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Electrocatalytic multicomponent assembling of aldehydes, dimedone and 1-naphthylamine for synthesis of novel tetrahydrobenzo[c]acridin-8(7H)-one derivatives

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Abstract

An efficient and convenient synthesis of novel tetrahydrobenzo[c]acridin-8(7H)-one derivatives is described using the electrogenerated anion of acetonitriles as the base in the presence of tetrabutylammonium fluoride as an effective supporting electrolyte in a one-pot, three-component condensation of aromatic aldehyde, dimedone and 1-naphthyl amine. The reaction carried out in an undivided cell containing an iron cathode and a graphite anode under a constant current density of 5 mA/cm^2 (I=20 mA, electrode surface=5 cm^2) in CH_3CN at room temperature was found to be optimum for the electrochemically induced chain process and resulted in the highest yield.

Keywords: Electrolysis transformation; electrogenerated base; multicomponent reaction; acridine; dimedone; 1-naphthyl amine.

Introduction

The acridine derivatives have been known first to be used as pigments and dyes since the 19th century [1]. A range of acridines continue to be used today for the treatment of actuelekaemia (amsacrine) [2], as anticancer agents (ledakrin) [3]. For hundreds years, leishmaniase have been the cause of death among millions of people throughout the world. Newly synthesized 4,5-disubstitued acridines were assessed for in vitro antileishmanial activities as compared to those of their 4-mono-substituted homologs [4]. Due to the planar ring systems of naphthalimide derivatives, in recent years, both their DNA intercalative and anti-tumor abilities have been studied widely [5]. Brana's group made great efforts on studying heterocycle-fused naphthalimide derivatives to improve their topoisomerase I inhibitory and anti-tumor abilities [6,7] (Figure 1).

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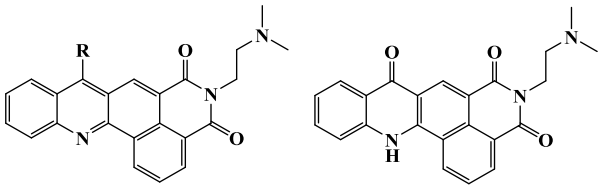
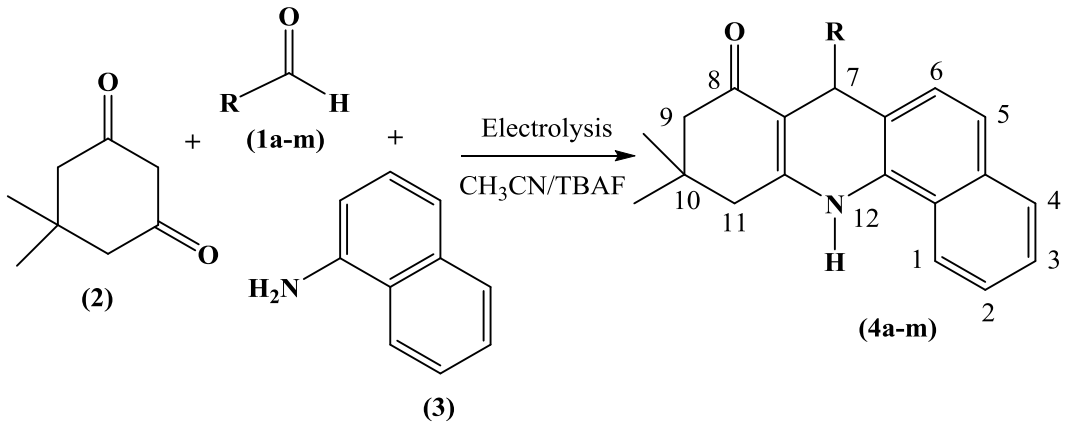


