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Utilization of Dissociation Constant (pK_a) Value Perspective of -CH Acid in Electrochemical Synthesis of 4*H*-Chromene and its Derivatives

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Activation of acidic-H in C-H chemistry through imposition of proper electrode potential is a matter of concern among synthetic research community. In this study, our main aim is to get deeper insight into the dissociation constant (pK_a) value perspective of -CH acid and its utilization in electro-catalytic transformation. Herein, a platinum cathode was being used to attract a covalently bonded electrons that exist between C and active-H of CH-acid (dimedone) toward itself *i.e*. cathodic part to form acidic-H and thus, form *in-situ* tautomeric enol form that acts as electro-generated base. Utilization of this notability has been accomplished by electrochemical synthesis of 4*H*-chromene and its derivatives by performing cathodic reduction. Due to acidic property of dimedone, cathodic platinum electrode draw the potential switched to lower side that is being recorded through the potential-cum-galvanostat which facilitates the faster transfer of electrons from -CH acid to form enolate ion of dimedone that act as electro-generated base for the reaction media which simultaneously undergoes cascade reaction (Michael addition/cyclization) on activated alkene (α-cyanocinnamonitrile derivatives). This approach offers several advantages such as good yield, mild reaction condition, easy accessible, simple work-up procedure and controlled potential selectivity at cathode. Use of no base is pivotal section of this methodology. Electro-generated base is used instead of chemical toxic bases, so the present protocol is green as electrons that acts as intrinsically sole reagent for the reaction media which is renewable, hence sustainable for the safe future.

Keywords: Tautomeric, Chromene, Dimedone, Dissociation constant, Electro-catalysis.

INTRODUCTION

In order to meet the notable criteria of cutting carbon footprint, synthetic chemist are nowadays searching such a method which will decouple the toxic chemical product and reduce emission of CO_2 [1] form the industry so that it may improve the efficiency of organic synthetic, especially in terms of the atom economy and cost effectiveness. For this reason, use of renewable sources [2] is becoming igniting topic among researchers of synthetic organic community. In view of this, electrochemical technologies [3] represents prototypical cleanest technology for safe and sustainable future and can be used for functional group interconversion and activation of C-H chemistry through Michael addition reactions (MARS) by imposition of a proper electrode potential is what lies behind organic electrosynthesis processes. Thus, *in situ* electro-generated bases (EGBS) are developed by imposing a proper electrode potential result in selectivity for the organic C-C bond transformation.

Naturally occurring chromene moiety represent major class of interest that show wide spectrum of biological activity [4]. Conventional protocol involves the use of organic solvents (*e.g*. DMF or acetic acid) [5], reagents (*e.g*. HMTAB, Na_2SO_4, TBAF, Ca-SiO_2, TEBA, RE$(PFO)_3$, NaBr, (S)-proline, KF-basic alumina) [6,7] under microwave activation [8] or ultrasonic irradiation [9,10], which bears certain demerits such as prolonged reaction times, stoichiometrically expensive reagents and toxic solvents that result in moderate yields of the product. Present protocol is somewhat different from reported electrochemical synthesis that either involves three component in one pot having different mechanistic pathway either (Knoevenagel/Michael/

cyclization or Knoevenagel/cyclization) [11-13]. Present protocol predominantly based on dissociation constant (pK_a value) perspective of –CH acid which involves two component in one pot and follows Michael/cyclization reaction pathway.

EXPERIMENTAL

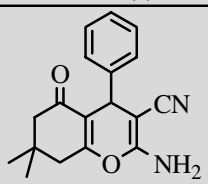
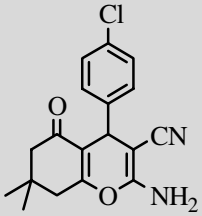
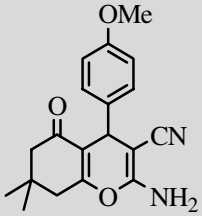
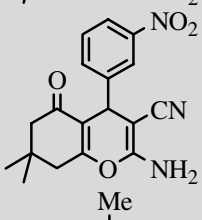
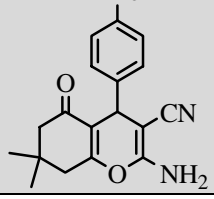
Method: The electrochemical synthesis was performed in 100 mL three-electrode cell assembly [15-18] with platinum plate (flattened sheet with dimension of 1 cm × 1 cm), counter electrode and saturated calomel electrode as reference electrode. IR spectra (KBr) were recorded on a Shimadzu 8201 PC IR spectrophotometer. ^{1}H & ^{13}C NMR spectra were recorded on a Bruker, DRX 400 spectrometer (400 MHz) in $CDCl_3$ using TMS as an internal standard. Chemical shift (δ) is quoted in ppm. All the chemicals used were of synthetic and AR grade and procured from Standard Chemical companies. These chemicals were used without further purification. All experiments were carried out at room temperature.

