MOLECULAR IODINE FOR THE SYNTHESIS OF 2-ARYLQUINOXALINES

Huynh Van Tien*, Bui Thu Ha, Nguyen Van Hoa,
Truong Bach Chien, Hoang Xuan The, Nguyen Thi Anh Ngoc
Ho Chi Minh City University of Food Industry
*Email: *tienhv@hufi.edu.vn*
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ABSTRACT

This study gave a new method to synthesize 2-arylquinoxalines from *o*-phenylenediamines and aryl methyl ketones. The reaction occurred via molecular iodine-promoted direct C(sp^3)-H bond functionalization of aryl methyl ketones under transition metal-free conditions. The utilities of this study are the (1) direct Csp^3-H bond functionalization, (2) inexpensive and abundant iodine source, (3) transition metal-catalyst free, and (4) different synthesis of 2-arylquinoxalines from common materials.

Keywords: o-phenylenediamines; molecular iodine; acetophenones; quinoxalines; Csp^3-H bond functionalization

1. INTRODUCTION

Direct C-H bond functionalization approaches were among the most important goals of synthesizing essential compounds with an extensive range of physical, chemical, and biological properties…[1]. C-H bond functionalization pathways would reduce co-product formation, providing more environmentally friendly procedures for chemical synthesis [2]. In previous reports, most of the C-H bond functionalization strategies require the presence of a transition metal catalyst and/or a strong oxidizing agent [3]. Recently, transition metal-free C-H bond activation progress has become a more interesting topic [4, 5]. Molecular iodine-promoted/catalyzed organic transformation has been investigated as an effective and environmentally friendly metal-free strategy in organic synthesis [6, 7].

Quinoxaline compounds are essential substances because of their several pharmaceuticals, agricultural, and industrial applications [8]. Over the last two decades of scientific publications, quinoxaline has always played an important role in medicinal science [9]. The synthesis of quinoxaline derivatives has been developed for a long time, most common approach was the condensation reactions of *o*-phenylenediamine with different carbonyls such as *α*-diketone, *α*-hydroxyl ketone, *α*-haloketone to form quinoxaline derivatives [10-15]. Aside from *α*-diketone, *α*-hydroxyl ketone, *α*-haloketone, a few substrates were used to synthesize quinoxalines, including epoxides [16, 17], alkenes [18]. In this work, we would like to demonstrate a molecular iodine functionalization synthesis of quinoxalines from o-phenylenediamines and acetophenones.

2. EXPERIMENTAL METHOD

2.1. Instrumentations

Gas chromatography (GC) analyses were performed by a Shimadzu GC 2010-Plus equipped with a flame ionization detector (FID) and an SPB-5 column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.25 μm). The temperature program for GC analysis held samples at 100 °C for 1 minute, then gradually raised the temperature from 100 °C to 280 °C with an increment of 40 °C /min, which took 4.5 minutes to reach the highest temperature, and finally held them at 280 °C for another 4.5 minutes. Inlet and detector temperatures were set constant at 280 °C. The internal standard used in the calculation of GC yield was diphenyl ether.

Gas chromatography coupled with mass spectrometry (GC-MS) analyses were performed on Shimadzu GCMS-QP2010Ultra with a ZB-5MS column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.25 μm). The temperature program for the GC-MS analysis held samples at 50 °C for 2 minutes, then gradually raised the temperature from 50 °C to 280 °C with an increment of 10 °C /min, which took 23 minutes to complete, and finally held them at 280 °C for another 10 minutes. The inlet temperature was set constant at 280 °C. Mass spectroscopy used the electron ionization (EI) method to convert the samples into ions, and mass spectra were compared with those gathered from the NIST library.

The ^{1}H and ^{13}C NMR (500 and 125 MHz, respectively) spectra were recorded in $CDCl_3$ solvent using TMS peak as a reference on the AvanceNEO 500MHz spectrometer.

2.2. Experimental procedure

The procedure for the synthesis of 2-phenylquinoxaline was conducted to be in a dry 8-mL vial containing a magnetic stirring bar was added *o*-phenylenediamine (21.6 mg, 0.2 mmol), acetophenone (72 mg, 0.6 mmol), diphenyl ether (16 mg) as an internal standard, and molecular iodine (76.14 mg, 0.3 mmol). After that, DMSO (1 mL) was added to the vial. The reaction tube was then stirred under air at 120 °C for 20 h. After the reaction was completed. It was cooled down to room temperature. The organic components were extracted into ethyl acetate (5 mL), and washed with saturated aqueous $NaHCO_3$ solution (5 mL), dried over anhydrous Na_2SO_4. Reaction yields were recorded from the GC analysis results regarding the diphenyl ether internal standard. Reaction yields were determined by GC analysis results regarding the diphenyl ether internal standard. The organic layer was concentrated in a rotary evaporator to obtain the desired product, and the residue was further purified by column chromatography on silica gel (ethyl acetate: n-hexane = 1:10) to afford the synthesis of 2-phenylquinoxaline (10.3 mg, 25% yield). Each product was checked by GC-MS, ^{1}H NMR, and ^{13}C NMR to ensure the structure is correct.

3. RESULTS AND DISCUSSION

Delighted by previous studies, five factors were investigated to improve the yield of the desired product and identify the parameters that favored the formation of 2-phenylquinoxaline. Those were reaction temperature, catalyst amount, mol ratio, solvent types, and reaction time [19, 20]. In this study, we screened conditions for the synthesis of 2-phenylquinoxaline via reaction temperature, iodine amount, mol ratio, solvent types, and reaction time.

