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A GREEN ELECTROCHEMICAL APPROACH FOR SYNTHESIS OF OXA-BICYCLOCARBAZOLE-1,3-DIONE DERIVATIVES

Narendra Kumar, Laxmi Kant Sharma, Abhishek Upadhayay, Rahul Dubey, R. K. P. Singh*

Electrochemical Laboratory of Green Synthesis,
Department of Chemistry, University of Allahabad, 211002 India.
Email: rkp.singh@rediffmail.com, (R. K. P. Singh); Tel :+91 9335179483

Abstract: A novel one-pot synthesis of oxa-bicyclocarbazole-1,3-dione derivative by electro-induced condensation of various carbazole and maleic anhydride is reported under constant current density in the presence of Bu_4NClO_4 as electrolyte . Clean synthesis, atom economy, mild reaction conditions are some features of this protocol.

Keywords: Maleic anhydride, Green chemistry, Platinum electrode, Addition reaction, Electroorganic synthesis

Introduction

Electrochemical reactions have been recently recognised as a powerful assets in synthetic organic chemistry[i]. Electroorganic synthesis plays an important role in green chemistry and provides many advantages over conventional methods[ii, iii]. The synthesized compounds have a wide range of pharmaceutical and biological activity including anti-inflammatory[iv], antimicrobial[v], antimalarial[vi], antifungal[vii], muscle relaxant[viii], anticancer[ix], analgesic[x], anti-HIV[xi], antitubercular[xii], anticonvulsant[xiii], antiproliferative[xiv], insecticidal[xv], antiparasitic[xvi], antiviral[xvii], antihypoglycemic[xviii], hypotensive[xix], muscarinic receptor agonist[xx], and photosensitisers[xxi]. These compounds were also used in organic light-emitting diodes (OLEDs) [xxii].

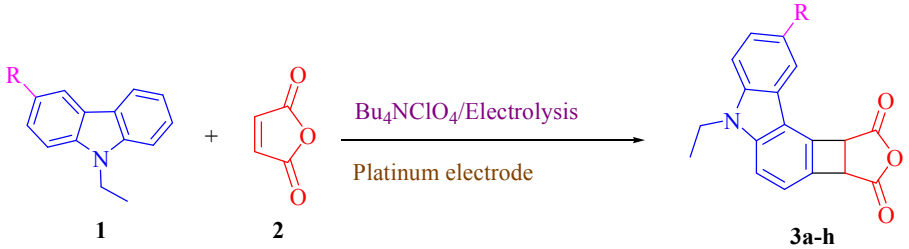
The synthesis of oxa-bicyclocarbazole-1,3-dione derivatives as oxazolocarbazolequinone, tetracyclocarbazoles, pyridocarbazoles, imidazocarbazoles, furocarbazoles and substituted carbazoles have been explored expansively in recent years. Various methods such as microwave synthesis[xxiii], spectroscopic fluorescent probe[xxiv], cationic photopolymerization[xxv], sensitivity of probes[xxvi], palladium-catalyzed oxidative coupling[xxvii], nickel catalyzed cross coupling[xxviii], have been reported. Conventional method have various drawback such as harsh reaction condition, difficult isolation, low yield and use of toxic organic solvents stimulated our interest to develop milder and simple approach. With increasing public concern over environmental degradation, the

principles of green route that chemical transformations should be designed to minimize energy input, use and formation of toxic chemicals.

The discovery of carbazoles leads to the improvement of medicinally important compounds with wide range of biological activities. As a part of our ongoing efforts towards synthesis of medicinally important compound, we developed a convenient and environmentally benign synthetic methodology. In the present work, we intend to demonstrate the electrochemical synthesis of medicinal compounds, which offer inexpensive, biodegradable, cost effective and excellent yield in an undivided cell at 30 °C under a constant current. In electrochemistry, electron serve as sole reagent hence there is no need of acid, base or catalyst. Electro-synthesis have many advantages as atom economy, decreased energy requirements and waste production in mild reaction condition. It has ability to perform a wide range of precisely tuned oxidation and reduction reaction.