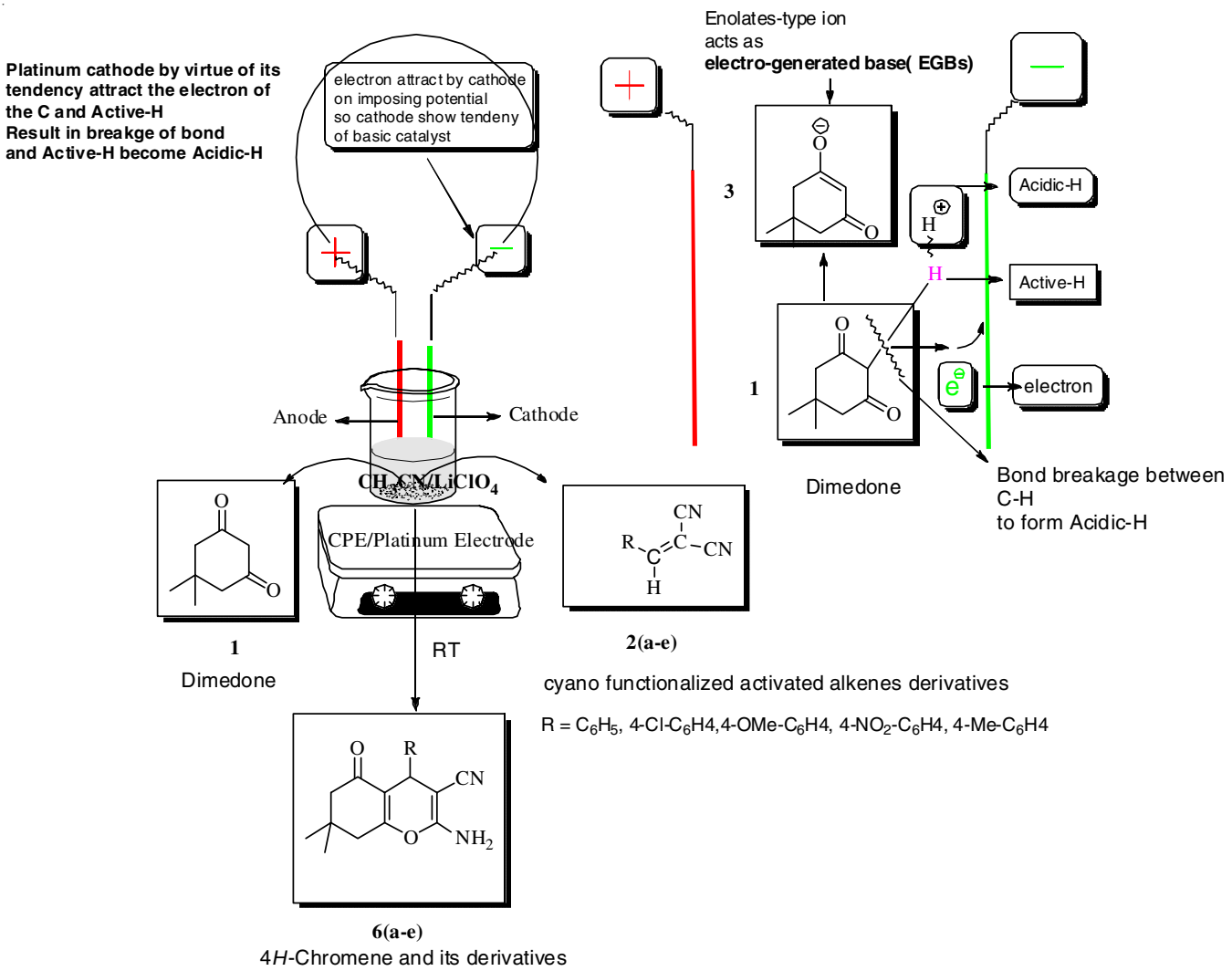
General procedure: Here in, considering the dissociation constant (pK_a) value as perspective and compared with reported literature [18]. Electrolysis was carried out at room temperature in an undivided cell using platinum electrode. The dimedone and cyano-functionalized activated alkene derivatives was taken as substrate. Experimental procedure was carried out by imposing a cathodic potential which is being recorded through potential cum galvanostat as shown in Table-1 using a two-component comprising dimedone (10 mmol, **1**) and α-cyano-cinnamonitrile derivatives (10 mmol, **2a-e**) [18] in 40 mL CH_3CN as solvent and 0.1 M $LiClO_4$ as supporting electrolyte at room temperature with proper mixing by magnetic stirrer. Reaction mixture was poured into ice water to precipitate a solid and filtered off. The residue was recrystallized in ethanol to obtain a desired product (**Scheme-I**). This protocol has easy workup through solvent extraction.

