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Eco-friendly Synthesis of Quinoxaline Derivatives Using Mineral Fertilizers as Heterogeneous Catalysts

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Abstract: The synthesis of quinoxaline derivatives were heterogeneously catalyzed by phosphate-based catalyst fertilizers, MAP, DAP, or TSP. The reaction affords the desired products in excellent yields at ambient temperature. A series of studies were conducted to investigate the effect of solvent reaction, its volume, and catalyst amount. A study of the recyclability of catalysts removed from the reaction mixture by simple filtration was also carried out to find that the three phosphate-based catalysts retain their catalytic activities up to six cycles.

Keywords: Phosphate, Fertilizers, MAP, DAP, TSP, Quinoxaline, Heterogeneous catalysts.

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INTRODUCTION

Since the US Environmental Protection Agency (EPA) had developed the concept of "green chemistry" to protect human health and environment (1), enormous research efforts have been devoted to designing clean and eco-friendly chemical processes (2-4). In this area, considerable interests have focused on heterogeneous catalysis (5-7) due to its advantages to reduce energy consumption but to recover and recycle the used catalyst. Thereby, a large variety of heterogeneous catalysts have been developed and widely used to carry out numerous organic syntheses (8). Among the greener catalysts developed, phosphate-based minerals appear as the obvious choice for Moroccan researchers as they represent the first mining wealth of their country. For this reason, they contribute to the valorization of these minerals as promising catalysts. S. Sebti and co-workers were the first team to introduce natural (9), doped (10) or modified (11) phosphate not only as heterogeneous catalysts for organic reactions but also as the support of metal catalysts (12-13).

Motivated by the desire to introduce a new generation of phosphate-based heterogeneous catalysts, our laboratory was particularly interested in the catalytic performance evaluation of some phosphate fertilizers for Knoevenagel condensation and 1-(benzothiazolylamino)-methyl-1-2-naphthol derivatives (14-15).

In continuation of our ongoing effort to extend the application of these novel fertilizer phosphates as green and reusable heterogeneous catalysts, we develop in the present paper a straightforward and efficient process to synthesize quinoxaline derivatives utilizing phosphate-based catalysts, mono-ammonium phosphate (MAP), di-ammonium phosphate (DAP), or triple superphosphate (TSP).

The quinoxaline derivatives are a class of nitrogen-containing fused heterocyclic compounds, which

attracted considerable interest since their basic skeleton involved as a core structure of several drug molecules such as quinacillin (15), brimonidine (16), varenicline (17), clofazimine (18), echinomycin (19-20) and actinomycin (21). Some other quinoxaline-containing compounds have shown many biological properties (22), such as antimicrobial (23), antidiabetic (24), anti-inflammatory (25), antioxidant (25), anticancer (26), antileishmanial and antitrypanosomal (27) activities. Additionally, quinoxaline derivatives act as inhibitors of the aldose reductase enzyme (28) and the kinase protein (29). Furthermore, the quinoxaline structural nucleus has recently identified to possess inhibitory effects on the corrosion of some metals (30-32).

In light of their importance, numerous methods have been designed to synthesize quinoxaline derivatives. Most broadly, they involve 1,4-addition of 1,2-diamines to diazenylbutenes (33), oxidative cyclization of α-haloketones and 1,2-diamines (34), oxidative coupling of epoxides with ene-1,2-diamines (35), and condensation of 1,2-diamines with 1,2-dicarbonyl compounds (36-37). The latter method was chosen as the reaction model.

EXPERIMENTAL

Chemicals and instruments

Chemicals were purchased from Fluka or Aldrich companies. The spectral data were compared with those of the known compounds reported in the literature. Melting points were recorded on a Wagner & Munz HEIZBANK Kofler bench. Thin layer chromatography (TLC) on silica gel SIL G/UV 254 plates were used to monitor the progress of the reactions.