The study was initiated with the reaction between *o*-phenylenediamine (**1a**) and acetophenone (**2a**) in the presence of molecular iodine (Table 1). Temperature, iodine amount, reactant molar ratio, solvent, and reaction time were the selection factors to observe the

maximum **3aa** product. First, the reaction was investigated at different temperatures, passing from room temperature to 140 °C, the best yield was achieved at 120 °C (Entry 5). Second, analyzing the reaction yield with several amounts of iodine showed that in a lack of iodine, no trace amount of **3aa** was detected (Entry 7) and 3 equivalents performed the best (Entry 10). Regarding the reactant molar ratio, the best result was obtained using 3 equivalents of **2a** (Entry 15)**.** In solvent-controlled, DMSO indicated the best performance (Entry 17), other normal solvents such as toluene, DMF, DMA, DMAc, and NMP created the desired product in lower yields compared to DMSO**.** Likewise, 20 h was the best reaction time for this reaction (Entry 26). In summary, the suitable reaction condition was concluded to be at 120 °C under air for 20 h in DMSO, using 0.2 mmol reactants 1, 0.4 mmol reactants 2, in the presence of 0.3 mmol iodine (3 equivalents).

Table 1. Screening conditions for the synthesis of 2-phenylquinoxaline[a]

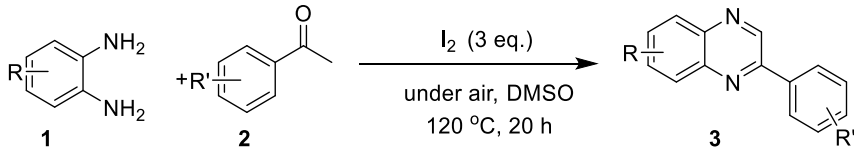
Entry	Temperature (°C)	Iodine amount (Equiv.)	**1a**:**2a** (mol:mol)	Solvent	Time (hours)	Yield[b] (%)
1	RT	2	1:2	DMSO	24	0
2	60	2	1:2	DMSO	24	5
3	80	2	1:2	DMSO	24	9
4	100	2	1:2	DMSO	24	17
5	**120**	**2**	**1:2**	**DMSO**	24	**24**
6	140	2	1:2	DMSO	24	22
7	120	0	1:2	DMSO	24	0
8	120	1	1:2	DMSO	24	15
9	120	2	1:2	DMSO	24	23
10	**120**	**3**	**1:2**	**DMSO**	24	**27**
11	120	4	1:2	DMSO	24	26
12	120	5	1:2	DMSO	24	26
13	120	3	1:1	DMSO	24	16
14	120	3	1:2	DMSO	24	26
15	**120**	**3**	**1:3**	**DMSO**	24	**28**
16	120	3	1:4	DMSO	24	27
17	**120**	**3**	**1:3**	**DMSO**	24	**28**
18	120	3	1:3	NMP	24	5
19	120	3	1:3	Toluene	24	trace
20	120	3	1:3	DMA	24	7
21	120	3	1:3	DMF	24	14
22	120	3	1:3	DMAc	24	12

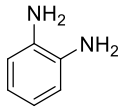
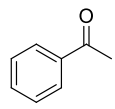
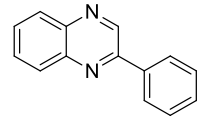
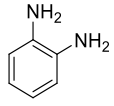
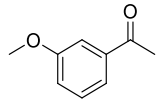
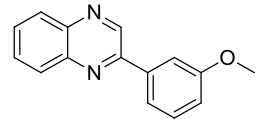
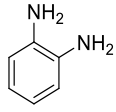
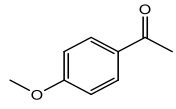
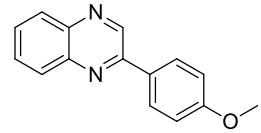
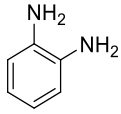
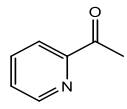
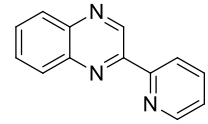
Entry	Temperature (°C)	Iodine amount (Equiv.)	**1a**:**2a** (mol:mol)	Solvent	Time (hours)	Yield[b] (%)
23	120	3	1:3	DMSO	8	5
24	120	3	1:3	DMSO	12	15
25	120	3	1:3	DMSO	16	22
26	**120**	**3**	**1:3**	**DMSO**	**20**	**28**
27	120	3	1:3	DMSO	24	28

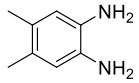
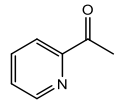
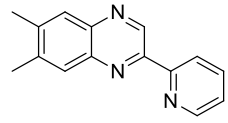
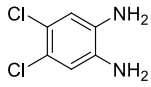
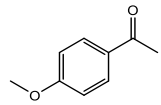
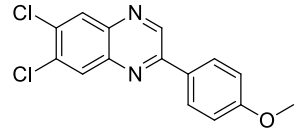
[a]Reaction conditions: *o*-phenylenediamine (0.2 mmol); solvent (1 mL); under air. The iodine amount was calculated based on 253.8 g/mol. Abbreviations: DMSO = dimethylsulfoxide; NMP = *N*-methyl-2-pyrrolidone; DMA = *N*,*N*-dimethylaniline; DMF = *N*,*N*-dimethylformamide; DMAc = dimethylacetamide. [b]GC yield.

With the suitable condition determined, the reaction scope was extended to synthesizing various substituted quinoxalines (Table 2).

Table 2. Synthesis of 2-phenylquinoxaline**s**[a]



Entry	Reactant 1	Reactant 2	Product	Isolated yield (%)
1			 **3aa**	25%
2			 **3ab**	22%
3			 **3ac**	19%
4			 **3ad**	20%

Entry	Reactant 1	Reactant 2	Product	Isolated yield (%)
5			 **3bd**	15%
6			 **3cc**	21%

[a] Reaction conditions: Reactant 1 (0.2 mmol); reactant 2 (0.4 mmol); iodine (0.3 mmol); DMSO (1 mL); 120 °C; under air; 20 h.

