Article

Improved Method for the Total Synthesis of Azaperone and Investigation of Its Electrochemical Behavior in Aqueous Solution

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Azaperone, with anti-anxiety and anti-aggressive activities used in veterinary medicine, is a member of the butyrophenone class. It is ordinarily utilized for a wide range of indications, such as sedation, obstetrics, and anesthesia. In this research, an improved synthetic route is presented for azaperone using a phase-transfer catalyst(PTC). In general, it was synthesized as a dopamine antagonist in four steps. The bis(2-chloroethyl) amine intermediate is easily obtained after the conversion of the alcohol groups into the chloride leaving group using thionyl chloride(95% yields). The alkylation of commercially available 2-amino pyridine in the presence of PTC was then carried out, giving 1-(pyridin-2-yl) piperazine with 75% yield. 1-(Pyridin-2-yl) piperazine was finally alkylated using 4-chloro-1-(4-fluorophenyl) butan-1-one to achieve azaperone with 60% yield. The butyrophenone intermediate was obtained *via* the Friedel-Crafts reaction of fluorobenzene with 4-chlorobutyryl chloride in the presence of $AlCl_3$. High efficiency, gentle reaction conditions, and fast and simple procedure are the advantages of this method. Also, the electrochemical oxidation behaviour of azaperone was investigated using cyclic and differential pulse voltammetry techniques. Cyclic voltammetric studies indicated an irreversible process for azaperone electro-oxidation with a peak potential of 0.78 V in a phosphate buffer solution(pH=7.0) *vs*. Ag/AgCl(saturated KCl) electrode. The value of the peak current *vs.* the azaperone concentration was enhanced linearly in the range of 10—70 μmol/L, and the detection limit was found to be 3.33 μmol/L.

Keywords Azaperone; Anesthetic drug; Chemical synthesis; Butyrophenone class; Electrochemical behavior

1 Introduction

Azaperone, with anti-anxiety and anti-aggressive activities used in veterinary medicine, is a member of the butyrophenone class. It is ordinarily utilized for a wide range of indications, such as sedation, obstetrics, and anesthesia in pigs. In most farming activities, there are some problems with the reaction of animals toward bad situations like carrying to the slaughterhouse. To solve this problem and reduce the stress in animals, azaperone has been proposed to be used[1—6]. Also, the aggressive relationship between a pair of rats about competing for food can be solved by azaperone. In this case, azaperone as a butyrophenone neuroleptic drug with tranquilizing and anti-thorn activities corrects and normalizes the aggressive interactions between rats at fewer doses[7—10]. Azaperone blocks dopamine receptors in the brain, and it is a strong blocker of α-receptor at low-dose, unlike antipsychotic neuroleptics, but the function of the receptors of dopamine can be disturbed at a high dosage[11—15]. Amine linkage is one way for coupling the molecules, providing that one species contains the amine group and the other contains the epoxide or alkyl halide moiety. With this description, the preparation of azaperone can also be done through the reaction of the amine with an alkyl chloride[16]. Kothakonda and his colleagues[17] reported the reaction of diethanolamine with thionyl chloride in benzene as a solvent giving bis-(2-chloroethyl) amine with a yield of 74%.

One of the derivatives of cyclic diamine or ethylenediamine is piperazine, a saturated heterocyclic structure containing two nitrogens[18]. It has a salty taste with a characteristic alkaline deliquescent crystal structure. Pyridylpiperazine is obtained by grafting pyridine to piperazine. In 2016, Patel *et al.*[19] synthesized 1-(pyridine-2-yl) piperazine from the reaction of bis-(2-chloroethyl) amine with 2-aminopyridine in the presence of potassium iodide and 2-(2-methoxy ethoxy) ethan-1-on. Also, Guo and his colleagues[20] synthesized phenyl-piperazine derivatives, 1-(4-bromophenyl)-2-[4-(pyridine-2-yl) piperazine-1-yl] ethan-1-one by the reaction between the 2-bromo-1-(4-bromophenyl)-ethanone and 1-(pyridin-2-yl) piperazine, in the presence of K_2CO_3 and acetonitrile.