Synthesis of quinoxaline derivatives: General procedure

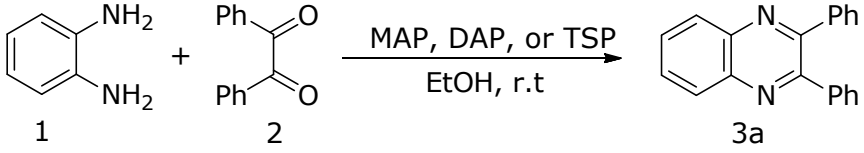
In a typical reaction, to a solution of 1,2-diamine (1 mmol) and 1,2-dicarbonyl (1 mmol) in EtOH (2 mL) was added phosphate-based catalyst MAP, DAP or TSP (0.006 g). The resulting mixture stirred at 800 rpm at ambient temperature for appropriate reaction time as indicated by TLC. The solid product formed was dissolved in hot EtOH and filtered to separate the catalyst, and the resulting filtrate was placed in ice-bath to give a pure product as crystals. All prepared products were identified as based on comparison of their melting points and their ^{1}H NMR and ^{13}C NMR data with authentic samples reported in the literature. Supplementary material includes the NMR data is joined to this paper.

Recyclability of MAP, DAP and TSP

The recyclability of the catalyst was examined using the model reaction under optimized reaction conditions. The catalyst is recovered by simple filtration at the end of the reaction, washed with hot EtOH, dried at oven at 80 °C for 6 hours, and then reused.

RESULTS AND DISCUSSION

In a preliminary study, the condensation of 1,2-diamines **1** with 1,2-dicarbonyl **2** (Scheme 1) chosen as a test reaction for the catalytic activity of catalysts MAP, DAP, and TSP. Table 1 gathers the results and noticeably displays that in the presence of catalysts, the reaction led to the expected product in higher yields (94-99%) within shorter reaction times (Table 1, entries 2-4).



1 2 3a

Scheme 1. Condensation of 1,2-diamines with 1,2-dicarbonyl compounds.

Table 1. Results and physical characteristics of 2,3-diphenylquinoxaline **3a.**

Entry	Catalyst	Time[a]	Yield[b] (%)
1	-	60	23
2	MAP	4	94
3	DAP	2	99
4	TSP	2	96

[a] Time reported in min monitored by TLC. [b] Isolated yields.

These encouraging results prompted us to investigate the solvent effect on the reaction. The results displayed in Table 2 show that the reagents react efficiently in the different solvents. However, the yields decreased smoothly when the reaction is carrying out in cyclohexane and THF. The best yields are obtained in EtOH. Consequently, we chose it as an optimal solvent for this reaction to avoid the use of the toxic solvent and thus to contribute to the protection of the environment.

Table 2. Solvent effect on the quinoxaline **3a** synthesis [a].

Entry	Solvent	Catalyst	Time (min)	Yield[b] (%)
1		MAP	4	94
2	EtOH	DAP	2	99
3		TSP	2	96
4		MAP	4	95
5	MeOH	DAP	2	96
6		TSP	2	90
7		MAP	4	98
8	Isopropanol	DAP	2	96
9		TSP	2	89
10		MAP	4	92
11	CH_3CN	DAP	2	95
12		TSP	2	94
13		MAP	4	92
14	AcOEt	DAP	2	94
15		TSP	2	94
16		MAP	4	94
17	Dioxane	DAP	2	93
18		TSP	2	92
19		MAP	4	92
20	$CHCl_3$	DAP	2	93
21		TSP	2	90
22		MAP	4	87
23	Cyclohexane	DAP	2	86
24		TSP	2	82
25		MAP	4	73
26	THF	DAP	2	78
27		TSP	2	74

[a] Reaction conditions: 1,2-diamine (1 mmol) and 1,2-dicarbonyl (1 mmol), Solvent (2 mL), 0.006 g of catalyst, r.t; [b] Isolated yields.

Further experiments were conducted to determine the optimum catalyst loading. As revealed in Figure 1, yields increase smoothly with about 1% when DAP amount increases, and decrease smoothly with 2% or 1% when MAP and TSP amounts increase, this result allows us to deduce that the amount of the optimal catalyst is 0.003 g, thus this quantity is widely sufficient to give good yields at 96% for MAP, at 98% for DAP and at 97% for TSP. One can also notice that the reaction times are concise 4, 2 and 2 min in the presence of MAP, DAP, and TSP catalysts, respectively.