Under the standard conditions, the **3aa** product was obtained in a 25% isolated yield. The reactions of **1a** with 3-methoxyacetophenone, 4-methoxyacetophenone, 1-(pyridine-2-yl)ethan-1-one provided **3ab, 3ac, 3ad** in 22%, 19% and 20% yields, respectively. In the case of 4,5-dimethylbenzene-1,2-diamine was the reactant 1, 1-(pyridine-2-yl)ethan-1-one was the reactant 2, and the desired product (**3bd**) was obtained in 15% yield. Likewise, the reaction of 4,5-dichlorobenzene-1,2-diamine with 4-methoxyacetophenone furnished **3cc** in a 21% yield. The protocol could extend to other *o*-phenylenediamine derivatives and a wide range of aryl methyl ketones to provide quinoxaline derivatives, respectively. Compared to previous studies, this study conducted a lower efficiency, but the molecular iodine-promoted activation of $C(sp^3)$-H binding of acetophenone to synthesize 2-phenylquinoxaline has not been published yet.

The target compounds were initially detected and analyzed by GC-MS, then verified by ^{1}H NMR and ^{13}C NMR. The results from NMR spectrums were characterized below.

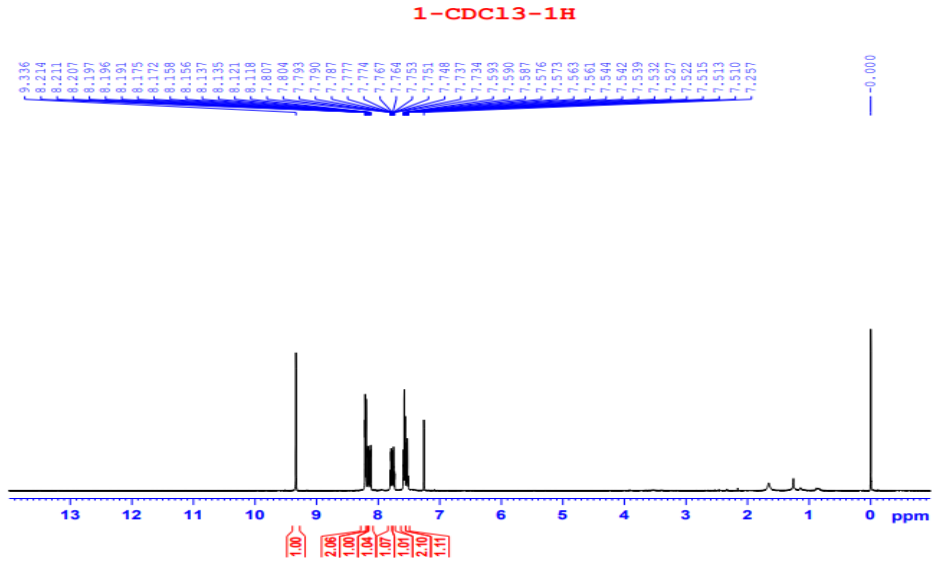


Figure 1. ^{1}H-NMR spectra of 2-phenylquinoxaline (3aa).

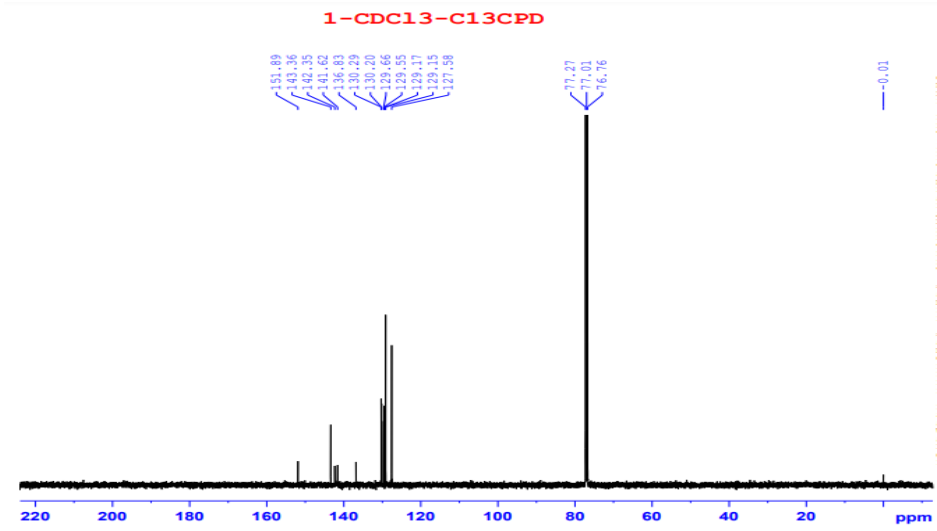
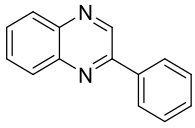


Figure 2. ^{13}C-NMR spectra of 2-phenylquinoxaline (3aa)

Characterization data for 2-phenylquinoxaline



^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.22 – 8.19 (m, 2H), 8.18 – 8.11 (m, 2H), 7.79 (ddd, *J* = 8.4, 6.9, 1.7 Hz, 1H), 7.75 (ddd, *J* = 8.4, 6.9, 1.6 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.55 – 7.50 (m, 1H).