The main purpose of the present study is to synthesize azaperone as an inexpensive and available compound. However, few synthesis methods have been developed to synthesize azaperone, most of which present some

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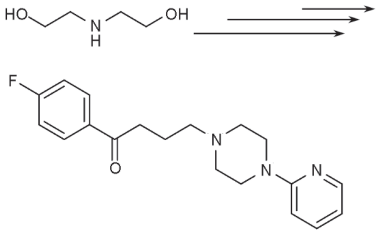
disadvantages, such as the use of toxic and harmful solvents and harsh reaction conditions[21—23]. So, based on previous experience, we decided to synthesize azaperone with a good yield using cheap and available raw materials. The intended synthetic pathway was shown in Scheme 1.

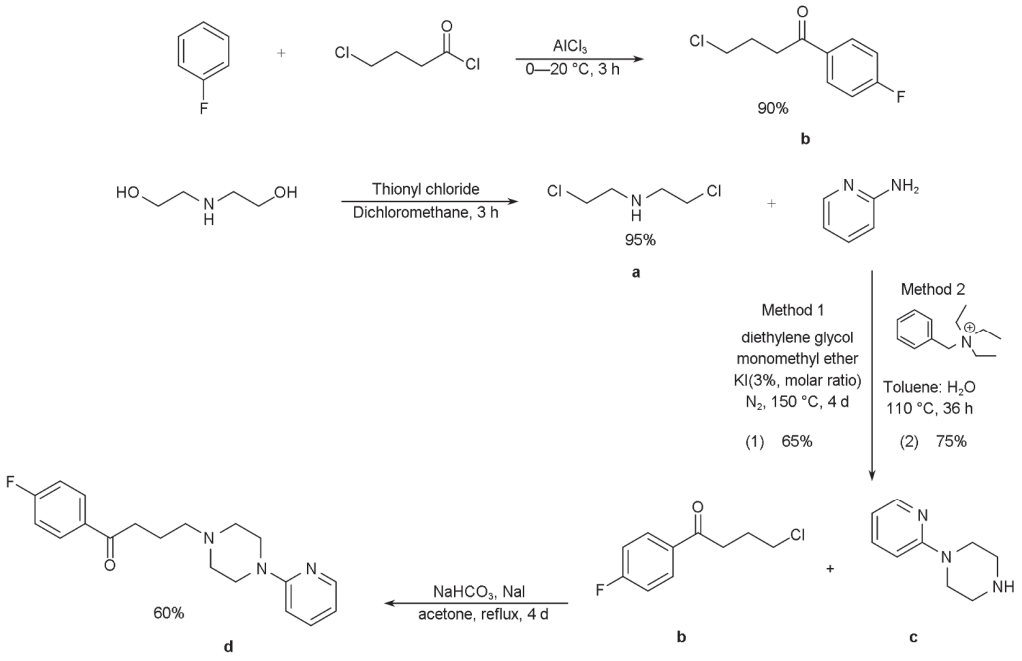
Electrochemical analysis has gained much attention among scientists for detecting different compounds due to the cost-effectiveness, high sensitivity, high selectivity, and ability to detect trace concentrations[24—32]. Glassy-carbon(GC) is a promising candidate with a suitable proven performance that acts as a suitable electrode substrate, abbreviated as GCE, applicable for the detection of different chemical and biological samples. GCE has very small pores and consists of aromatic ribbon molecules, which in some cases bonded by oxygen-containing functional groups[33—38]. It usually slowly oxidizes and facilitates the mediated redox reactions on its surface, which can be noticeable by decreased over-potential and increased faradaic current. The prominent potential of the GCE in the role of the working electrode in electroanalytical applications has been abundantly reported[39—41]. To the best of our knowledge, no electrochemical study has been reported to detect azaperone in an aqueous solution. Thus, the voltammetry technique was utilized for the electrochemical detection of azaperone using GCE under physiological conditions(*i.e.*, pH=7.0).