Spectral data

Compound 6a: m.w.: 294; IR (KBr, ν_{max}, cm^{-1}): 3280, 3250, 3040, 2990, 2980, 2245, 1650, 1600, 1480, 740, 700; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01(3H, s, CH_3), 1.10 (3H, s, CH_3), 2.21 (2H, s, CH_2), 2.56 (2H, s, CH_2), 3.06 (2H, br, s, NH_2), 4.28 (1H, s, CH), 7.27 (5H, s, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$/TMS): δ = 197.6, 176.6, 160.8, 137.7, 129.2, 128.4, 125.5, 117,

TABLE-1
CURRENT POTENTIAL DATA OF 4*H*-CHROMENE AND ITS DERIVATIVES WITH PUBLISHED MELTING POINT IN ACCORDANCE WITH LITERATURE

Entry	R (alkyl group)	Product (6)	Potential (V)	Current (A)	Yield (%)	Time (h)	m.p. (°C) [Ref. 9]
a	C_6H_5		1.60	0.50	92	3.0	230-232
b	4-ClC_6H_4		1.45	0.52	94	2.5	209-211
c	4-$OMeC_6H_4$		1.65	0.48	88	3.5	199-200
d	4-$NO_2C_6H_4$		1.40	0.41	90	4.0	213-215
e	4-MeC_6H_4		1.75	0.32	84	4.5	213



Scheme-I: One pot two component syntheses of known 4*H*-chromene and its derivatives **6(a-e)** through electro-catalytic transformation

108.8, 57.4, 54.3, 47.1, 27.1, 15.9; MS found for $C_{18}H_{18}N_2O_2$: *m/z* 294.13.

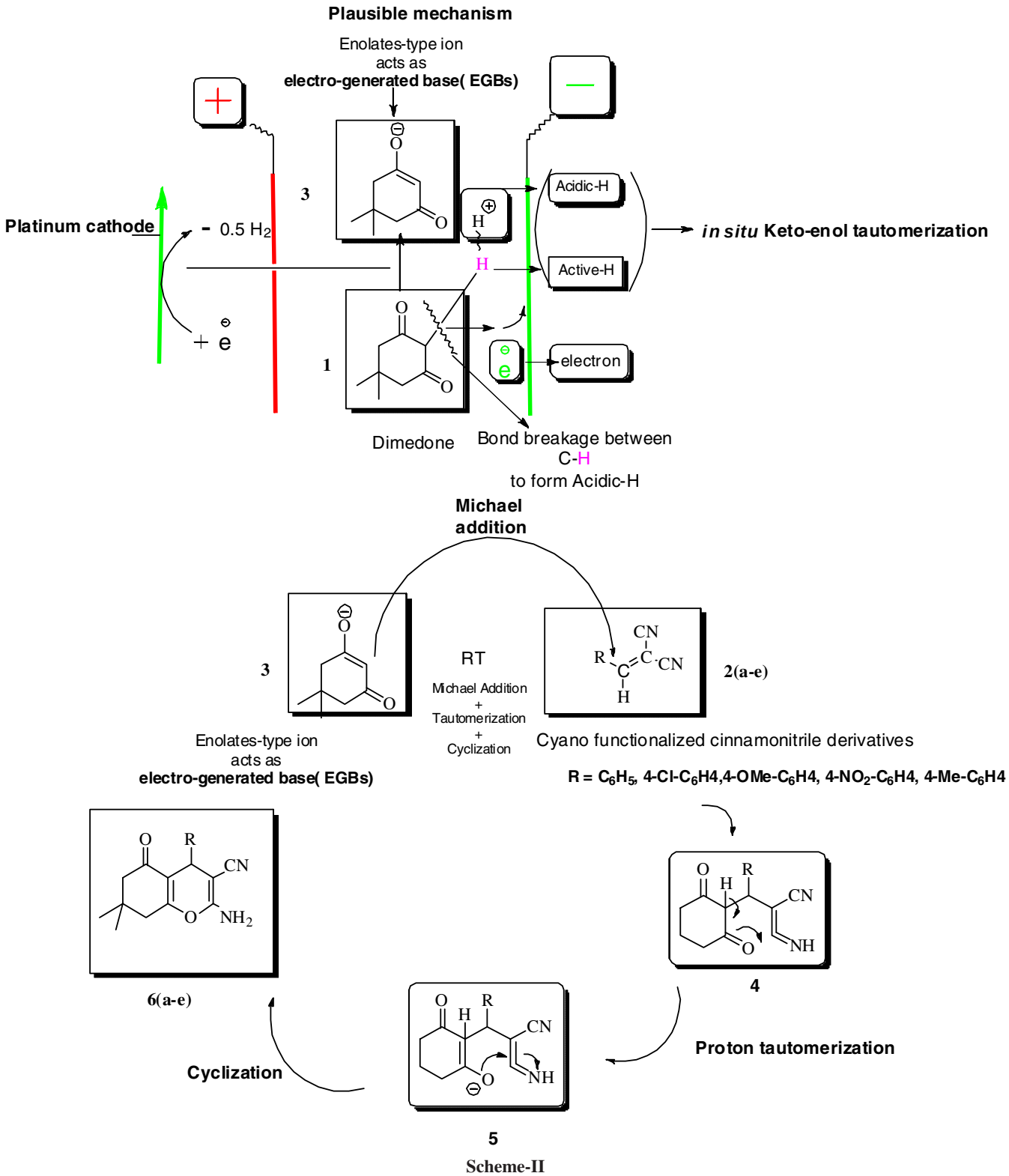
Compound 6b: m.w.: 328; IR (KBr, ν_{max}, cm^{-1}): 3300, 3200, 3040, 2990, 2970, 2240, 1650, 1610, 1490, 850; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (3H, s, CH_3), 1.09 (3H, s, CH_3), 2.22 (2H, s, CH_2), 2.59 (2H, s, CH_2), 3.07 (2H, br, s, NH_2), 4.30 (1H, s, CH), 7.30 (4H, s, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$/TMS): δ 197.6, 176.6, 160.8, 130.6, 117.2, 108.8, 128.0, 135.8, 130.6, 57.4, 54.3, 47.1, 27.1, 15.9; MS found for $C_{18}H_{17}N_2O_2Cl$: *m/z* 328.09.

