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Efficient Three-Component One-Pot Synthesis of 4*H*-Pyrans

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Abstract—Clean, practical, and efficient electrochemical synthesis of pharmaceutically relevant 4*H*-pyran derivatives by one-pot three-component combination of an aryl aldehyde, malononitrile, and a dicarbonyl compoundis developed. The synthesis is performed in ethanol with lithium perchlorate as a supporting electrolyte in an undivided cell on a platinum electrode under constant potential electrolysis conditions.

Keywords: anodic oxidation, electrogererated base, Michael addition, controlled potential electrolysis (CPE), cyclic voltammetry

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INTRODUCTION

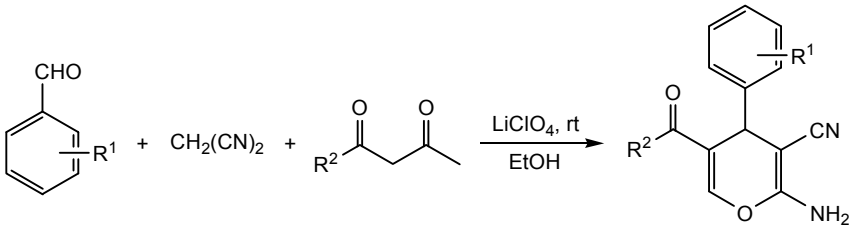
The discovery of new synthetic methodologies that facilitate the construction of organic compounds is a focal point of research activity in the field of modern organic, bioorganic, and medicinal chemistry [1]. The concept of "privileged medicinal structures or scaffolds" [2] has emerged as one of the guiding principles of the drug discovery process and consist of a rigid hetero- ring system that assumes a well-defined orientation of appended functionalities for target recognition [3].

Multicomponent reactions (MCRs) are important because of their wide range of applications in the pharmaceutical industry for the rapid generation of structurally diverse combinatorial libraries for drug discovery [4, 5]. In addition, MCRs are environmentally benign and atom economic, involve no time-consuming and costly purification processes, [6, 7] and dramatically reduce the generation of chemical wastes. In MCRs), three or more reactants are combined together in a single reaction flask to generate a product incorporating most of the atoms contained in the starting materials [8]. These reactions constitute an especially useful synthetic strategy and provide mild, easy, and rapid access to large libraries of organic molecules with diverse substitution patterns.

4*H*-Pyran-based heterocyclic compounds are privileged pharmacological scaffolds due to their distinct structures and great potential for further transformations into various compounds [9–12]. The interest in these compounds is explained by their useful pharmaceutical and biological properties, including antiviral [13], antimicrobial [14], antifungal [15] and anticancer activity [16].

The conventional method of synthesis of pyrans using various catalysts [17] is associated with considerable difficulties, such as complicated isolation of products, low yields, and corrosive nature of reagents and solvents [18–22]. The electrochemical method is quite competitive in modern organic chemistry and offers novel and versatile synthetic advantages. Electrochemical organic reactions produce electrogenerated bases (EGBs) from methylene-active compounds employing such a clean chemical reagent as electricity in a simple undivided cell and provide high yields of products not necessitating harsh conditions, such as high temperatures, large quantities of organic solvents, tedious work-up processes, and toxic reagents. Considering the synthetic and therapeutic significance of 4*H*-pyran derivatives and proceeding with our work on the multicomponent synthesis of heterocyclic compounds, we designed a facile, efficient, and clean synthetic approach to 4*H*-pyrans, based on the electrochemical transformation of various aromatic aldehydes, malononitrile, and dicarbonyl compounds in an undivided cell.

Scheme 1.