^{13}C-NMR ($CDCl_3$, 125 MHz) δ(ppm) 127.5, 129.1, 129.5, 129.6, 130.1, 130.3, 136.8, 141.6, 142.3, 143.3, 151.7

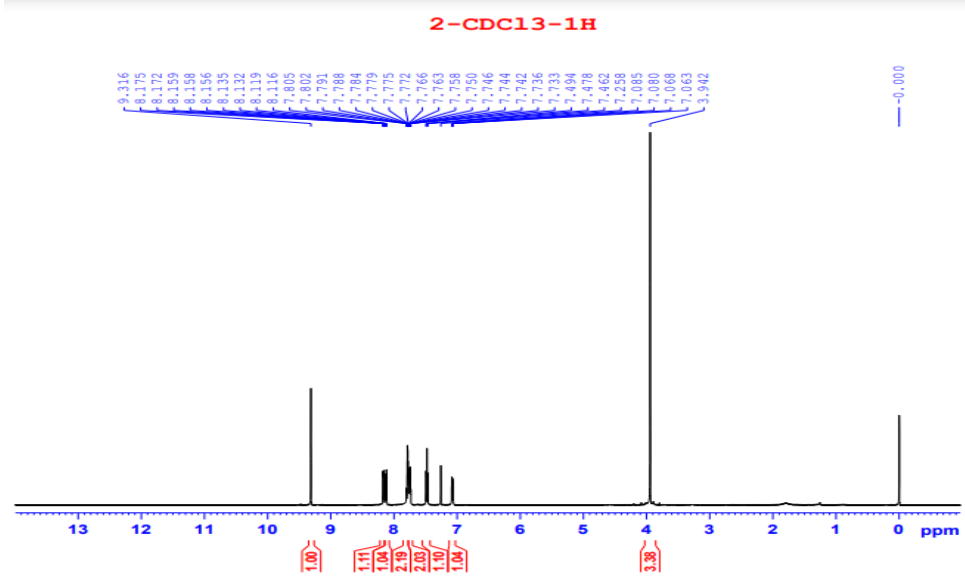


Figure 3. ^{1}H-NMR spectra of 2-(3-methoxyphenyl)quinoxaline (3ab)

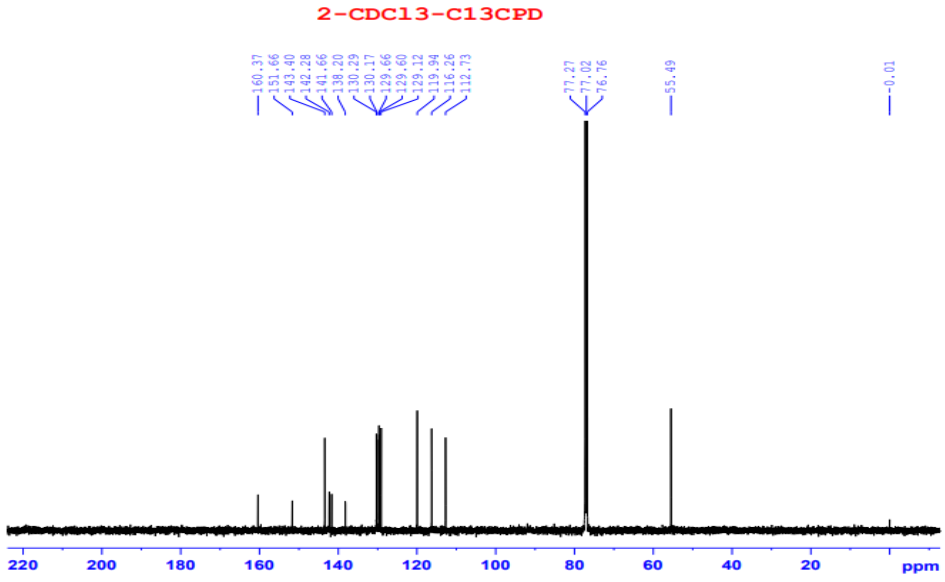
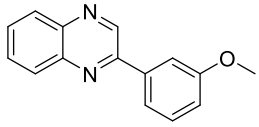


Figure 4. ^{13}C-NMR spectra of 2-(3-methoxyphenyl)quinoxaline (3ab)

Characterization data for 2-(3-methoxyphenyl)quinoxaline



^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.18 – 8.11 (m, 2H), 7.81 – 7.73 (m, 4H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.07 (ddd, *J* = 8.3, 2.7, 0.9 Hz, 1H), 3.94 (s, 3H).

^{13}C-NMR ($CDCl_3$, 125 MHz) δ(ppm) 53.8, 110.7, 160.3, 114.4, 129.3, 121.8, 137.4, 142.2, 148.3, 126.5, 142.8, 143.3, 127.8, 129.0, 129.9