The present work lead to the improvement of a facile and environmentally benign strategy for the synthesis of some oxa-bicyclocarbazole-1,3-dione derivatives in CH_3CN as solvent, TBAP, $LiClO_4$, $NaClO_4$ and Bu_4BrN as supporting electrolyte and small amount of current was used as non-polluting reagent.

Our initial experiments were focused on the electrochemical synthesis of carbazoles **1** and maleic anhydride **2** as a simple model substrate using different solvents, electrolytes and applied potential[xxix], the results are listed in table 1 and table 2.



R = H, CH_3, OCH_3, CH_2CH_3, Ph, OPh, OCH_2CH_3, NO_2

Scheme 1. Electroorganic synthesis for oxa-bicyclocarbazole-1,3dione derivatives.

EXPERIMENTAL SECTION

Chemicals and apparatus

All chemicals were reagent grade and purchased from Aldrich, Alfa Aesar, Merck, Spectrochem and Qualigens and were used without further purification. The reactions were monitored using pre-coated Aluminium TLC plates of silica gel G/UV-254 of 0.25 mm thickness (Merck 60 F-254). NMR spectra were recorded on a Bruker Avance-II 400FT spectrometer at 400 MHz (1H) and 100 MHz (^{13}C) in DMSO or $CDCl_3$ using TMS as an internal reference. Mass spectra (EIMS) were obtained on a Waters UPLC-TQD mass spectrometer. IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer. Elemental analyses were carried out in a Thermo Scientific (FLASH 2000) CHN Elemental Analyser.

General experimental procedure

A solution of Bu_4NClO_4 (0.8 mmol) in DCM (25 mL) containing carbazole derivatives (2.0 mmol) and maleic anhydride (2.0 mmol) was stirred and electrolyzed in an undivided cell equipped with platinum plates as anode and cathode at room temperature under a constant potential. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction (180–225 min.), the solvent was evaporated under reduced pressure,

reaction mixture was added with water (10 mL) and extracted with chloroform (3 × 5 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. Finally the resulting crude product was purified by recrystallization from EtOH to furnish the desired product. All the compounds were characterized by spectral data with those reported in the literature.

6-ethyl-3-aH-3-oxa-bicyclo[3.2.0]hept-6-eno[6,7-c]carbazole-1,3(6H,10dH)-dione (3a)

^{1}H NMR (400 MHz, DMSO): δ 1.49 (t, 3H), 3.84 (q, 2H), 4.65 (d, 2H), 6.92 (d, 1H), 7.01 (d, 1H), 7.04 (d, 1H), 7.10 (m, 1H), 7.39 (d, 1H), 7.40 (m, 3H), 7.56 (d, 1H). ^{13}C NMR (100 MHz, DMSO): δ 15.6, 35.7, 38.5, 49.0, 106.2, 110.2, 111.2, 119.0, 119.4, 120.2, 122.3, 125.0, 128.4, 129.6, 135.8, 136.1, 168.0. IR (KBr, cm^{-1}): 752, 1085, 1128, 1230, 1453, 1595, 1778, 1896, 1929, 2215, 2314, 2851, 2979, 3051; EIMS: (m/z): 291.02 (M^+), Anal. calcd. for $C_{18}H_{13}NO_3$: C; 74.22, H; 4.50, N; 4.81, O; 16.48; found C; 74.20, H; 4.47, N; 4.82, O; 16.50.

6-ethyl-9-methyl-1-3aH-3-oxa-bicyclo[3.2.0]hept-6-eno[6,7-c]carbazole-1,3(6H,10dH)-dione (3b)

^{1}H NMR (400 MHz, DMSO): δ 1.50 (t, 3H), 2.36 (s, 3H), 3.87 (q, 2H), 4.68 (d, 2H), 6.89 (m, 1H), 6.94 (d, 1H), 6.98, (d, 1H), 7.28 (d, 1H), 7.35 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ 15.6, 25.0, 35.8, 38.6, 48.3, 106.2, 110.4, 111.0, 118.5, 119.5, 120.2, 125.2, 128.8, 129.3, 135.8, 136.3, 168.0. IR (KBr, cm^{-1}): 752, 1019, 1085, 1128, 1450, 1595, 1680, 1778, 1896, 1929, 2240, 2314, 2850, 3051; EIMS: (m/z): 305.10 (M^+), Anal. calcd. for $C_{19}H_{15}NO_3$: C; 74.74, H; 4.95, N; 4.95; O; 15.72; found C; 75.01, H; 4.93, N; 4.60, O; 15.73.