1a–1i **2** **3a**, **3b** **4a–4n**

1, R^1 = H (**a**), *p*-Cl (**b**), *m*-OH (**c**), *p*-$(CH_3)_2N$ (**d**), *p*-CH_3O (**e**), *o*-Cl (**f**), *o*-CH_3O (**g**), *m*-NO_2 (**h**), *p*-CH_3 (**i**); **3**, R^2 = H (**a**), C_2H_5 (**b**); **4**, $R^1 = R^2$ = H (**a**); R^1 = *p*-Cl, R^2 = H (**b**); R^1 = *m*-OH, R^2 = H (**c**); R^1 = *p*-$(CH_3)_2N$, R^2 = H (**d**); R^1 = *p*-CH_3O, R^2 = H (**e**); R^1 = *o*-Cl, R^2 = H (**f**); R^1 = *o*-CH_3O, R^2 = H (**g**); R^1 = *m*-NO_2, R^2 = H (**h**); R^1 = *p*-CH_3, R^2 = H (**i**); R^1 = H, $R^2 = C_2H_5$ (**j**); R^1 = *p*-Cl, $R^2 = C_2H_5$ (**k**); R^1 = *m*-OH, $R^2 = C_2H_5$ (**l**); R^1 = *p*-$(CH_3)_2N$, $R^2 = C_2H_5$ (**m**); R^1 = *p*-CH_3O, $R^2 = C_2H_5$ (**n**).

RESULTS AND DISCUSSION

In the present study we report our results on the electrochemically induced multicomponent chain transformation of acyclic 1,3-diketones, aryl aldehydes, and malononitrile into 4*H*-pyrans under mild conditions by constant potential electrolysis in an undivided cell. The reaction was performed in alcoholic solvents with $LiClO_4$ as an electrolyte (Scheme 1).

For environmental and economic reasons, we have used a $LiClO_4$–EtOH pair in our present protocol. $LiClO_4$ as a supporting electrolyte offers a lot of advantages. It is highly soluble in many organic solvents, used as a co-catalyst in coupling reactions, and is can be easily recovered and reused in subsequent reactions. Ethanol as a solvent is preferable to MeOH and *n*-PrOH, because it readily dissolves both the reactants and electrolyte, and the reaction products are easy to isolate by directs filtration after electrolysis. The low chemical reactivity of EtOH makes it a popular choice in cyclic voltammetry. Further advantage of the $LiClO_4$–EtOH pair consists in its nontoxicity.

Table 1. Electrochemical transformation of aldehydes, malononitrile, and dicarbonyl compounds into 4*H*-pyrans under constant potential electrolysis conditions

Entry no.	Aldehyde no.	Dicarbonyl compound no.	Potential, V	Current density, mA/cm^2	Time, min	Product no.	Yield, %
1	**1a**	**3a**	1.85	21	200	**4a**	92
2	**1b**	**3a**	2.50	19	220	**4b**	86
3	**1c**	**3a**	2.65	17	210	**4c**	87
4	**1d**	**3a**	2.52	16	240	**4d**	89
5	**1e**	**3a**	2.40	19	215	**4e**	85
6	**1f**	**3a**	2.25	18	220	**4f**	88
7	**1g**	**3a**	2.30	19	225	**4g**	83
8	**1h**	**3a**	2.15	18	230	**4h**	86
9	**1i**	**3a**	2.42	19	210	**4i**	82
10	**1j**	**3b**	1.80	20	180	**4j**	90
11	**1k**	**3b**	2.20	19	195	**4k**	85
12	**1l**	**3b**	2.10	18	205	**4l**	86
13	**1m**	**3b**	2.10	19	220	**4m**	89
14	**1n**	**3b**	2.15	17	210	**4n**	84

Table 2. Choice of solvent for the electrochemical synthesis of 4*H*-pyrans for the model reaction of benzaldehyde, malononitrile, and acetylacetone

Entry no.	Solvent	Potential, V	Current density, mA/cm^2	Yield of **4a**, %
1	Ethanol	1.80	21	>90
2	Methanol	1.90	19	>85
3	Acetonitrile	2.00	9	>60
4	DMF	2.50	10	>50
5	AcOH	2.70	8.0	>40
6	DCM	3.0	5	>15
7	Dioxane	3.1	6	>15
8	THF	4.7	6	>12

To evaluate the synthetic potential of the proposed protocol, its scope and generality were examined with a variety of substrates (Scheme 1, Table 1) and optimized it for the synthesis of different 4*H*-pyrans.