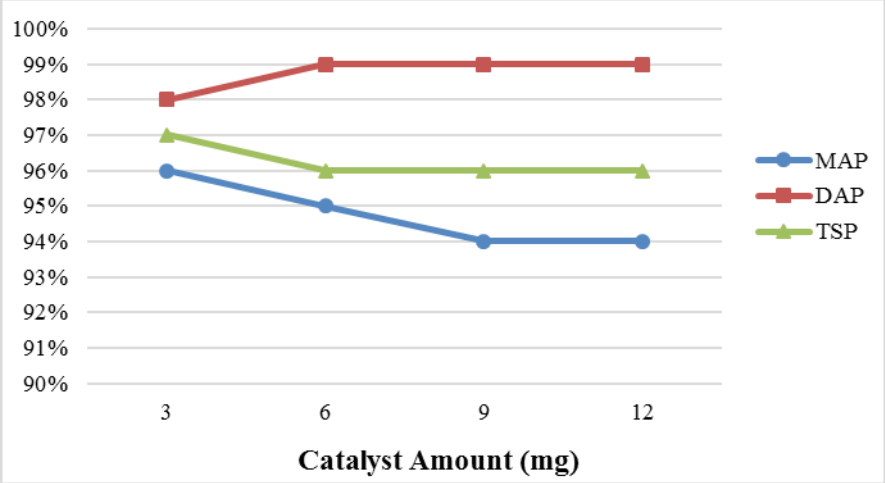
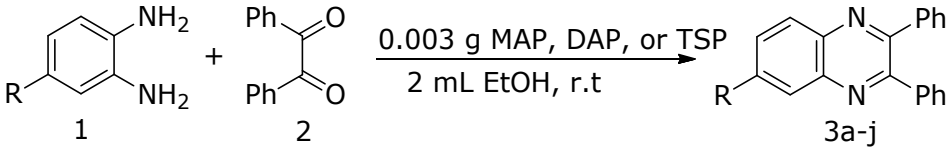


Figure 1. Effect of the catalyst amount on the quinoxaline **3a** synthesis.

In order to explore the reliability of the protocol developed to synthesize the quinoxaline derivatives, various aryl 1,2-diamines were condensed with various 1,2-dicarbonyl compounds (Scheme 2) under the optimal reaction conditions. Table 3 shows that the heterogeneous catalysts MAP, DAP,

and TSP afford the products in high to excellent yields 89-99% in short reaction times 2-4 min.



Scheme 2. Condensation of aryl 1,2-diamines with 1,2-dicarbonyl compound.

Table 4 collects the yields and reaction times of the condensation of 1,2-diamines with 1,2-dicarbonyl catalyzed by MAP, DAP, and TSP and those brought out in the literature. As can be seen, phosphate fertilizers MAP, DAP, and TSP underwent the reaction more rapidly than Fe_3O_4@SiO_2–imid–PMA^n, $VOSO_4$, and MIL-101-Cr-NH-RSO_3H, though the yields were comparable.

Table 4. Comparison between the present results and those given in the literature.

Entry	Catalyst	Condition	Time (min)	Yield (%)	Ref
1	Fe_3O_4@SiO_2–imid–PMA^n (0,5 mol%)	EtOH, r.t.	10	97	(38)
2	$VOSO_4$ (3 mol%)	EtOH, r.t.	20	96	(39)
3	MIL-101-Cr-NH-RSO_3H (3.9 mol%-SO_3H)	MeOH, 45 °C	12	93	(40)
4	MAP (0.003 g)	EtOH, r.t.	4	96	This work
5	DAP (0.003 g)	EtOH, r.t.	2	98	This work
6	TSP (0.003 g)	EtOH, r.t.	2	97	This work

The catalytic efficiency of the catalyst is determined not only by its capacity to lead to the formation of the desired product with a good yield and short reaction time but also by its recyclability and its natural regeneration. Finally, it seemed necessary to check the reusability of the three catalysts (MAP, DAP, and TSP) in the optimum reaction conditions.