6-ethyl-9-methoxy-3-aH-3-oxa-bicyclo[3.2.0]hept-6-eno[6,7-c]carbazole-1,3(6H,10dH)-dione (3c)

^{1}H NMR (400 MHz, DMSO): δ 1.50 (t, 3H), 3.76 (s, 3H), 3.89 (q, 2H), 4.68 (d, 2H), 6.58 (m, 1H), 6.94 (d, 1H), 6.98 (d, 1H), 7.28 (d, 1H), 7.35 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 15.8, 35.7, 38.7, 48.2, 60.0, 102.0, 106.2, 109.6, 110.4, 112.2, 120.0, 125.10, 128.50, 129.60, 136.0, 155.60, 168.0. IR (KBr, cm^{-1}): 730, 1020, 1085, 1151, 1450, 1595, 1680, 1778, 1896, 1929, 2240, 2314, 2850, 3065; EIMS: (m/z): 321 (M+), Anal. calcd. for $C_{19}H_{15}NO_4$: C; 71.02, H; 4.71, N; 4.36, O; 19.92 found C; 71.00, H; 4.70, N; 4.38, O; 19.90.

6-ethyl-9-phenyl-3aH-3-oxa-bicyclo[3.2.0]hept-6-eno[6,7-c]carbazole-1,3(6H,10dH)-dione (3d)

^{1}H NMR (400 MHz, DMSO): δ 1.52 (t, 3H), 3.89 (q, 2H), 4.66 (d, 2H), 6.97 (d, 1H), 6.99 (d, 1H), 7.22 (m, 1H), 7.28 (d, 1H), 7.33 (m, 2H), 7.45 (d, 1H), 7.49 (d, 2H), 7.80 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 35.7, 38.6, 48.3, 106.1, 110.2, 111.8, 117.2, 119.5, 119.7, 125.3, 127.8, 127.9, 128.5, 129.4, 129.8, 135.8, 136.7, 136.8, 143.8, 168.0. IR (KBr, cm^{-1}): 752, 1085, 1151, 1450, 1595, 1680, 1778, 1896, 1929, 2250, 2891, 2933, 3051; EIMS: (m/z): 354 (M+), Anal. calcd for $C_{23}H_{16}NO_3$: C; 77.95, H; 4.55, N; 3.95, O; 13.54; found C; 77.93, H; 4.56, N; 3.98, O; 13.55.

6,9-diethyl-3aH-3-oxa-bicyclo[3.2.0]hept-6-eno[6,7-c]carbazole-1,3(6H,10dH)-dione (3e)

^{1}H NMR (400 MHz, DMSO): δ 1.25 (t, 3H), 1.52 (t, 3H), 2.60 (q, 2H), 3.89 (q, 2H), 4.67 (d, 2H), 6.90, (d, 1H), 6.95 (d, 1H), 6.99 (d, 1H), 7.32 (d, 1H), 7.40 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 14.5, 15.7, 32.8, 35.7, 38.7, 48.3, 106.0, 110.2, 111.1, 117.2, 119.0, 119.7, 125.3, 128.5, 130.0, 130.4, 135.8, 136.2, 168.0; IR (KBr, cm^{-1}): 724, 1085, 1152, 1450, 1595, 1680, 1778, 1896, 1929, 2227, 2870, 3050; EIMS: (m/z): 319 (M+), Anal. calcd. for $C_{20}H_{17}NO_3$: C; 75.22, H; 5.37, N; 4.39, O; 15.03; found C; 75.02, H; 5.35, N; 4.38, O; 15.10.