The conversion of the starting materials into a series of products (Table 1) with excellent yields was performed under constant potential electrolysis conditions at the current density of 16–21 mA/cm^2 and the quantity of electricity of 0.48–0.71 F/mol. An increase in the potential and current density slightly decreased the reaction yield by activating the undesired oligomerisation of the starting materials.

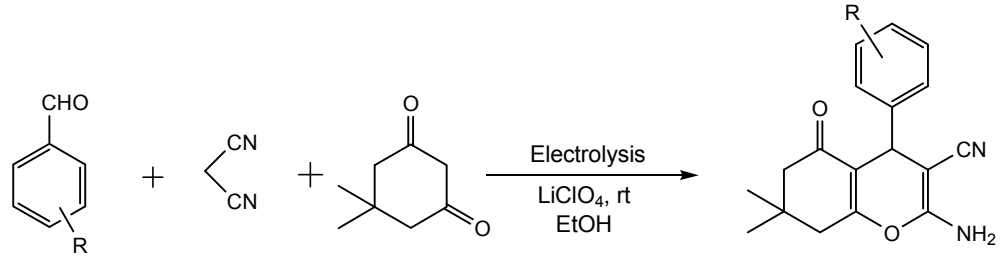
To find an appropriate medium for the synthesis of 4*H*-pyrans, we performed a model reaction between benzaldehyde (**1a**), malononitrile **2**, and acetylacetone **3a** to obtain 5-acetyl-2-amino-6-methyl-4-phenyl-4*H*-pyran-3-carbonitrile (**4a**) in different solvents at room temperature (Table 2). The highest yields of about 85–90% were obtained in ethanol, the reaction was complete within 3–4 h, and the precipitated product was easily separated by filtration.

Having optimized the solvent, we decided to check whether the developed protocol can be extended to the synthesis of 4*H*-benzo[*b*]pyrans using dimedone as an alternative methylene-active reagent instead of the linear acetylacetone (Scheme 2, Table 3). In accordance with our expectations, these reactions proceeded smoothly and afforded the corresponding products in good yields.

The purity of the products was checked by TLC, and their compositions and structures were characterized by analytical, physicochemical, and spectral (IR, ^{1}H and ^{13}C NMR and mass spectra) data. The melting points and spectral characteristics of known compounds are consistent with published data, and the characteristics of previously unknown compounds are presented in Experimental.

To gain insight into the mechanism of the reaction, we employed cyclic voltammetry. The cyclic voltammograms were measured for mixtures of substrates in EtOH–$LiClO_4$ at room temperature at a scan rate of at scan rate of 0.01 V s^{-1}.

Scheme 2.



1 **2** **4** **5a**–**5f**

R = H (**1a**, **5a**), *p*-Cl (**1b**, **5b**), *p*-OMe (**1e**, **5c**), *m*-NO_2 (**1h**, **5d**), *p*-OH (**1o**, **5e**), *p*-NO_2 (**1p**, **5f**).

Table 3. Electrochemical synthesis of 4*H*-benzo[*b*]pyrans by the three-component reaction of aldehydes, malononitrile, and dimedone

Entry no.	Aldehyde no.	Potential, V	Current density, mA/cm^2	Product no.	Yield, %
1	**1a**	1.80	24	**5a**	87
2	**1b**	2.05	22	**5b**	84
3	**1e**	2.10	18	**5c**	85
4	**1h**	2.00	20	**5d**	86
5	**1o**	2.08	19	**5e**	82
6	**1p**	2.15	20	**5f**	84

The cyclic voltammogram of a solution of benzaldehyde (**1a**), malononitrile **2**, and acetylacetone **3a** (1 mmol each) in EtOH–$LiClO_4$ exhibits two anodic peaks at 0.90 and 1.8 V and one reduction peak at 0.4 V. The anodic peaks correspond respectively to the transformation of malononitrile and dicarbonyl compound **3a** (methylene-active compounds) into *electrogenerated bases* (EGB) by removal of one electron, which is the key step of formation of product **4a**, and the reduction peak indicates the conversion of the ethoxide ion into ethanol during electrolysis (Fig. 1).