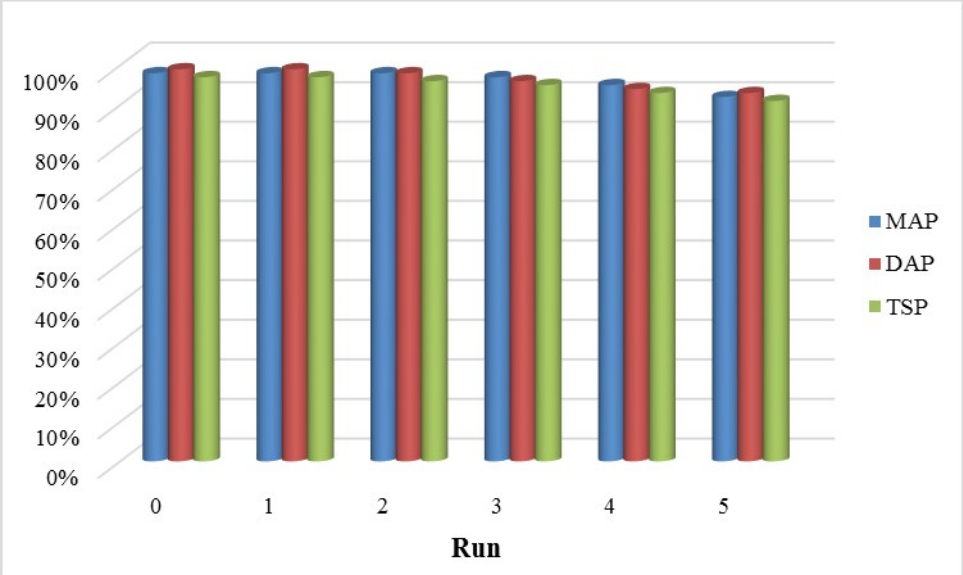
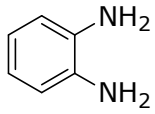
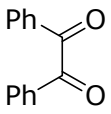
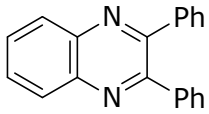
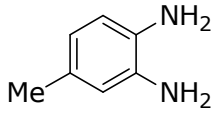
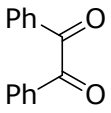
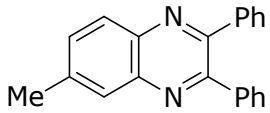
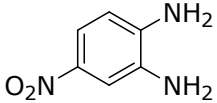
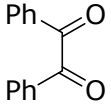
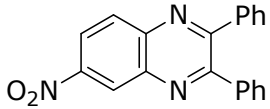
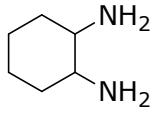
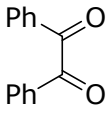
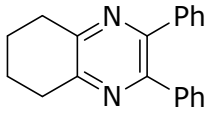
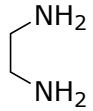
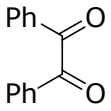
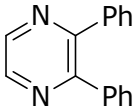
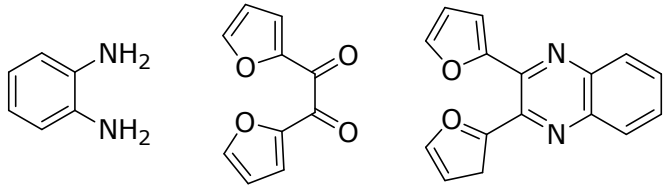
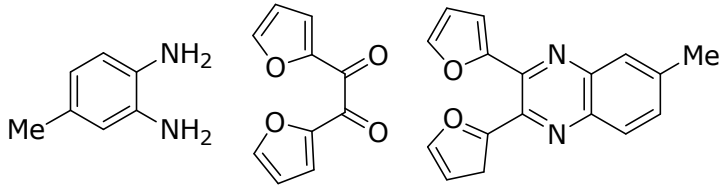
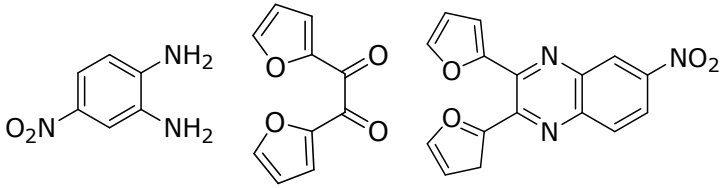
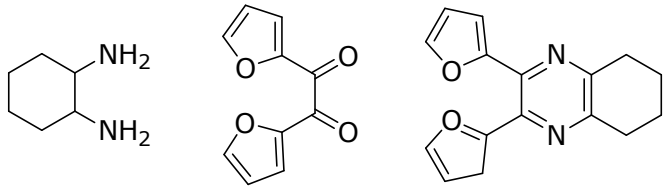
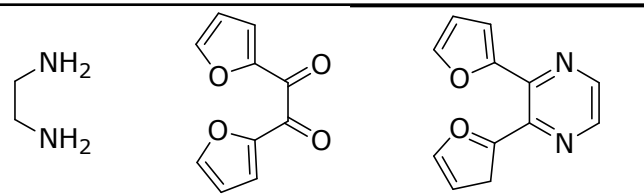