R:Cl, SCH_2CH_3, $HN(CH_2CH_2)NCH_3$, H

Figure 1. The structures of isoquino[4,5-bc]acridine derivatives as anti-tumor

A number of methods have been developed for the synthesis of acridin compound containing 1,4-dihydropyridines, from dimedone, aldehydes and different anilines or ammonium acetate *via* traditional inorganic solvents [8], in water catalyzed by TEBAC [9], under microwave irradiation [10], using L-Proline [11], and by the condensation of appropriate aldehyde, 1-naphthylamine and dimedone using the ultrasound-promoted method [12,13]. However, many of these methods suffer from drawbacks such as the use of hazardous organic solvents, long reaction time and low-yields. Therefore, the development of a mild generalized method to overcome these shortcomings still remains an ongoing challenge for the synthesis of tetrahydrobenzo[c]acridin-8(7*H*)-one derivatives. To the best of our knowledge, there are no report on electrocatalytic transformation of 4-nitrobenzaldehyde, dimedone and 1-naphthylamin to tetrahydrobenzo[c]acridin-8(7*H*)-ones at room temperature. Therefore, in this research, we wish to report the electrocatalytic chain procedure for the preparation of these compounds in the environmentally-friend reactor (without catalyst) *via* electrolysis of three-component mixture in the undivided electrochemically cell at room temperature (Scheme 1).



R: C_6H_5, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 2-OHC_6H_4, 4-OHC_6H_4, 4-ClC_6H_4, 2-ClC_6H_4, 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 4-FC_6H_4, 2-FC_6H_4, 4-$CF_3C_6H_4$, 4-$N(CH_3)_2C_6H_4$, 4-BrC_6H_4

Scheme 1. Synthesis of 10,10-dimethyl-7-aryl-9,10,11,12-tetrahydrobenzo[c]acridin-8(7H)-one (**4a-m**) catalyzed by an electrogenerated base

Experimental

General

Chemicals were purchased from Merck, Fluka and used without further purification. The NMR spectra were recorded on a Bruker Avance DEX500 MHz instrument. The spectra were measured in DMSO-d6 relative to TMS as the internal standard. Mass spectra were recorded on a VG micromass

7070H and Finnigan mat 1020B mass spectrometers operating at 70 eV. Elemental analyses were performed on Yanco-CHN CORDER elementary analyzer. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer from KBr pelletes. All reagents were purchased from Merck and Aldrich and were used without further purification. Analytical TLC was performed on DC-Alufolien Silica gel $60F_{254}$ Merck. All yields refer to isolated products after purification.

Typical electrolysis procedure

A solution of appropriate arylaldehydes (2 mmol), dimedone (2 mmol) and 1-naphthylamine (2 mmol) and tetrabutyl ammonium fluoride (TBAF) (0.1 mmol) in CH_3CN (20 mL) was electrolyzed in an undivided cell with a magnetic stirrer, an iron cathode and graphite anode at room temperature under a constant current of 5 $mAcm^{-2}$ (I=25 mA, electrodes aquare 5 cm^2) until the catalytic quantity of electricity was paased. The solid product separated was filtered and washed with cold ethanol to obtain the pure products.

Spectroscopic data for selected examples are shown below:

10,10-Dimethyl-7-(4-nitrophenyl)-9,10,11,12-tetrahydrobenzo[c]acridin-8(7H)-one (4g)

0.378 g (95%); Yellow solid; mp 280–282 °C. IR (KBr): 3306, 3065, 2897, 1643, 1567 (C = O), 1512, 1421, 1142, 819 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ(ppm) 1.18 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.08–2.34 (dd, 2H, C9-H), 2.56–2.83 (dd, 2H, C11-H), 5.89 (s, 1H, C7-H), 7.18–7.98 (m, 9H, Ar-H), 8.74 (d, 1H, *J* = 8.0, C6-H), 9.67 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ(ppm) 27.21, 29.33, 31.43, 33.43, 42.49, 52.55, 66.54, 74.88, 88.76, 106.88, 117.43, 121.33, 122.21, 123.30, 124.21, 126.10, 129.11, 129.43, 129.42, 131.34, 133.54, 147.21, 153.65, 157.87, 196.33. MS (EI), m/z (%) = 398 (M+, 70), 196 (94). Anal Calcd for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03. Found: C, 75.30; H, 5.87; N, 7.21.