To obtain further evidence, we measured the cyclic voltammogram of a solution of 1-mmol aldehyde **1a** and 1 mmol of malononitrile in EtOH–$LiClO_4$. The voltammogram shows a well-defined anodic peak assignable to the formation of an EGB from malononitrile (Fig. 2).

The mechanism of formation of substituted 4*H*-pyrans is generally considered as two-step process involving the Knoevenagel condensation of arylaldehydes with malononitrile followed by addition of a dicarbonyl compound and cyclization [26]. The initial step of the reaction is the deprotonation of malononitrile to form the malononitrile anion (EGB). This anion undergoes Knovenagel condensation with aldehyde **A** to form benzylidenemalononitrile **B** with the elimination of a water molecule [27]. Further on dicarbonyl anion **C** (EGB) generated from the second methylene-active reagent (acetylacetone, ethyl acetoacetate, or methyl acetoacetate) reacts with intermediate **B** to form Michael adduct **D** whose intramolecular cyclization leads to the corresponding 4*H*-pyran **F** (Scheme 3).

EXPERIMENTAL

All arylaldehydes, malononitrile, dicarbonyl compounds, lithium perchlorate, ethanol, chloroform, and ethyl acetate were of analytical grade from Merck and Fluka. Water was double distilled.

The melting points were measured on a Mel_Temp capillary melting point apparatus and are uncorrected. The IR spectra were registered on a Shimadzu 8201 PC spectrometer in KBr pellets. The ^{1}H and ^{13}C NMR

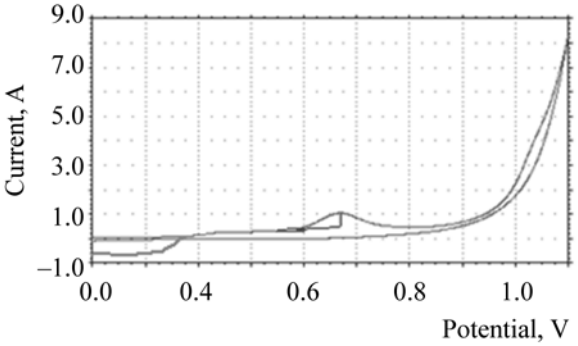


Fig. 1. Cyclic voltammogram of a solution of benzaldehyde, malononitrile, and acetylacetone in 0.05 M $LiClO_4$–EtOH.