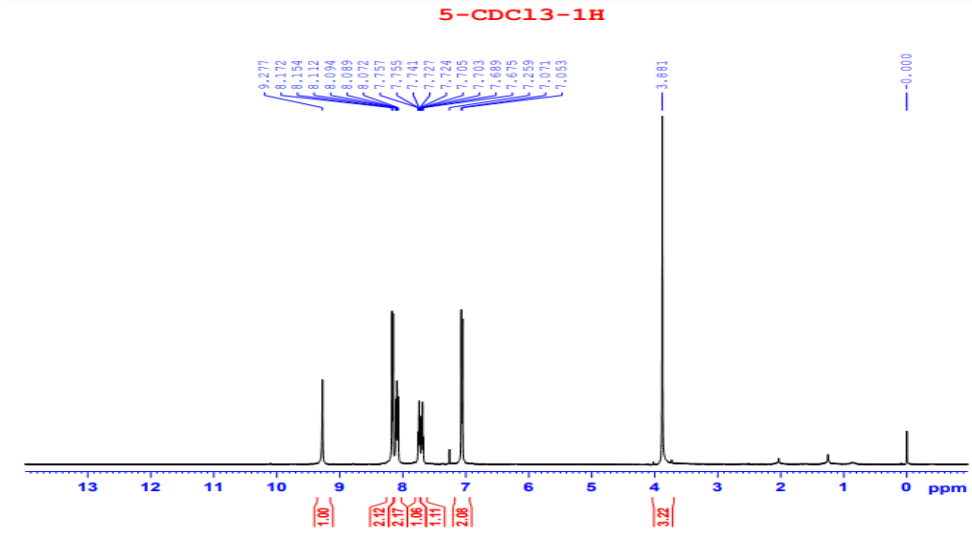


Figure 5. ^{1}H-NMR spectra of 2-(4-methoxyphenyl)quinoxaline (3ac)

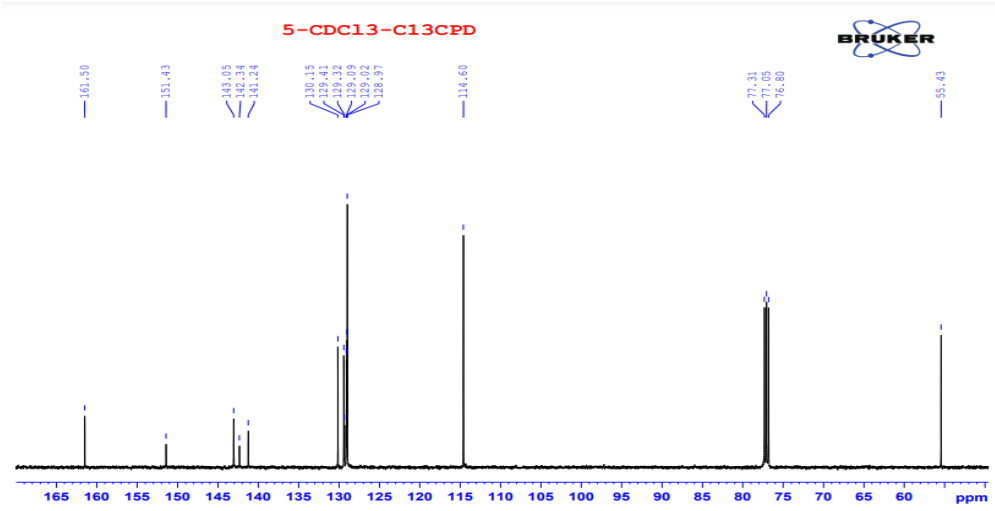
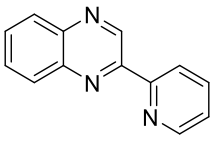


Figure 6. ^{13}C-NMR spectra of 2-(4-methoxyphenyl)quinoxaline (3ac)

Characterization data for 2-(4-methoxyphenyl)quinoxaline



^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.19 – 8.14 (m, 2H), 8.09 (ddd, *J* = 11.7, 8.3, 1.5 Hz, 2H), 7.71 (dddd, *J* = 25.8, 8.3, 6.9, 1.6 Hz, 2H), 7.10 – 7.03 (m, 2H), 3.88 (s, 3H).

^{13}C-NMR ($CDCl_3$, 125 MHz) 55.5, 114.6, 128.7, 129.3, 129.0, 129.4, 130.1, 141.2, 142.3, 143.0, 151.4, 161.4

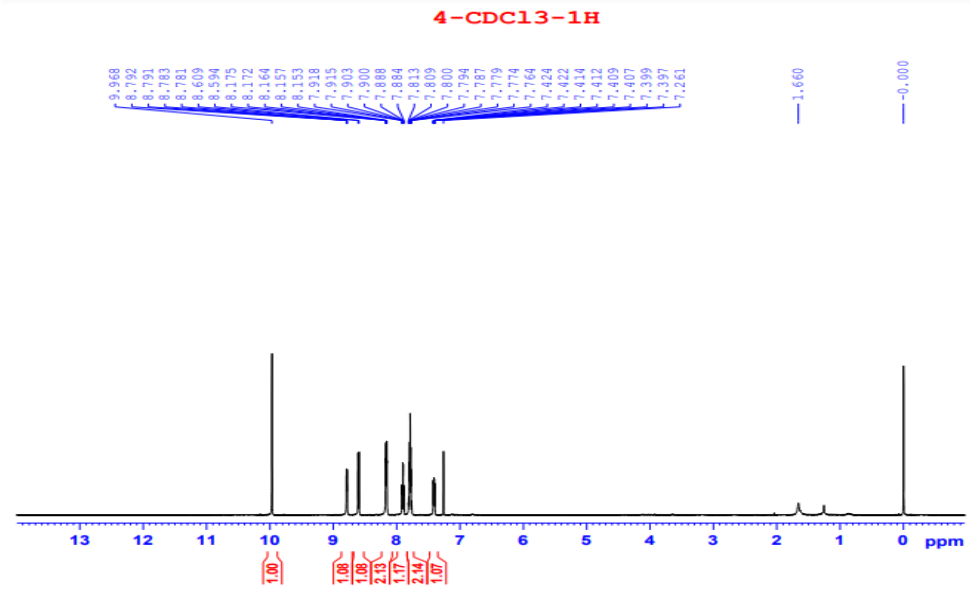


Figure 7. ^{1}H-NMR spectra of 2-(pyridin-2-yl)quinoxaline (3ad)