Scheme 1 Synthesis of azaperone using diethanolamine

2 Experimental

The chemicals used in this study were purchased from Merck and Fluka companies. The solvents were distilled before use. Distilled solvents were dried with appropriate dryers, such as magnesium sulfate and calcium chloride. Reaction progress was monitored by thin-layer chromatography(TLC) prepared on Merck silica gel 60 F254 plates, and visualization was performed with UV light. Normal hexane and ethyl acetate solvents were used for TLC analysis. The products were separated and purified by extraction and recrystallization techniques. The melting points were determined on an electrothermal IA9100 Standard Digital melting point apparatus. Infrared(IR) spectra were obtained on a Shimadzu model FTIR 8900 using potassium bromide pellets. Proton nuclear magnetic resonance ^{1}H NMR and ^{13}C NMR spectra were obtained by a Bruker-400 MHZ spectrometer. The presented chemical shifts were in δ relative to tetramethylsilane(TMS) as internal standard. Coupling constants were reported in Hertz(Hz). All ^{1}H NMR and ^{13}C NMR spectra were recorded in deutero dimethyl sulfoxide(DMSO-d_6) or deutero chloroform($CDCl_3$) solvents at room temperature. All ^{1}H NMR and ^{13}C NMR spectra were shown in the Electronic Supplementary Material of this paper. The full synthesis pathway of azaperone from employed materials is demonstrated in Scheme 2.



Scheme 2 Full synthesis pathway of azaperone

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2.1 Synthesis of Bis(2-chloroethyl) Amine

To prepare bis(2-chloroethyl) amine, a solution of diethanolamine(0.29 mL, 3 mmol) and dichloroethanol(10 mL) was added to 0.5 mL(7 mmol) of thionyl chloride, and the mixture was refluxed with stirring for 3 h at 50 °C. The reaction mixture was then cooled down to room temperature. Finally, the solvent was removed by vacuum evaporation, and yellow crystals were obtained. Yield: 95%. m. p. 210—212 °C; ^{1}H NMR (400 MHz, DMSO), δ: 3.37(2H, t, CH_2), 3.98(2H, t, CH_3), 9.78(1H, s, NH). ^{13}C NMR(100 MHZ, $CDCl_3$), δ: 39.5, 48.3.

2.2 Synthesis of 4-Chloro-1-(4-fluorophenyl) Butane-1-one

The solution consisting of 9 mL(3.4 mmol) of dichloromethane, 0.3 mL(3.2 mmol) of fluorobenzene, and 0.33 mL(3 mmol) of 4-chloro-butyryl chloride was cooled in an ice bath, and 0.42 g(3.2 mmol) of aluminum chloride was added with stirring for 5 min. The mixture was stirred for 1.5 h at 0 °C, and the reaction was continued for 1.5 h at 20 °C. Then 5 g of ice was added to the mixture, and after thawing the ice, the product was extracted with ethyl acetate(2×25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 4-chloro-1-(4-fluorophenyl) butane-1-one as a yellow liquid with a yield of 90%. FTIR(KBr), $\tilde{\nu}$/cm^{-1}: 2966, 1684, 1598. ^{1}H NMR(400 MHz, chloroform-d), δ: 8.10—7.99(m, 1H), 7.18(t, J=8.5 Hz, 1H), 3.72(t, J=6.1 Hz, 1H), 3.20(t, J=6.9 Hz, 1H), 2.32—2.22(m, 1H). ^{13}C NMR(100 MHz, chloroform-d), δ: 197.37, 130.68(d, J=9.3 Hz), 115.78(d, J=21.9 Hz), 44.66, 35.21, 26.71, 1.05. MS, m/z [M]$^+$: 200(3), 123(100), 138(60), 95(65), 75(35).

2.3 Synthesis of 1-(Pyridine-2-yl) Piperazine

This compound can be synthesized *via* two methods.

Method 1: synthesis of 1-(Pyridin-2-yl) piperazine in diethylene glycol monomethyl ether: the mixture of 2 mL of diethylene glycol monomethyl ether, 0.14 g(1.5 mmol) of 2-amino pyridine, 0.21 g(1.5 mmol) of bis(2-chloroethyl)amine, and potassium iodide(3%, molar fraction) was refluxed under nitrogen for 4 d at 150 °C. After completion of the reaction(monitored with TLC), the organic phase was washed with a solution consisting of sodium carbonate and brine[$NaCl_{(aq)}$]. The combined organic extracts with ethyl acetate(2x25 mL) were dried over $MgSO_4$ and filtered and concentrated under reduced pressure to afford a yellow liquid product. Yield 65%.