7-(4-Fluorophenyl)-10,10-dimethyl-9,10,11,12-tetrahydrobenzo[c]acridin-8(7H)-one (4i)

0.352 g (95%); White solid; mp 218–219 °C. IR (KBr): 3315, 3069, 2973, 1640, 1531 (C = O), 1514, 1439, 1125, 836 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ(ppm) 1.10 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 2.08–2.34 (dd, 2H, C9-H), 2.45–2.81 (dd, 2H, C11-H), 5.92 (s, 1H, C7-H), 7.11–7.89 (m, 9H, Ar-H), 8.62 (d, 1H, *J* = 7.5, C6-H), 9.61 (s, 1H, NH); ^{13}C NMR (DMSO- d_6, 125 MHz): δ(ppm) 27.32, 31.03, 33.04, 37.23, 44.92, 58.41, 69.29, 78.44, 89.70, 119.02, 120.44, 120.89, 123.07, 124.26, 125.04, 125.89, 129.12, 129.54, 131.07, 133.52, 139.54, 149.43, 157.56, 159.42, 198.98. ^{19}F NMR (DMSO- d_6, 470 MHz): δ 60.09. MS (EI), m/z (%) = 371 (M+, 70), 276 (92). Anal Calcd for $C_{25}H_{22}FNO$: C, 80.84; H, 5.97; N, 3.77. Found: C, 80.42; H, 6.05; N, 3.73.

Results and discussion

To find out the suitable conditions for the reaction, a series of experiments were performed with the standard reaction of 4-nitrobenzaldehyde (**1g**), dimedone (**2**), 1-naphthylamin (**3**) as a model reaction in CH_3CN, in an undivided cell containing an iron electrode as the cathode and a graphitr as the anode at comstant current in the presence of various electrolytes at room temperature (Table 1). We found that, when the electrolysis was supported by KBr, NaBr, and NaF as the eclectrlyte, the yield of (**4g**) was not satisfacrory (Table 1, Entries 1-3). In contrast,

electrolysis in the presence of tetrabutylammonium hydroxide (TBAOH), tetrabutylammonium bromide (TBAB), and tetrabutylammonium chloride (TBAC) as the supporting electrolye, gave the product (**4g**) in good yields (Table 1, Entries 4-6). However, improved results were obtained when the reaction was carried out in the presence of tetrabutylammonium fluoride (TBAF) as the electrolyte (Table 1, Entries 4-7). The effect of current density was examined, and the results are summarized in Table 1; it could be seen that excellent conversions of the strating compounds obtained after 0.15 $Fmol^{-1}$ of electricity had been passed. A current density of 5 $mAcm^{-2}$ (*I*=25 mA, electrode surface=5 cm^2) in CH_3CN at room temperature was found to be optimum for the electrochemically induced chain process and resulted in the highest yield (90%) of (**4g**). An increase of the current density up to 6, 10, 15 and 20 $mAcm^{-2}$ (*I*=30, 50, 75 and 100 mA) rsulted in a slight decrease of the yields, which may be connected with the activation of potential undesired direct electrochemical processes under these conditions leading to oligomerization of the starting material (Table 1, Entries 9-12).