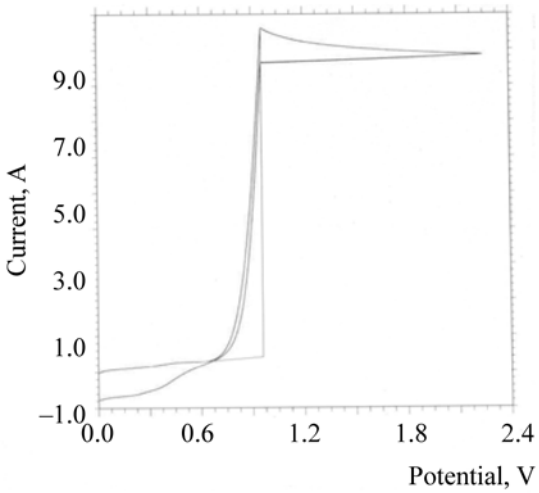
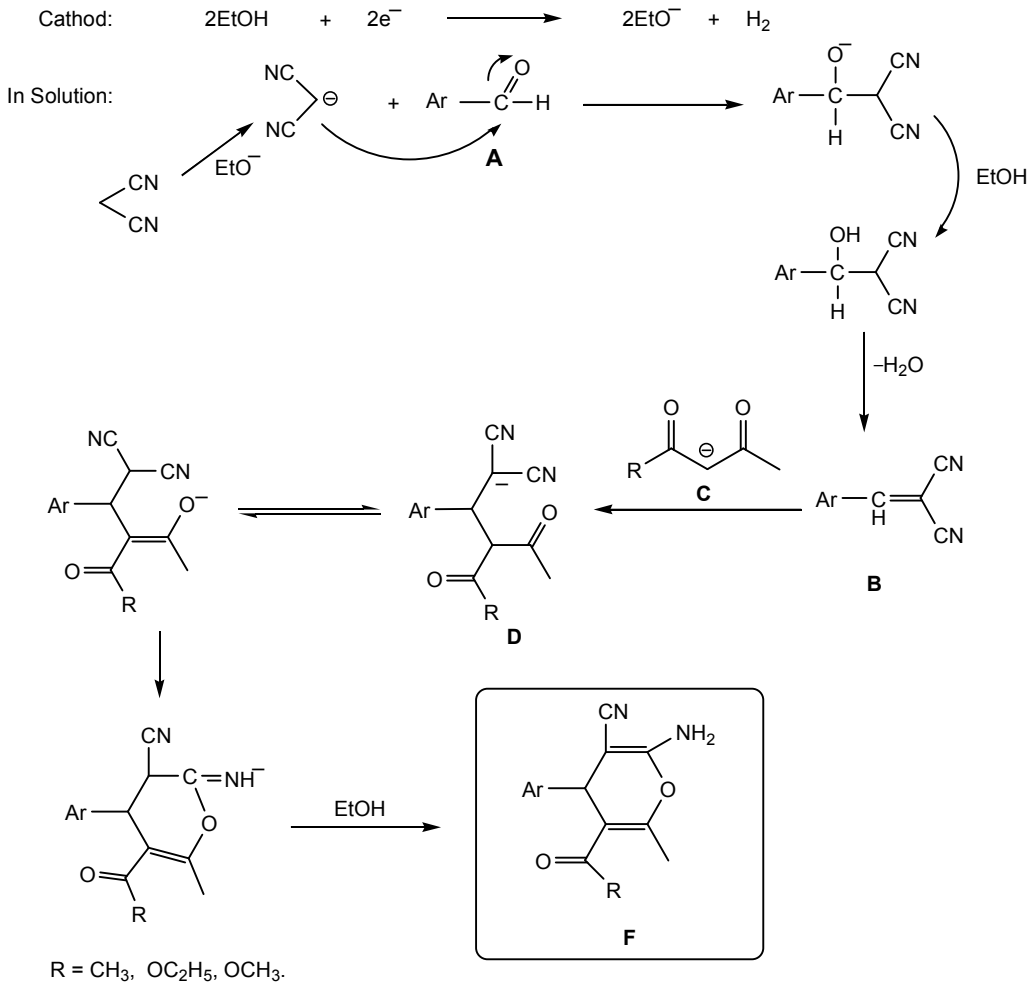


Fig. 2. Cyclic voltammogram of a solution of benzaldehyde and malononitrile in 0.05 M $LiClO_4$–EtOH.

Scheme 3.



spectra were measured with a DRX 400 (400 MHz) spectrometer in $CDCl_3$ or DMSO against internal TMS. The EI mass spectra were obtained with a Shimadzu GCMS-QP5050A instrument. The elemental analyses were obtained on a Carlo Erba CHNS-OEA 1108 elemental analyser.

Cyclic voltammetry was performed on a CH Instruments Model 600A electrochemical analyzer using a traditional three-electrode cell with a platinum working and counter electrode and an Ag/AgCl reference electrode.

Electrochemical synthesis of 4*H*-pyran derivatives (*general procedure*). A mixture of aldehyde (0.53 g, 5 mmol), malononitrile (0.33 g, 5 mmol), acetylacetone (or dimedone) (5 mmol), and $LiClO_4$ (0.40 g , 5mmol) in ethanol (50 mL) was electrolyzed under constant potential conditions (Table 1) [23, 24] at room temperature for 3–4 h in an undivided cell assembly with platinum plates (1 cm^2) as working and counter electrodes and Ag/AgCl as a reference electrode with magnetic stirring (for the applied potentials and current densities, see Tables 1–3. The reaction progress was monitored by TLC on silica as sorbent and hexane with ethyl acetate as eluent. After electrolysis was complete, the solid product was filtered off, washed with a cold aqueous ethanol (2 × 3 mL), and dried under reduced pressure to afford the corresponding 4*H*-pyran in an excellent yield. The purity of the products was checked by TLC, and their compositions and structures were characterized by analytical, physicochemical, and spectral data. The melting points and spectral characteristics of known compounds are consistent with published data, and the characteristics of previously unknown compounds are presented below.