Method 2: synthesis of 1-(pyridin-2-yl) piperazine in toluene and water: the mixture of 4 mL of toluene, 4 mL of water, 0.14 g(1.5 mmol) of 2-Amino pyridine, 0.21 g(1.5 mmol) of bis(2-chloroethyl) amine, and benzyl triethylammonium phase transfer catalyst(8%, molar ratio) was refluxed for 36 h at 110 °C. After the completion of the reaction(determined with TLC), no product was observed in the organic phase and the whole product was observed in the aqueous phase of the reaction mixture. The mixture was extracted with ethyl acetate(3x25 mL), and the organic layer was separated. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the product 1-(pyridin-2-yl) piperazine(yield 75%). FTIR(KBr), $\tilde{\nu}$/cm^{-1}: 3282, 3005, 2843, 1595, 1484, 1436. ^{1}H NMR(400 MHz, chloroform-d), δ: 8.20(d, J=4.6 Hz, 1H), 7.48(t, J=7.8 Hz, 1H), 6.69—6.59(m, 2H), 3.54—3.47(m, 6H), 3.02—2.96(m, 6H), 1.78(s, 1H). ^{13}C NMR(101 MHz, chloroform-d), δ: 159.82, 147.94, 137.44, 113.29, 107.06, 46.38, 45.99. MS, m/z [M]$^+$: 163(56), 121(100), 107(85), 95(85).

2.4 Synthesis of 1-(4-Fluorophenyl)-4-[4-(pyridin-2-yl) Piperazine-1-yl] Butan-1-one

The mixture of 0.22 g(1.1 mmol) of 4-chloro-1-(4-fluorophenyl) butane-1-one, 0.15 mL(1 mmol) of 1-(pyridine-2-yl) piperazine, 0.33 g(4 mmol) of sodium bicarbonate and sodium iodide in 10 mL of acetone(25%, molar fraction) was refluxed under nitrogen for 4 d. The reaction mixture was separated in *n*-hexane:ethyl acetate:methanol(1:4:4, volume ratio) by chromatography column. Yield 60%. m. p. 91—93 °C. FTIR(KBr), $\tilde{\nu}$/cm^{-1}: 2948, 2805, 1681, 1595, 1563, 1437, 1149, 1006. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 2.02(2H, m, CH_2), 2.50(2H, t, CH_2), 2.58(4H, s, 2CH_2), 3.05(2H, t, 2CH_2), 3.52(4H, s, 2CH_2), 6.65(2H, d, 2CH) 7.16(2H, t, 2CH), 7.50(1H, t, CH), 8.03(2H, d, 2CH), 8.21(1H, s, CH). ^{13}C NMR(100 MHz, $CDCl_3$), δ: 21.5, 36.1, 45.1, 52.9, 57.7, 107, 113.2, 115.5, 115.7, 130.6, 130.7, 137.4, 147.9(C=N), 159.5, 198.4(C=O). MS, m/z [M]$^+$: 327(2), 123(100), 107(72), 95(85), 78(57).

2.5 Electrode Preparation

Firstly, the GCE surface was cleaned by polishing on an alumina slurry containing pad and then rinsing with deionized water followed by 5 min sonication in deionized water. After drying under room condition, the electrode was placed in 0.1 mol/L sodium bicarbonate solution and subjected to the consecutive cyclic voltammetric experiment(CV, 20 scans) in the potential range of –1.2—1.5 V at the scan rate of 50 mV/s[42]. The cyclic voltammograms of the standard azaperone solutions were recorded in the potential window of 0.1—1.0 V. Also, the differential pulse voltammetry(DPV) was applied by modulation time of 70 ms, pulse amplitude of 50 mV, and a scan rate of 5 mV/s.

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3 Results and Discussion

3.1 Optimization of the Synthesis Conditions

The reaction conditions were optimized for the synthesis of the desired products(**a**, **c**, **d**). Here, the influence of various reaction parameters, such as solvent, temperature, time, catalyst, and different concentrations of the catalyst was studied, and their roles in enhancing the reaction rates and yield of the products were evaluated.

First, the preparation of bis(2-chloroethyl) amine(**a**) was performed in the presence of various solvents, including thionyl chloride, dichloromethane, and 1,2-dichloroethane under reflux condition to study the effect of solvents(Table 1). The outcomes showed that the reaction in the 1,2-dichloroethane gives the product with a higher yield(95%) in comparison to dichloromethane. Besides, the synthesis of 1-(pyridin-2-yl) piperazine(**c**, with method 1) in diethylene glycol monomethyl ether was performed, which lasted 4 d, leading to the high-yield product(65%). Moreover, it can be inferred from Table 1 that the high yield(75%) is obtained when the toluene and H_2O are used as solvents. Finally, it is clear that the most promising improvement was observed when acetone was used as a solvent for the synthesis of azaperone(**d**) from 4-chloro-1-(4-fluorofenil) butane-1-on and 1-(pyridine-2-yl) *p*-pyrazine and the high yield(60%) was obtained.