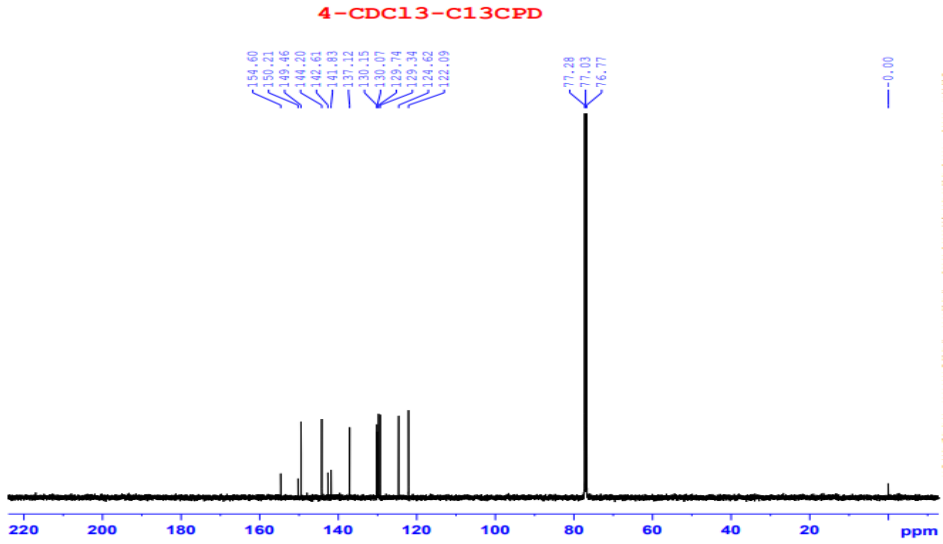
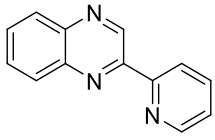


Figure 8. ^{13}C-NMR spectra of 2-(pyridin-2-yl)quinoxaline (3ad)

Characterization data for 2-(pyridin-2-yl)quinoxaline



^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 8.79 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 8.60 (dt, *J* = 8.1, 1.1 Hz, 1H), 8.19 – 8.13 (m, 2H), 7.90 (td, *J* = 7.7, 1.8 Hz, 1H), 7.82 – 7.74 (m, 2H), 7.41 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 125 MHz) 122.1, 124.7, 129.3, 129.7, 130.0, 130.1, 137.2, 141.8, 142.5, 144.1, 149.4, 150.2, 154.5

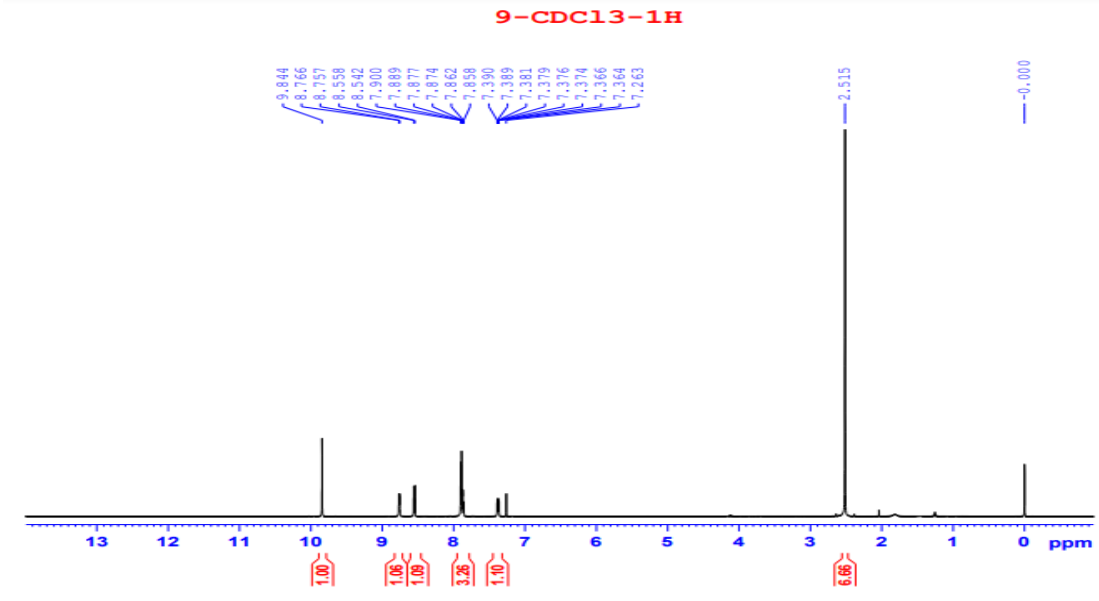


Figure 9. ^{1}H-NMR spectra of 6,7-dimethyl-2-(pyridin-2-yl)quinoxaline (3ba).

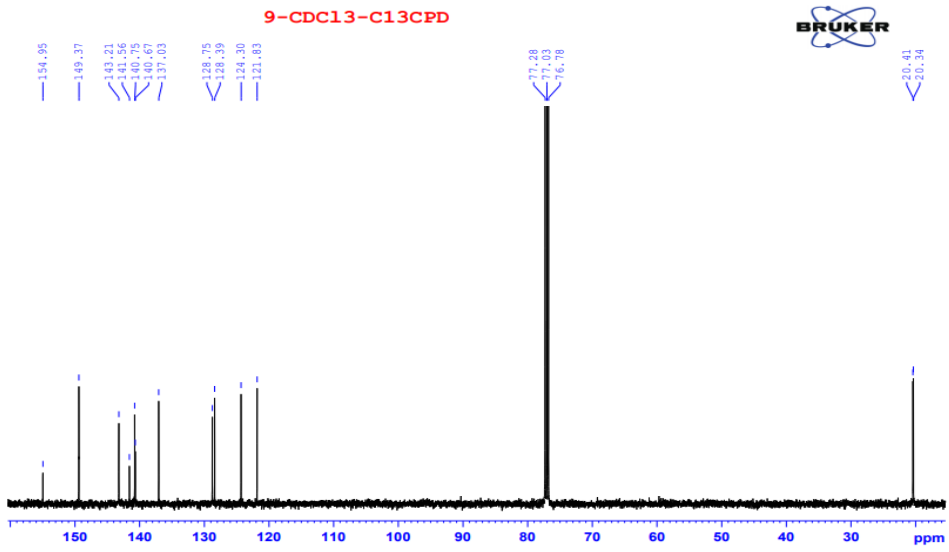
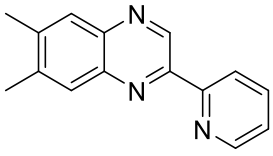