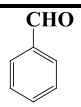
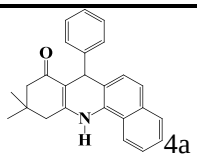
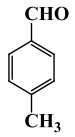
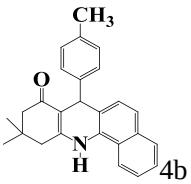
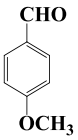
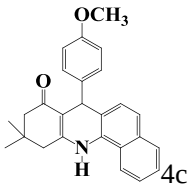
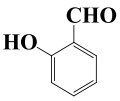
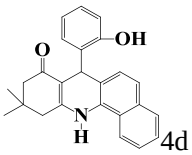
Table 1. Electrocatalytic transformation of 4-nitrobenzaldehyde (**1g**), dimedone (**2**) and 1-naphthyl amine (**3**) into **4g**[a]

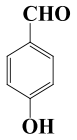
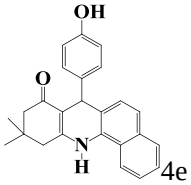
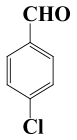
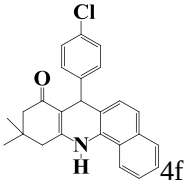
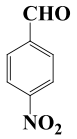
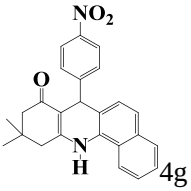
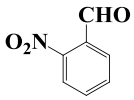
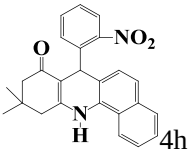
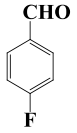
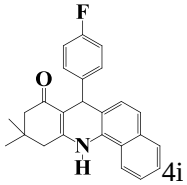
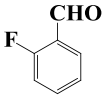
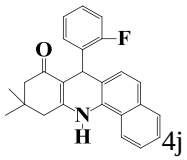
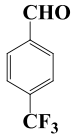
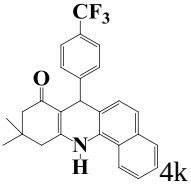
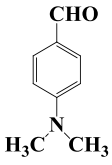
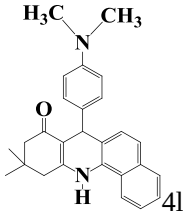
Entry	Electrolyte	I (mA)	Current density (mA/cm^2	Electricity passed (F/mol)	Time (min)	Yield (%)[b]
1	NaBr	25	5	0.15	20	35
2	KBr	25	5	0.15	20	30
3	NaF	25	5	0.15	20	46
4	TBAOH	25	5	0.15	20	65
5	TBAB	25	5	0.15	20	75
6	TBAC	25	5	0.15	20	75
7	TBAF	25	5	0.15	20	90
8	TBAF	10	2	0.06	20	80
9	TBAF	30	6	0.18	20	86
10	TBAF	50	10	0.62	40	84
11	TBAF	75	15	0.35	15	82
12	TBAF	100	20	0.31	10	80

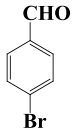
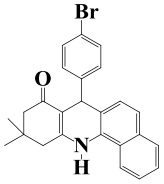
[a]Reaction conditions: 4-nitrobenzaldehyde (2 mmol), dimedone (2 mmol), 1-naphthylamin (2 mmol), CH_3CN (20 mL), TBAF (0.1 mmol), Fe cathode (5cm^2), graphite anode (5 cm^2), room temperature
[b]Isolated yields

Using the optimized conditions, we also probed the scope and, generally, the reaction of several aryl aldehydes with dimedone and 1-naphthylamine for synthesis of 10,10-dimethyl-7-aryl-9,10,11,12-tetrahydrobenzo[c]acridin-8(7H)-one derivatives (Table 2, **4a-m**). As shown in Table 2, products were obtained in excellent yields. It was found that aromatic aldehydes both with electron withdrawing and donating groups in reaction with other atarting materials have excellent isolated yield. In all the reactions, at the beginning of electrolysis, a brown solution was obtained rapidly, which indicated that the reactions had commenced; TLC results showed that the corresponding tetrahydrobenzo[c]acridin-8(7H)-ones (**4a-m**) were obtained within 10-55 min (Table 2). Notably, in examining their synthetic performance, it has been shown that this method is capable of promoting organic synthesis of 10,10-dimethyl-7-aryl-9,10,11,12-tetrahydrobenzo[c]acridin-8(7H)-ones (**4a-m**) in an environmentally friendly condition.