Subsequently, the effect of temperature on the reaction yield was ascertained, and the results are given in Table 2.

Table 1 Optimization of the solvent for the synthesis of compounds a, c, d

Product	Constant parameter	Solvent	Time/h	Yield(%)
a	Reflux	Dichloromethane	24	80
		1,2-Dichloroethane	3	95
c[a]	Reflux, KI catalyst(3%, molar fraction)	Diethylene glycol	96	0
		Diethyleneglycol monomethyl ether	96	65
c[b]	110 °C, benzyl trimethylammonium(8%, molar fraction) as catalysts	Dichloromethane: H_2O	36	Negligible
		Toluene:H_2O	36	75
		H_2O	36	Negligible
d	Reflux, NaI catalyst (25%, molar fraction)	Dichloromethane	96	20
		Acetone	96	60
		Ethanol	96	3

a. Method 1; *b*. method 2.

Table 2 Optimization of the temperature for the synthesis of compounds a, c, d

Product	Constant parameter	Temperature/°C	Time/h	Yield(%)
a	Based on the reaction on 1,2-dichloroethane as a solvent	25	3	20
		40	3	60
		50	3	95
c[a]	Diethyleneglycol monomethyl ether as a solvent, KI catalyst(3%, molar fraction)	25	—	0
		100	96	18
		150	96	65
		196	96	65
c[b]	Toluene:H_2O(volume ratio 1:1) as a solvent, benzyl triethyl ammonium phase(catalyst, 8%, molar fraction)	25	36	Negligible
		80	36	36
		110	36	75
d	Acetone as a solvent, NaI catalyst(25%, molar fraction)	30	96	Negligible
		40	96	43
		56	96	60

a. Method 1; *b*. method 2.

The results show that the reaction yield(for the synthesis of compounds **a**, **c**, **d**) is directly related to the reaction temperature, and the reaction yield increases with the increasing temperature.

Further studies on the optimization showed that the reactions were highly time-dependent. In the synthesis of bis(2-chloroethyl) amine(**a**), when the reaction time increased from 1 h to 4 h, its effect was directly reflected in the production yield(Table 3). The maximum yield(95%) was obtained after 4 h reaction and after that, no further progress was found. In the case of 1-(pyridin-2-yl) piperazine(**c**, method 1), an increase in time up to 4 d increased the reaction yield(65%), and no change in yield was observed as more time passed. Likewise, 1-(pyridin-2-yl) piperazine(**c**, method 1) was prepared with the highest yield(75%) in the presence of toluene and water as solvents after 3 h of reaction with no change in yield after that time. Finally, in the synthesis of azaperone(**d**), the maximum yield(60%) was obtained after 4 d of reaction, and after that, no further increment in the yield was observed.

Then, we examined the effect of the presence and absence of the catalyst on the reaction yield to further optimize the conditions to reach better yields. The results in Table 4 show that 1-(pyridin-2-yl) piperazine in the presence of the catalyst (method 1) was synthesized with a high yield compared to the synthesis in the absence of the catalyst(method 2). Also, the effect of sodium iodide and potassium iodide on the synthesis of azaperone was investigated. Consequently, the best result was obtained by using sodium iodide as a catalyst in this

Table 3 Optimization of the reaction time for the synthesis of compounds a, c, d

Product	Constant parameter	Time/h	Temperature/°C	Yield(%)
a	Reflux, 1,2-dichloroethane as a solvent	1	50	40
		2	50	70
		3	50	95
		4	50	95
c[a]	Diethyleneglycol monomethyl ether as a solvent, KI catalyst(3%, molar fraction)	2	150	20
		3	150	40
		4	150	65
		5	150	65
c[b]	Toluene:H_2O(volume ratio 1:1) as a solvent, benzyl triethylammonium(catalyst 8%, molar fraction)	12	110	26
		24	110	63
		36	110	75
		48	110	75
d	Acetone as a solvent, NaI catalyst(25%, molar fraction)	48	56	20
		72	56	40
		96	56	60
		120	56	60

a. Method 1; *b*. method 2.