5-Acetyl-2-amino-6-methyl-4-phenyl-4*H*-pyran-3-carbonitrile (4a), mp 195–197°C {published data: mp 193–195°C [28(b)]}.

5-Acetyl-2-amino-6-methyl-4-(4-chlorophenyl)-4*H*-pyran-3-carbonitrile (4b). $C_{15}H_{13}ClN_2O_2$, M.w. 288.73, mp 135–137°C. IR spectrum (KBr), ν, cm^{-1}: 1665 (C=O), 2194 (C≡N), 3333(NH_2). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.85 s (3H, CH_3), 2.12 s (3H, $COCH_3$), 4.25 s (1H, CH), 6.75 s (2H, NH_2), 6.90 d (2H, Ar), 7.14 d (2H, Ar). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 18.8, 29.6, 38.2, 57.5, 114.9, 120.2, 128.8, 129.4, 129.4, 130.2, 131.8, 143.7 155.3, 158.2, 198.5.

5-Acetyl-2-amino-6-methyl-4-(3-hydroxy-phenyl)-4*H*-pyran-3-carbonitrile (4c). $C_{15}H_{14}N_2O_3$. M.w. 270.28, mp 165–167°C. IR spectrum (KBr), ν, cm^{-1}: 1666 (C=O), 2196 (C≡N), 3337 (NH_2). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.85 s (3H, CH_3), 1.95 m (3H, CO–CH_3), 4.17 s (1H, CH), 6.35–6.40 m (3H, Ar), 6.67 s (2H, NH_2) 6.92 t (1H, Ar), 9.28 s (1H, Ph–OH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 18.8, 29.5, 39.7, 59.7, 114.9, 115, 115.9, 118.7, 120.8, 129.7, 146.5, 155.6, 157.8, 158.9, 198.8.

5-Acetyl-2-amino-4-[4-(dimethylamino)phenyl]-6-methyl-4*H*-pyran-3-carbonitrile (4d). $C_{17}H_{19}N_3O_2$. M.w. 297.35, mp 178–180°C. IR spectrum (KBr), ν, cm^{-1}: 1665 (C=O), 2199 (C≡N), 3339 (NH_2). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.71–1.78 s (6H, CH_3) 2.32 s (3H, –CO–CH_3), 2.85 m (3H, CH_3), 3.94 s (1H, CH), 6.47–6.88 m (4H, Ar), 6.82 s (2H, NH_2). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 18.3, 29.7, 38.6, 41.3, 57.7, 114.2, 114.5, 114.8, 117.7, 119.8, 130, 132.5, 146.5, 157.6, 158.2, 159.8, 198.4.

5-Acetyl-2-amino-4-(4-methoxyphenyl)-6-methyl-4*H*-pyran-3-carbonitrile (4e), mp 184–187°C {published data: mp 210–213°C [28(b)]}.

5-Acetyl-2-amino-4-(2-chlorophenyl)-6-methyl-4*H*-pyran-3-carbonitrile (4f). $C_{15}H_{13}ClN_2O$. M.w. 288.73, mp 203–205°C. IR spectrum (KBr), ν, cm^{-1}: 1693(C=O), 2202 (C≡N), 3339 (NH_2). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 2.01 s (3H, CH_3), 2.21 s (3H, CH_3), 4.93 s (1H, CH), 6.89 br.s (2H, NH_2), 7.14–7.16 m (1H, Ar), 7.21–7.23 m (1H, Ar), 7.27–7.29 m (1H, Ar), 7.37–7.39 m (1H, Ar). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 18.4, 29.9, 36.2, 58.1, 115.3, 119.3, 128.8, 129.2, 130.4, 132.2, 136.8, 143.7, 154.3, 159.3, 198.5.