6-ethyl-9-phenoxy-3aH-3-oxa-bicyclo[3.2.0]hept-6-eno[6,7-c]carbazole-1,3(6H,10dH)-dione (3f)

^{1}H NMR (400 MHz, DMSO): δ 1.51 (t, 3H), 3.87 (q, 2H), 4.67 (d, 2H), 6.75 (d, 1H), 6.92 (d, 2H), 6.94 (d, 1H), 6.98 (d, 1H), 7.10 (m, 1H), 7.20 (s, 1H), 7.22 (m, 2H), 7.38 (d, 1H); ^{13}C NMR (100 MHz, DMSO): δ 15.7, 35.6, 38.8, 48.4, 105.3, 106.2, 110.5, 110.8, 112.7, 117.6, 119.4, 122.0, 125.1, 128.5, 128.7, 135.8, 136.2, 149.2, 157.0, 168.0; IR (KBr, cm^{-1}): 722, 1085, 1151, 1470, 1595, 1680, 1778, 1896, 1929, 2260, 2875, 3051; EIMS: (m/z): 383 (M+), Anal. calcd. for $C_{24}H_{17}NO_4$: C; 75.19, H; 4.47, N; 3.65, O; 16.69; found C; 75.20, H; 4.50, N; 3.67, O; 16.65.

6-ethyl-9-nitro-3aH-3-oxa-bicyclo[3.2.0]hept-6-eno[6,7-c]carbazole-1,3(6H,10dH)-dione (3g)

^{1}H NMR (400 MHz, DMSO): δ 1.52 (t, 3H), 3.85 (q, 2H), 4.67 (d, 2H), 6.92 (d, 1H), 7.00 (d, 1H), 7.65 (d, 1H), 8.10 (d, 1H), 8.49 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ 15.7, 35.5, 38.7, 48.1, 106.2, 110.2, 112.0, 114.5, 115.6, 119.8, 125.2, 128.3, 129.6, 135.8, 136.2, 141.5, 168.0; IR (KBr, cm^{-1}): 753, 1085, 1290, 1350, 1465, 1550, 1595, 1680, 1778, 1896, 1929, 2245, 2875, 3060; EIMS: (m/z): 336 (M+), Anal. calcd. for $C_{18}H_{12}N_2O_5$: C; 64.29, H; 3.60, N; 8.33, O; 23.79; found C; 64.26, H; 3.57, N; 8.32, O; 23.80.

9-ethoxy-6-ethyl-3aH-3-oxa-bicyclo[3.2.0]hept-6-eno[6,7-c]carbazole-1,3(6H,10dH)-dione (3h)

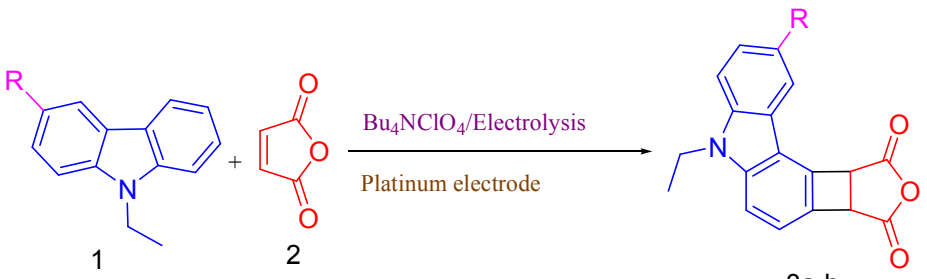
^{1}H NMR (400 MHz, DMSO): δ 1.33 (t, 3H), 1.48 (t, 3H), 3.90 (q, 2H), 3.98 (q, 2H), 4.68 (d, 2H), 6.59 (d, 1H), 6.95 (d, 1H), 6.98 (d, 1H), 7.08 (s, 1H), 7.29 (d, 1H); ^{13}C NMR (100 MHz, DMSO): δ 14.8, 15.9, 35.7, 38.7, 48.4, 64.8, 102.0, 106.0, 109.7, 110.2, 111.7, 119.6, 125.2, 128.5, 129.7, 136.0, 136.3, 152.5, 168.01. IR (KBr, cm^{-1}): 725, 1085, 1290, 1320, 1465, 1550, 1595, 1685, 1778, 1896, 1929, 2230, 2933, 3052; EIMS: (m/z): 335 (M+), Anal. calcd. for $C_{20}H_{17}NO_4$: C; 71.63, H; 5.11, N 4.18; O; 19.08; found C; 71.62, H; 5.12, N; 4.20, O; 19.01.