Table 2. Electrocatalytic transformation of 10,10-dimethyl-7-aryl-9,10,11,12-tetrahydrobenzo[c]acridin-8(7H)-one[a]

Entry	Carbonyl compound	Product	Time (min)	Electricity passed (Fmol^{-1})	Yield (%)[b]	Mp (°C)	
						Found	Reported
1		 4a	40	0.31	80	257-258	258-259 [14, 15]
2		 4b	55	0.43	75	210-211	212-214 [11]
3		 4c	50	0.39	73	205-206	206-207 [11]
4		 4d	45	0.35	71	221-223	220-222 [13]

5		 4e	40	0.32	73	276-277	278-280 [12]
5		 4f	35	0.27	78	263-264	264-266 [9]
6		 4g	20	0.15	90	280-282	281-283 [13]
7		 4h	25	0.19	88	227-228	228-229 [11]
8		 4i	10	0.08	85	217-218	218-219 [11]
9		 4j	15	0.12	83	230-231	231-233 [11]
10		 4k	10	0.08	85	275-276	276-277 [11]
11		 4l	35	0.27	75	274-275	275-277 [9]

12		 4m	40	0.31	76	282-284	280-282 [9]

[a]Reaction conditions: 4-nitrobenzaldehyde (2 mmol), dimedone (2 mmol), 1-naphthylamin (2 mmol), CH_3CN (20 mL), TBAF (0.1 mmol), Fe cathode ($5cm^2$), graphite anode ($5\ cm^2$), current density=5 $mAcm^{-2}$, room temperature
[b]Isolated yields