5-Acetyl-2-amino-4-(2-methoxyphenyl)-6-methyl-4*H*-pyran-3-carbonitrile (4g). $C_{16}H_{16}N_2O_3$. M.w. 284.31, mp 190–192°C. IR spectrum (KBr), ν, cm^{-1}: 1690 (C=O), 2205 (C≡N), 3340 (NH_2). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.72 s (3H, CH_3), 2.30 s (3H, CO–CH_3), 3.73 s (3H, OCH_3), 4.95 s (1H, CH), 6.89 br.s (2H, NH_2), 6.65–6.66 m (2H, Ar), 6.95–6.96 m (2H, Ar). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 17.4, 29.9, 30.2, 57.2, 58.1, 115.2, 119.3, 120, 122.0, 122.4, 128.8, 130.4, 159.7, 154.3, 159.3, 198.5.

5-Acetyl-2-amino-6-methyl-4-(3-nitrophenyl)-4*H*-pyran-3-carbonitrile (4h), mp 168–170°C {published data: mp 161–162°C [28(b)]}.

5-Acetyl-2-amino-6-methyl-4-*p*-tolyl-4*H*-pyran-3-carbonitrile (4i), mp 190–192°C {published data: mp 274–276°C [28(b)]}.

Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate (4j), mp 197–199°C {published data: mp 194–196°C [28(a)]}.

Ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (4k), mp 178–180°C {published data: mp 173–174°C [28(a)]}.

Ethyl 6-amino-4-(3-hydroxyphenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (4l), mp 167–169°C {published data: mp 161–162°C [28(a)]}.

Ethyl 6-amino-4-(4-(dimethylamino)phenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (4m). $C_{18}H_{21}N_3O_3$. M.w. 327.38, mp 174–176°C. IR spectrum (KBr), ν, cm^{-1}: 1665 (C=O), 2199 (C≡N), 3339 (NH_2). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.08–1.12 m (6H, CH_3), 1.71 s (3H, CH_3), 3.82 s (1H, CH), 4.15 m (2H, CH_2), 4.94 s (2H, NH_2), 6.47–6.88 m (4H, Ar). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 16.4, 18.3, 38.6, 41.3, 41.5, 57.7, 63.1, 107.5, 114.8, 117.7, 119.8, 130, 130.2, 132.5, 146.5, 157.6, 158.2, 168.4.

Ethyl-6-amino-4-(4-methoxyphenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (4n), mp 180–182°C {published data: mp 135–136°C [28(a)]}.

2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-phenyl-4*H*-chromene-3-carbonitrile (5a), mp 235°C {published data: mp 230–232°C [25(a)]}.

2-Amino-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitrile (5b), mp 219°C {published data: mp 215–217°C [25(b)]}.

2-Amino-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbo-

nitrile (5c), mp 199°C {published data: mp 200–203°C [28(b)]}.

2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-4*H*-chromene-3-carbonitrile (5d), mp 220°C {published data: mp 215–217°C [25(b)]}.

2-Amino-5,6,7,8-tetrahydro-4-(4-hydroxy-phenyl)-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitrile (5e), mp 210°C {published data: mp 206–208°C [25(b)]}.

2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-4-phenyl-4*H*-chromene-3-carbonitrile (5f), mp 185°C {published data: mp 186–188°C [25(a)]}.

CONCLUSION

In summary, we have developed a simple, mild, green, and sustainable synthesis of a series of biologically and pharmacologically important 4*H*-pyran derivatives. This novel electrocatalytic chain process offers an efficient and convenient way to produce 4*H*-pyran derivatives in excellent yields. The notable highlights of this protocol are operational simplicity, wide substrate scope, excellent functional group tolerance, environmental safety, mild reaction conditions, easy workup, high yields, short reaction time, and easy handling. The developed methodology represents a novel synthetic concept for multicomponent reactions and brings us a step closer to the notation of "ideal synthesis" [6, 28].

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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