Result and Discussion

In this paper we are reporting the novel synthetic approach using DCM solvent in electrolyte Bu_4NClO_4 at potential range of 0.88 V with excellent yield. We observed that when supporting electrolytes such as NaBr, $LiClO_4$, $NaClO_4$, and Bu_4BrN (Table 1, Entries 6, 7, 8, 9, 10, 11) were used in place of Bu_4NClO_4 the yield of product also changes.

During the course of reaction we screened many solvents and supporting electrolyte and found that DCM was good current sponsor for the reaction of carbazoles and Maleic anhydride at room temperature. Combination of DCM and Bu_4NClO_4 shows maximum yield (Table 1, Entry 4). The influence of solvent on the reaction was evaluated, maximum solvents synthesize product between 48% to 70% yield. Acetonitrile, ethyl alcohol and methanol show comparatively low yield, longer reaction time along with waste product (Table 1), though DCM provided the best solubility of substrate and electrolyte, better yield, excellent purity (Table 1, Entry 4). Hence DCM was selected as a solvent under the reaction pathway of green products.

Table 1. Optimization of solvent and electrolyte effect on the reaction conditions for oxa-bicyclocarbazole-1,3-dione derivatives **3**.



Entry	Solvent	Electrolyte	Potential (V)	Time (min)	Current (mA)	Yield (%)
1	DCM	Bu_4NClO_4	0.70	245	30	48
2	DCM	Bu_4NClO_4	0.82	180	42	50
3	DCM	Bu_4NClO_4	0.85	165	45	70
4	DCM	Bu_4NClO_4	0.88	142	27	94
5	MeOH	Bu_4NClO_4	0.88	210	28	50
6	MeCN	NaBr	0.88	170	37	62
7	MeCN	$LiClO_4$	0.88	235	42	60
8	MeCN	$NaClO_4$	0.88	190	36	55
9	MeCN	Bu_4NBr	0.88	170	42	70
10	EtOH	$NaClO_4$	0.88	195	38	72
11	EtOH	$LiClO_4$	0.88	210	40	65

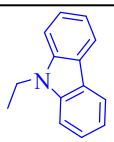
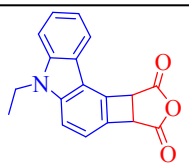
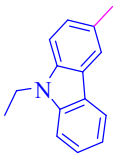
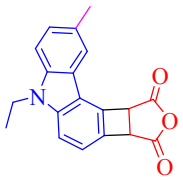
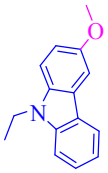
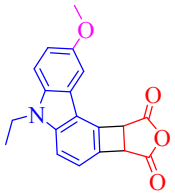
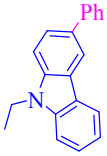
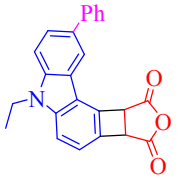
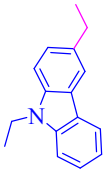
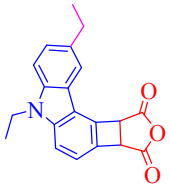
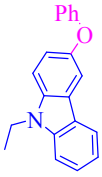
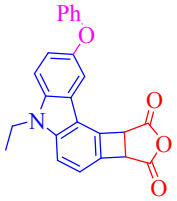
[a]General procedure: carbazole (2.0 mmol), maleic anhydride (2.0 mmol), electrolyte (0.8 mmol), solvent (25 mL), platinum plates as cathode and anode (1 cm^{-2}), room temperature.
[b]Isolated yield

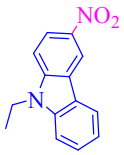
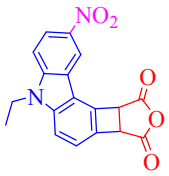
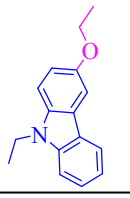
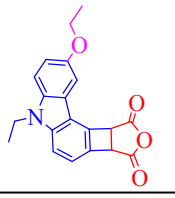
Electrolysis were carried out in a 50 mL undivided cell assembly equipped with two platinum electrodes (flattened sheet of dimension 1.0 × 1.0 cm^{-2}) as working as well as the auxiliary electrode and saturated calomel electrode as reference electrode. In a usual procedure, (2.0 mmol) carbazole derivatives, (2.0 mmol) maleic anhydride, Bu_4NClO_4 (0.8g, 0.1N) was dissolved in DCM solvent under constant potential. After the electrolysis, the reaction mixture was extracted with chloroform. The residue was purified by recrystallization from EtOH to furnish the desired product. All compounds were stable solids whose structures were established by IR, ^1H and ^{13}C NMR spectroscopy and elemental analysis.