Table 4 Optimization of the catalyst for the synthesis of compounds c, d

Product	Constant parameter	Catalyst type	Time/h	Yield(%)
c[a]	150 °C, Diethyleneglycol monomethyl ether as a solvent	KI	96	65
		No catalyst	96	10
c[b]	150 °C, Toluene:H_2O(volume ratio 1:1) as a solvent	Benzyl triethyl ammonium	36	75
			36	Negligible
		No catalyst		
d	Reflux, acetone as a solvent	NaI	96	60
		KI	96	40
		No Catalyst	96	30

a. Method 1; *b*. method 2.

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reaction(Table 4).

Also, various concentrations of catalysts were selected for appropriate validation, and the results were listed in Table 5. In the synthesis of 1-(pyridin-2-yl) piperazine(**c**, method 1), the reaction yields of 35%, 50%, and 65% were obtained by adding 1%, 2%, and 3%(molar ratio) of potassium iodide as a catalyst, respectively. The use of only 3% KI(molar fraction) was enough to push the reaction forward, and higher concentrations of the catalyst did not affect the reaction yields. Thus, 3%(molar fraction) of the catalyst was chosen as a suitable amount for these reactions. Subsequently, we recognized that 8%(molar fraction) of benzyl triethylammonium could effectively catalyze the synthesis of 1-(pyridin-2-yl) piperazine(**c**, method 2), and no change in the reaction yield was observed after this concentration. Finally, in the synthesis of azaperone(**d**), the best result was obtained using 25%(molar fraction) of sodium iodide. When the reaction was carried out using 10%, 15%, 20% and 25%(molar fraction) of the catalyst, the reaction rate progressed consistently with good yields. Therefore, the chemical yield of 60% was obtained when 25%(molar fraction) of the catalyst was employed, but no change in reaction yield was observed after this concentration.

In 2019, Wang *et al*.[22] developed a synthesis procedure for alkylation of *β*-chloro ketones through domino dehydrochlorination, in which alkyl-alkyl cross-coupling reaction proceeded by Mn(metal state) enabled the radical-based process. They produced meperone and azaperone compounds in the presence of Mn di-tert-butyl peroxide(DTBP) as catalysts. At first, 4-chloro-1-(4-fluorophenyl) butan-1-one was synthesized with 51% yield. This product further reacted with 1-(pyridin-2-yl) piperazine(as a secondary amine), which led to the synthesis of the azaperone with 73% yield. Notably, we simply synthesized 4-chloro-1-(4-fluorophenyl) butan-1-one(product **1b**) with 90% yield and a final product of compound 1**d** with 60% yield. Compared to Wang *et al*.[22] work, the findings of the present study are valuable and significant and have provided a new path for the synthesis of intended compounds.

Table 5 Optimization of the catalyst concentration for the synthesis of compounds c, d

Product	Constant parameter	Catalyst molar fraction(%)	Time/h	Yield(%)
c[a]	150 °C, Diethyleneglycol monomethyl ether as a solvent, KI(catalyst)	1	96	37
		2	96	50
		3	96	65
		4	96	65
c[b]	110 °C, Toluene:H_2O(volume ratio 1:1) as a solvent, benzyl triethylammonium(catalyst)	6	36	38
		8	36	56
		10	36	75
		15	36	76
d	Reflux, acetone as a solvent, NaI(catalyst)	10	96	43
		15	96	47
		20	96	52
		25	96	60
		30	96	60

a. Method 1; *b*. method 2.

3.2 Electrochemical Behavior of Azaperone

Fig.1(A) indicates the cyclic voltammetry response of GCE in the electrolyte containing 20 μmol/L azaperone and 0.1 mol/L phosphate buffer. The oxidation peak potential for the electro-oxidation of azaperone at the GCE is about 0.78 V with an oxidation peak current of 4.2 μA. In the reverse scan, no reduction peak appeared corresponding to the oxidation products of azaperone, indicating the irreversibility of its