Compound 6c: m.w.: 324; IR (KBr, ν_{max}, cm^{-1}): 3400, 3300, 3040, 2990, 2980, 2970, 2240, 1680, 1610, 1510, 840; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (3H, s, CH_3), 1.02 (3H, s, CH_3), 2.23 (2H, s, CH_2), 2.48 (2H, s, CH_2), 3.28 (2H, br, s, NH_2), 3.73 (3H, s, OCH_3), 4.12 (1H, s, CH), 6.87–6.99 (4H, m, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$/TMS): δ = 197.6, 176.6, 160.8, 159.3, 130.6, 117.2, 114.6, 108.8; MS found for $C_{19}H_{20}N_2O_3$: *m/z* 324.14.

Compound 6d: m.w.: 339; IR (KBr, ν_{max}, cm^{-1}): 3300, 3200, 3040, 2990, 2970, 2240, 1650, 1610, 1490, 850; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.86 (2H, s, CH_2), 2.83 (2H, s, CH_2), 3.07 (2H, br, s, NH_2), 4.30 (1H, s, CH), 7.30-8.08 (4H, s, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$/TMS): δ = 197.6, 176.6, 160.8, 145.2, 143.8, 130.6, 117.2, 108.8, 123.5, 57.4, 54.3, 47.1, 27.1, 15.9; MS found for $C_{18}H_{17}N_3O_4$: *m/z* 339.12.

Compound 6e: m.w.: 308; IR (KBr, ν_{max}, cm^{-1}): 3300, 3200, 3040, 2990, 2970, 2240, 1650, 1610, 1490, 850; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.86 (2H, s, CH_2), 2.83 (2H, s, CH_2), 3.07 (2H, br, s, NH_2), 4.30 (1H, s, CH), 2.35 (3H, s, CH_3), 6.94 (4H, s, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$/TMS): δ = 197.6, 176.6, 160.8, 134.1, 129.2, 117.2, 108.8, 123.5, 57.4, 54.3, 47.1, 27.1, 20.9, 15.9; MS found for $C_{19}H_{20}N_2O_2$: *m/z* 308.15.

A plausible mechanism for the formation of functionalized 4*H*-chromene and its derivatives (**6a-e**) is outlined in **Scheme-II**. Selective imposed potential on dimedone result in enolates ion (**3**) formation through cathodic reduction (**1**) at the platinum electrode that acted as electro-generated base for the reaction media containing inert $LiClO_4$ as supporting electrolyte and CH_3CN as organic solvent. This electro-generated base (**3**) undergoes Michael addition reaction (MARS) on cyanofunctionalized activated alkene derivatives (**2a-e**) followed by proton tautomerization (**4**) and cyclization (**5**) to form desired product *i.e.*



Scheme-II

functionalized 4H-chromenes (**6a-e**) in good yields 84-94%. All the isolated products give melting point and spectral data in accordance those with published data [9,10].