To study the electrochemical synthesis of this protocol, a library of oxa-bicyclocarbazole-1,3-dione derivatives (3a-h) were synthesized using carbazole derivatives and maleic anhydride at platinum electrode are summarized in Table 2.

Table 2. Scope of electroorganic synthesis for oxa-bicyclocarbazole-1,3-dione derivatives.

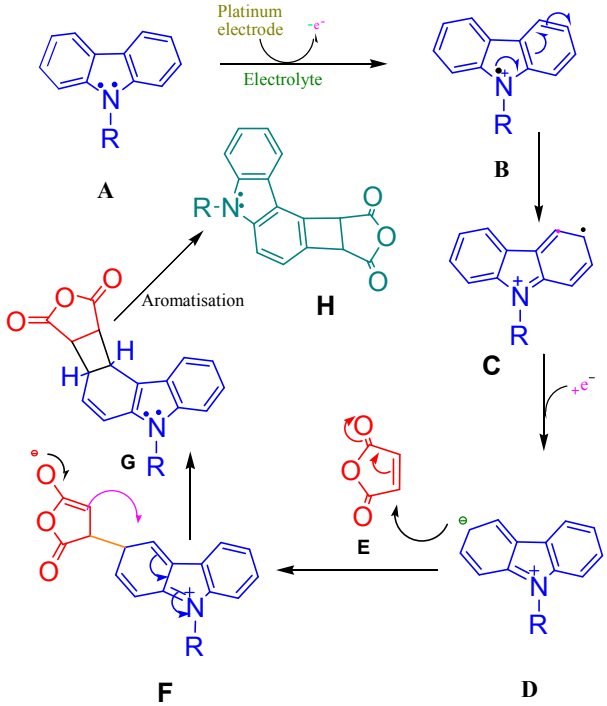
R = H, CH_3, OCH_3, CH_2CH_3, Ph, OPh, OCH_2CH_3, NO_2

Entry	Substrate	Product	Time (Min)	Current (V)	Potential (mA)	Yield (%)	m.p.
1			178	37	0.88	94	115-117
2			180	35	0.90	89	102-104
3			180	39	1.40	86	122-126
4			184	37	1.20	90	117-119
5			175	37	1.30	88	112-116
6			180	40	1.10	90	119-123

7			180	37	1.20	84	127-129
8			182	36	0.88	90	122-126

[a]General procedure: carbazole derivative (2.0 mmol), maleic anhydride (2.0 mmol), Bu_4NClO_4 (0.8 mmol), DCM (25 mL), room temperature
[b]Yield of isolated product

A plausible mechanism for the synthesis of oxa-bicyclocarbazole-1,3-dione derivatives is shown in (Scheme 2). Initially carbazole A is converted into radical cation B. B tautomerized to radical cation C which undergoes one electron reduction to form dipolar compound D. Compound D reacts with maleic anhydride E via Michael addition reaction to give compound F, F undergoes intramolecular cyclization with maleic anhydride and carbazole to give four member cyclic compound G which undergo aromatization and converted into oxa-bicyclocarbazole-1,3-dione derivative H.



Scheme 2. Plausible mechanism for the synthesis of oxa-bicyclocarbazole-1,3-dione derivatives.

Conclusion

In conclusion, we have developed an efficient one pot electrochemical reaction of carbazole derivatives and maleic anhydride using Bu_4NClO_4 as an electrolyte. According to our result, 1,4-

Michael addition of nucleophile to the maleic anhydride leads to the formation of new oxa-bicyclocarbazole-1,3-dione derivatives.

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