. The reason being graphite is inexpensive, inert having high sublimation temperature while iron electrode is low cost, having high conductivity.

Table 2 Electrochemical transformation of aromatic aldehyde, malononitrile and 6-amino uracil into pyrido[2,3-*d*]pyrimidine derivatives.[a b]



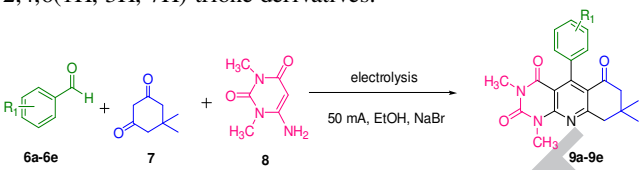
1a - 1h 2 3 4a - 4h

$R_3 = CH_3$, $R_2 = H$
$R_3 = R_2 = CH_3$

Entry	Aryl	Product	Time (min.)	Yield[c] (%)	mp (^{0}C)
1	1a	4a	25	90	299-301
2	1b	4b	30	92	300-303
3	1c	4c	30	93	300-302
4	1d	4d	30	93	298-300
5	1e	4e	25	92	298-300
6	1f	4f	20	90	296-298
7	1g	4g	20	90	300-302
8	1h	4h	25	92	301-303

[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.[12, 20, 21]
[c] Yields of isolated pure compounds 4a – 4h.

Table 3 Electrochemical transformation of aromatic aldehyde, dimedone and 6-amino-1,3-dimethyluracil into 8,9-dihydro-1,3,8,8-tetramethyl-5-phenylpyrimido[4,5-b] quinoline 2,4,6(1H, 3H, 7H)-trione derivatives.[a b]



6a-6e 7 8 9a-9e

Entry	Aryl	Product	Time (min.)	Yield[c] (%)	mp (^{0}C)
1	6a	9a	25	88	298-300
2	6b	9b	30	92	299-301
3	6c	9c	25	92	220-222
4	6d	9d	25	93	287-289
5	6e	9e	30	90	281-283

[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.[22, 23]
[c] Yields of isolated pure compounds 9a – 9e.

In conclusion, we have developed an efficient, fast and simple method for the one-pot synthesis of pyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives and 8,9-dihydro-1,3,8,8-tetramethyl5-phenylpyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione derivatives. The use of inexpensive starting materials, non-hazardous reaction conditions, high yields and separation of products through simple filtration avoiding column chromatography are some significant features of present strategy which make this an attractive protocol for synthesis of fused pyridines.

Acknowledgments

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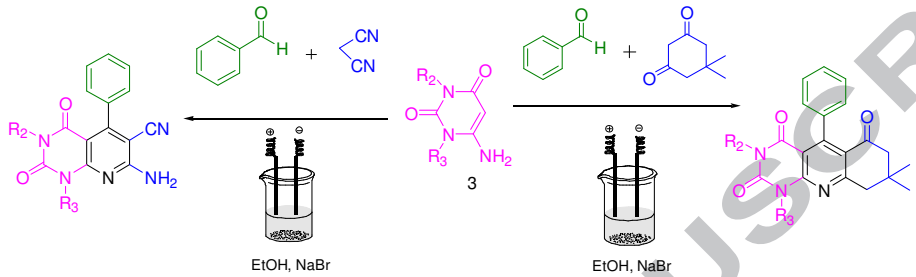

Highlights

- **E**lectro-induced condensation of aldehydes, dimedone or malononitrile and 6-amino uracil.
- EGB promots 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.