RESULTS AND DISCUSSION

In present context, we focussed on the cyclic 1,3-diketone *i.e.* dimedone, a versatile motif of –CH acid which exhibits tautomerization due to the presence of active methylene group [14]. This physical property can be utilized in C-C bond transformation. As part of our current studies [15-17], an efficient two-component electrosynthetic route was carried out to prepare functionalized chromene and its derivatives, where dimedone and α-cyanocinnamonitrile derivatives *i.e.* activated alkene as model substrate were chosen in one pot and performed the

electrolytic conditions using potential cum galvanostat. So from this end, we encourage the involvement of electrosynthetic organic research community to galvanize this field and to unleash its huge potential. This imposed selectivity (C-C bond formation) through cathodic potential was obtained through controlled potential electrolysis, which depends upon the behaviour and reactivity of the CH-acid of active methylene group.

In order to understand notability of CH-acid and its formation of tautomeric enolic form through electrochemically, the perspective view of the pK_a value have been taken into the account [19]. Generally, the CH-acid that have low pK_a value show higher value of acidity. The polarographic acidity scale for CH-acids in DMF was first tailored by Reutov *et al*. [20], which involved the use of selected pK_a data and the irreversible reduction potentials of organo-mercuric compounds (R_2Hg). Later on Sawyer *et al*. [21] presented a voltammetry method for determination of effective acidities of Brønsted acids [21] and the redox potentials of radical/carbanion couples were also proposed [22]. Thermodynamic coupled with electrochemical potentials have been applied for the determination of pK's of reactive intermediates [23-25]. Maran *et al*. [19,26] suggested the formation of basic species, such as carbanions, radical anions, and dianions through electrochemical reduction of organic compounds.

From the literature, it is clearly understood that CH-acid containing lower pK_a value have higher tendency to convert its active-H into acidic-H. So from the electrochemistry perspective view of electrode, a very small electromotive force will be given from potentiostat-cum-galvanostat to attract the bonded electron that exist between C and active-H of CH-acid towards itself *i.e*. cathodic part. Hence, lower cathodic potential is being recorded from the potential-cum-galvanostat which needs of hours in term of speedy reaction in perspective view of green chemistry. In other word, pK_a value has direct effect in the formation of enolates-type base formation which is designated as electro-generated base. Hence, use of base is avoided as electrode acts as basic catalyst which utilized the physical nature of CH-acid.

In previous study [27], malononitrile was used as one of CH-acid whose pK_a value was 11.2 and in present context, dimedone whose pK_a value is 11.6 [28-30]. Thus, based on pK_a value, acidity of dimedone will be lower than malononitrile and hence, less electromotive force will be applied. Evans [31] clarifies the versatility of synthetic electrochemical method to unleash galvanize potential to form conjugate base and H_2 gas during cathodic reduction of CH acid on the platinum cathode. He described the formation of *in-situ* generated electro-generated base at cathode under mild condition without addition of chemical base. This prompted us to study the reactivity of the CH-acid in $CH_3CN/LiClO_4$ electrolyte system. In present study, lithium perchlorate as supporting electrolyte was used which is inert and gives good yield without formation of any byproduct at the platinum electrode. Acetonitrile may conflict one aspect of green chemistry (green solvent) but it have higher value of acidity (pK_a) [32] that may not interfere in the reaction media result in proper imposed potential on dimedone.

Conclusion

Use of no base is pivotal section of this methodology that depends on physical nature of dimedone *i.e*. tautomerization that depend upon the pK_a value perspective. Due to acidic property of dimedone, cathodic electrode draw the potential switched to lower side that is being recorded through the potential-cum-galvanostat which facilitates the faster transfer of electron from –CH acid to form enolate ion of dimedone that act as electro-generated base, which simultaneously undergoes cascade reaction (Michael addition/cyclization) on activated alkene (α-cyanocinnamonitrile derivatives). In other word, pK_a value has direct effect in formation of enolates-type base formation which is known as electro-generated base. Thus, electro-generated base is used instead of chemical toxic bases, so the present protocol is green, as electron acts as intrinsically sole reagent for the reaction media which is renewable, hence sustainable for the safe future. Procedure involves low cost, high yields and separation of products take place through simple filtration method avoiding column chromatography in a simple equipment and undivided cell.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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