Figure 10. ^{13}C-NMR spectra of 6,7-dimethyl-2-(pyridin-2-yl)quinoxaline (3ba)

Characterization data for 6,7-dimethyl-2-(pyridin-2-yl)quinoxaline



^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 8.79 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 8.60 (dt, *J* = 8.1, 1.1 Hz, 1H), 8.19 – 8.13 (m, 2H), 7.90 (td, *J* = 7.7, 1.8 Hz, 1H), 7.82 – 7.74 (m, 2H), 7.41 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 125 MHz) 122.1, 124.7, 129.3, 129.7, 130.0, 130.1, 137.2, 141.8, 142.5, 144.1, 149.4, 150.2, 154.5

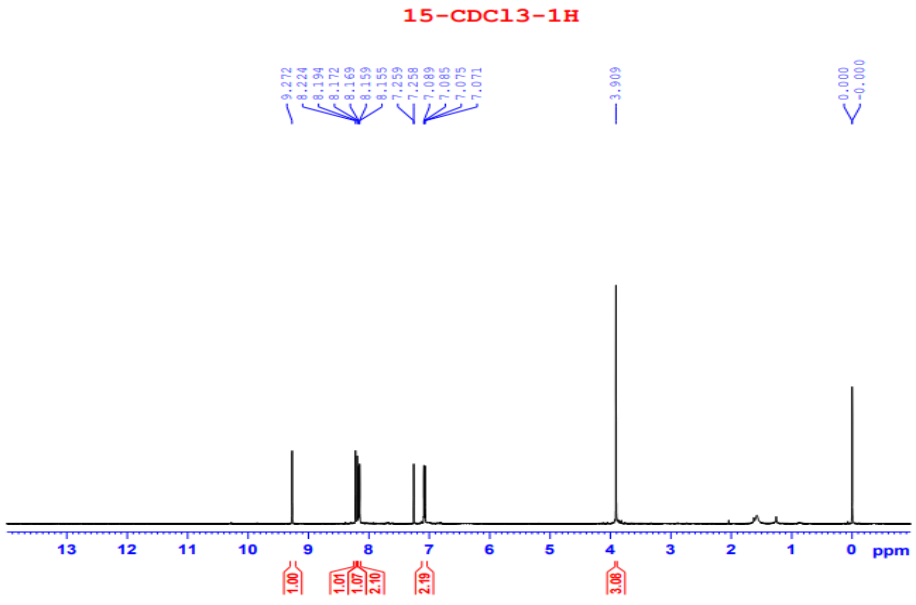


Figure 11. ^{1}H-NMR spectra of 6,7-dichloro-2-(4-methoxyphenyl)quinoxaline (3cc)

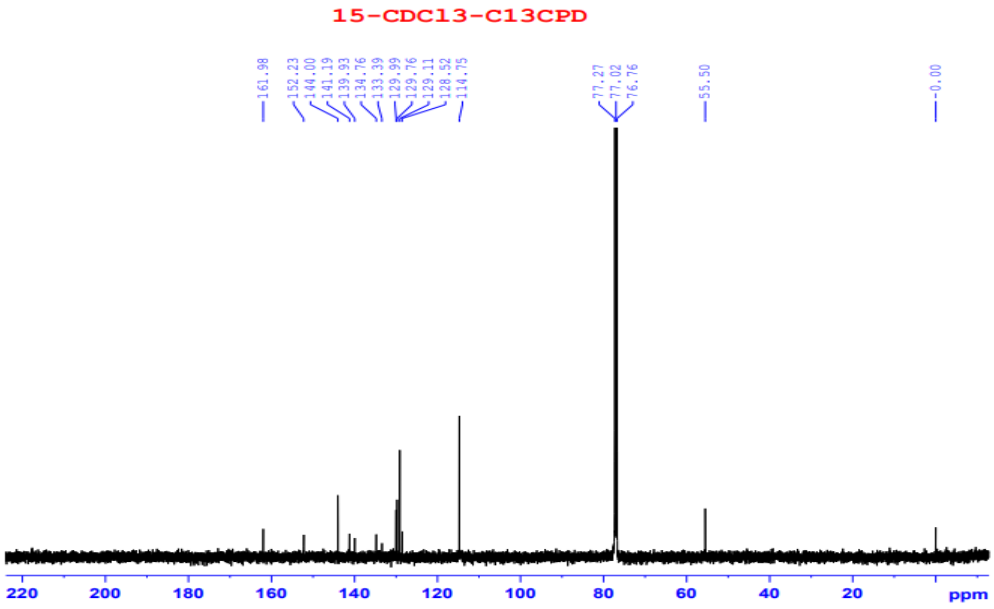
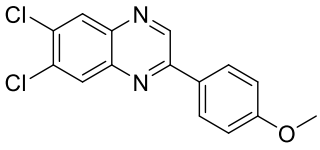