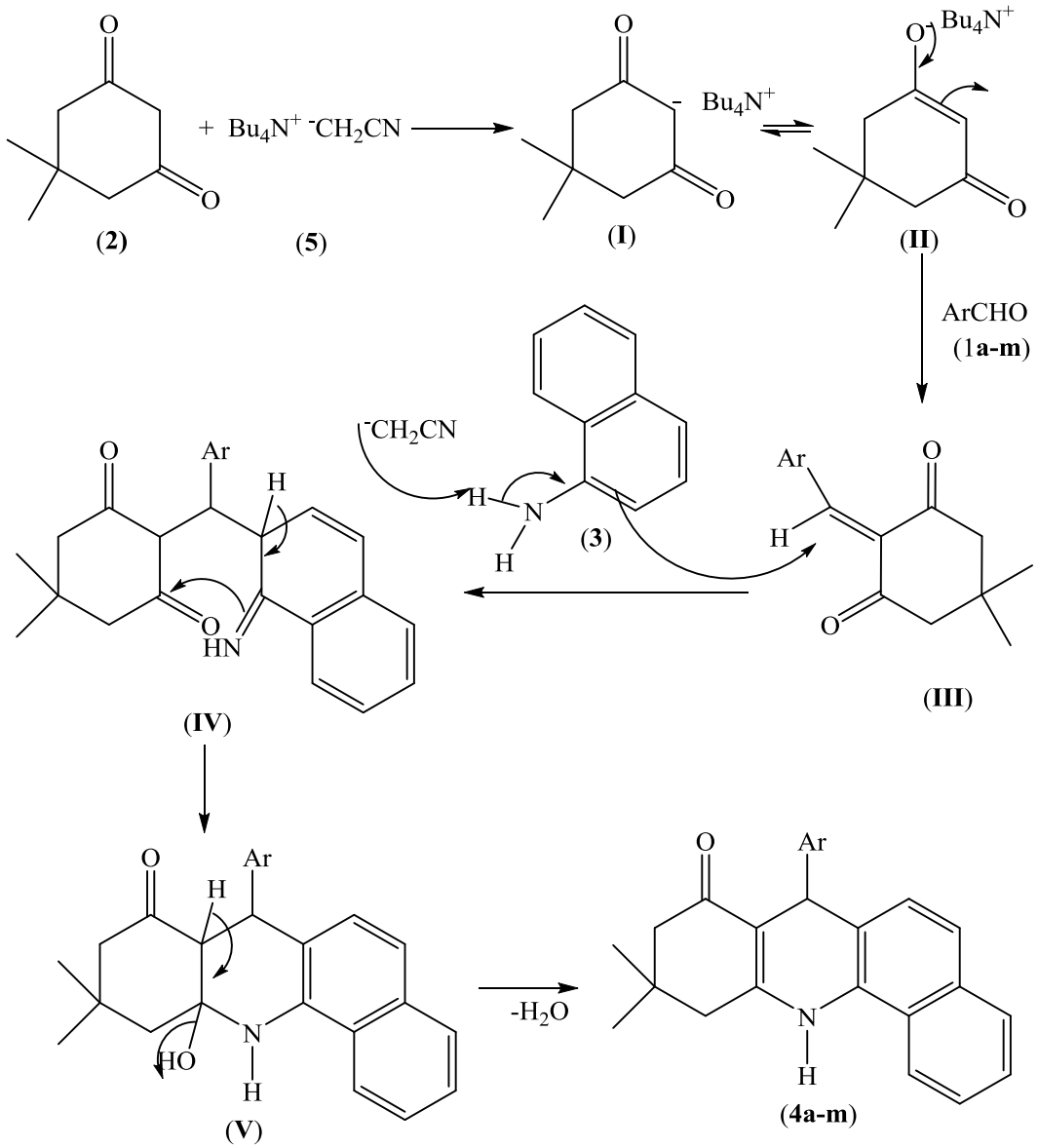
Taking into consideration the above results, the following mechanism for this electrocatalytic chain transformation is proposed. As the initition step, deprotonation of CH_3CN at the cathode leads to the formation of cyanomethyl anion (**5**). The subsequent reaction in solution between (**5**) and dimedone (**2**) gives rise to the enolate anion (**I**) and (**II**). Next, Knovenagel condensation of (**II**) with the aromatic aldehydes (**2a-m**) takes place in the solution with the elimination of one water molecule and formation of 2-arylidene -5,5-dimethylcyclohexane-1,3-dione (**III**). The subsequent cyanomethyl anion promoted Micjael addition of 1-naphthylamine (3) to electron-deficient Knovenagel adduct (**III**) followed by intramolecular cyclization leads to the corresponding 10,10-dimethyl-7-aryl-9,10,11,12-tetrahydrobenzo[c]acridin-8(7H)-one derivatives (**4a-m**) (Scheme 2).

Anode: $2F^- \longrightarrow F_2 + 2e^-$

Cathode: $2CH_3CN/Bu_4NF + 2e^- \longrightarrow 2Bu_4N^+ {}^-CH_2CN + 2F^- + H_2$

(5)

in solution:



Scheme 2. Proposed mechanism for the syntheis of 10,10-dimethyl-7-aryl-9,10,11,12-tetrahydrobenzo[c]acridin-8(7*H*)-on (**4a-m**) catalyzed by an electrogenerated base in CH_3CN and TBAF as electrolyte at room temperature

Conclusion

In conclusion, we have developed an efficient green procedure for the one-pot synthesis of 10,10-dimethyl-7-aryl-9,10,11,12-tetrahydrobenzo[c]acridin-8(7*H*)-one derivatives *via* electrolytic transformation of aryl aldehydes, dimedone and 1-naphthylamine at room temperature. The structures of all the products were confirmed by FT-IR,

^{1}H, and ^{13}C NMR spectroscopy and by elemental analysis. The very short reaction time, high yields, simple workup and the non-chromatographic purification of products will make the present merthod an important addition to the available methodologies for synthesis of the products.

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