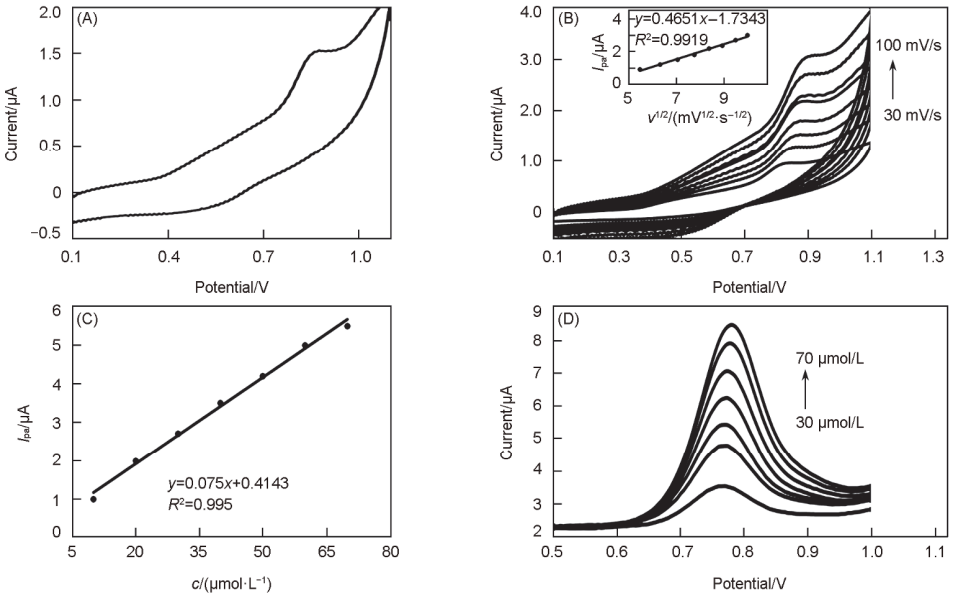

Fig.1 CV response of the GCE in an electrolyte containing 20 μmol/L azaperone and 0.1 mol/L phosphate buffer(pH=7.0)(A), the CVs of azaperone solution recorded at the GCE with various scan rates from 30 to 100 mV/s(B), and the calibration curves and DPVs of the GCE recorded in the presence of 30—70 μmol/L azaperone(C, D)

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electrochemical oxidation. The effect of the potential sweep rate in CV technique on the electro-oxidation of azaperone was investigated using GCE in the range of 30 to 100 mV/s[Fig.1(B)]. The plot of I_{pa} *vs.* square root of scan rate($v^{1/2}$)[inset in Fig.1(B)] showed good linearity, revealing a diffusion-controlled process for the electrochemical oxidation of azaperone[39]. As a highly sensitive technique capable of detecting trace value of electroactive compounds, DPV was utilized for the azaperone analysis. The determination of the azaperone concentration in a wide linear dynamic range of 1—70 μmol/L in the buffer solution with pH=7.0[Fig.1(C) and (D)] was successfully performed. The estimated limit of detection(LOD) for azaperone quantify was equal to 3.3 μmol/L with the calculated relative standard deviation of less than 4.31%(n=3) on the whole linear range of measurement. Considering the electrochemical activity of the azaperone, electrochemical sensors based on high efficient modified electrodes can be developed for accurate and sensitive analysis of this biocompound in various media, such as pharmaceutical and biological samples.

4 Conclusions

In this work, an improved method was presented for the synthesis of azaperone. The bis(2-chloroethyl) amine was generated after the reaction of bis diethanolamine with thionyl chloride. Then, the alkylation of 2-amino pyridine with bis(2-chloroethyl) amine was accomplished in the presence of a catalyst with 75% yield. Finally, alkylation of 4-chloro-1-(4-fluorophenyl) butan-1-oneto was carried out by using 1-(pyridin-2-yl) piperazine to achieve azaperone with a high yield. The total synthesis of azaperone under this condition was performed in four steps with a 42% overall yield. Finally, the electroactivity of azaperone in pH=7.0 was studied by cyclic voltammetry at the GCE. Electrochemical studies showed that the oxidation of azaperone takes place at 0.78 V *vs.* Ag/AgCl reference electrode. The electrochemical performance of the GCE for the analysis of azaperone was evaluated by the DPV technique in a wide linear concentration range. The LOD for azaperone determination was estimated to be 3.33 μmol/L with a relative standard deviation of 4.31%(n=3).

Electronic Supplementary Material

Supplementary material is available in the online version of this article at http://dx.doi.org/10.1007/s40242-021-1061-2.

Conflicts of Interest

The authors declare no conflicts of interest.

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