Figure 12. ^{13}C-NMR spectra of 6,7-dichloro-2-(4-methoxyphenyl)quinoxaline (3cc)

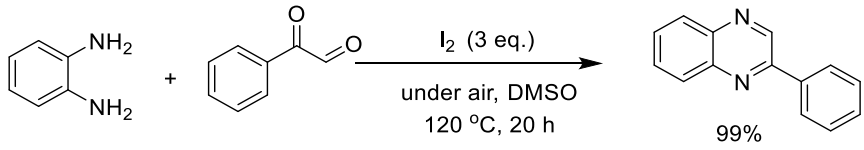
Characterization data for 6,7-dichloro-2-(4-methoxyphenyl)quinoxaline



^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.22 (s, 1H), 8.19 (s, 1H), 8.18 – 8.14 (m, 2H), 7.10 – 7.05 (m, 2H), 3.91 (s, 3H).

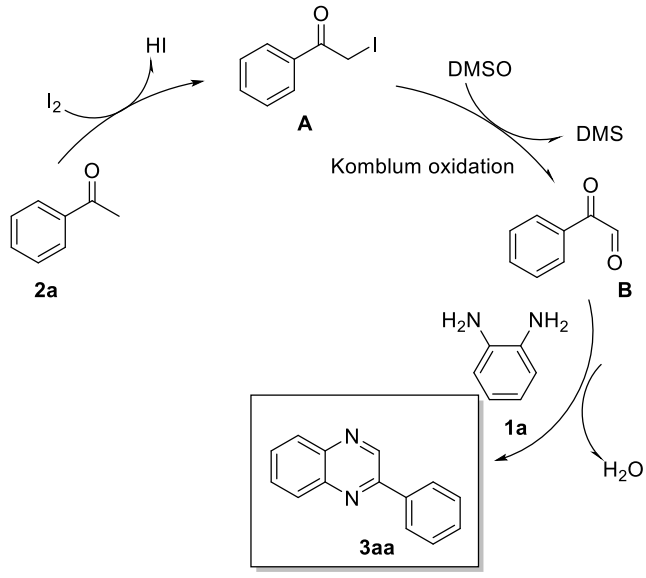
^{13}C-NMR ($CDCl_3$, 125 MHz) 55.4, 76.7, 77.0, 77.2, 114.7, 128.4, 129.1, 129.7, 129.9, 133.3, 134.7, 139.9, 141.1, 143.9, 144.0, 152.2, 161.9

In order to explain the mechanism, the reaction between *o*-phenylenediamine and phenylglyoxal was demonstrated under the standard condition. The transformation result was **3aa** in 99% GC yield.



Scheme 1. The reaction between *o*-phenylenediamine and phenylglyoxal

The two steps possible mechanism is proposed in Scheme 3. In the first step, followed by the Komblum oxidation type, in the presence of elemental iodine, DMSO acetophenone was oxidized to form phenylglyoxal (**B**) [21-24]. The second step was a condensation of phenylglyoxal (**B**) with o-phenylenediamine (**1a**) afforded to **3aa** [25, 26].



Scheme 2. Mechanism proposal

4. CONCLUSIONS

In summary, a new synthesis of 2-aryquinoxalines from o-phenylenediamines and aryl methyl ketones in the presence of molecular-iodine was demonstrated. The reaction occurred at 120 °C, under air for 20 h in DMSO. The differences of 2-aylquinoxalines were obtained in this way and a possible mechanism also was proposed. Although the reaction yields were not high, this protocol is new and can promote further investigations in the synthesis of quinoxalines using a large range of aryl methyl ketone derivatives.

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TÓM TẮT

SỬ DỤNG IOD TRONG TỔNG HỢP CÁC DẪN XUẤT CỦA 2-ARYLQUINOXALINE

Huỳnh Văn Tiến*, Bùi Thu Hà, Nguyễn Văn Hòa,
Trương Bách Chiến, Hoàng Xuân Thế, Nguyễn Thị Ánh Ngọc
Trường Đại học Công nghiệp Thực phẩm TP.HCM
*Email: *tienhv@hufi.edu.vn*

Nghiên cứu đưa ra phương pháp mới trong tổng hợp các dẫn xuất 2-arylquinoxaline từ các dẫn xuất của *o*-phenylenediamine và các dẫn xuất của ayl methyl ketone. Phản ứng được thực hiện ở 120 °C, trong không khí, thời gian phản ứng là 20 h, trong dung môi DMSO, dưới sự có mặt của iod nguyên tố. Nhiều dẫn xuất của 2-aylquinoxaline đã được tổng hợp thành công bằng con đường này và cơ chế phản ứng phù hợp cũng đã được đề xuất. Mặc dù hiệu suất phản ứng chưa cao nhưng phương pháp sử dụng iod nguyên tố kích hoạt liên kết $C(sp^3)$-H của các dẫn xuất acetophenone để tổng hợp thành các dẫn xuất quinoxaline là mới, phương pháp này hứa hẹn sẽ thúc đẩy các nghiên cứu sâu hơn trong tổng hợp các dẫn xuất của quinoxaline bằng cách sử dụng các dẫn xuất của aryl methyl ketone làm tác chất ban đầu. Ưu điểm của nghiên cứu là: (1) trực tiếp kích hoạt liên kết Csp^3-H, (2) nguồn iodine dồi dào, rẻ tiền, (2) không sử dụng xúc tác kim loại chuyển tiếp, (4) tổng hợp được các dẫn xuất 2-arylquinoxaline khác nhau từ các tác chất ban đầu phổ biến.

Từ khóa: o-phenylenediamines, Iod; acetophenones, quinoxalines, kích hoạt liên kết Csp^3-H.