Figure 2. Recyclability of MAP, DAP, and TSP (0.003 g) in the condensation of 1,2-diamines with 1,2-dicarbonyl compounds at optimal conditions.

The catalysts remain functional throughout the six runs with a slight loss of their catalytic capacity that can be estimated by about 5% in yield.

Table 3. Quinoxaline derivatives synthesis catalyzed by MAP, DAP, and TSP at room temperature [a].
[a] Reaction conditions: 1,2-diamine (1 mmol) and 1,2-dicarbonyl (1 mmol), EtOH (2 mL), 0.003 g of catalyst, r.t. [b] Isolated yields.

Entry	aryl 1,2-diamines	1,2-dicarbonyl	Product	Molecular weight (g/mol)	Catalyst	Time (min)	Yield[b] (%)	TON	TOF (h^{-1})
1(3a)				282.3	MAP	4	96	36.67	547.31
					DAP	2	98	43.17	1308.18
					TSP	2	97	75.78	2296.36
2(3b)				296.4	MAP	4	97	37.16	554.63
					DAP	2	98	43.17	1308.18
					TSP	2	99	77.34	2343.64
3(3c)				327.3	MAP	4	95	36.39	543.13
					DAP	2	94	41.41	1254.85
					TSP	2	97	75.78	2296.36
4(3d)				314.4	MAP	4	88	33.71	503.13
					DAP	2	90	39.65	1201.51
					TSP	2	90	70.31	2130.60
5(3e)				232.28	MAP	4	90	34.48	514.63
					DAP	2	88	38.77	1174.85
					TSP	2	91	71.09	2154.24

6(3f)		262.26	MAP	4	90	34.48	514.63
			DAP	2	93	40.97	1241.51
			TSP	2	91	71.09	2154.24
7(3g)		276.29	MAP	4	94	36.02	537.61
			DAP	2	92	40.53	1228.18
			TSP	2	97	75.78	2296.36
8(3h)		307.26	MAP	4	91	34.86	520.29
			DAP	2	89	39.21	1188.18
			TSP	2	92	71.87	2177.88
9(3i)		266.29	MAP	4	86	32.95	491.79
			DAP	2	89	39.21	1188.18
			TSP	2	88	68.75	2083.33
10(3j)		212.2	MAP	4	88	33.72	503.28
			DAP	2	86	37.88	1147.88
			TSP	2	90	70.31	2130.61

CONCLUSION

To sum up the present study, phosphate-based fertilizers MAP, DAP, and TSP act as active heterogeneous catalysts for the synthesis of quinoxalines from various 1,2-diamines and 1,2-dicarbonyl compounds at ambient temperature. The optimum reaction conditions were not determined only by choice of the "greener" solvent and its volume, but also by the determination of the most appropriate weight of the catalyst, in order to present an environmentally benign protocol for this synthesis. Moreover, the study of the recyclability results shows that the catalysts can be quickly recovered and reused for at least six runs.

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Eco-friendly Synthesis of Quinoxaline Derivatives Using Mineral Fertilizers as Heterogeneous Catalysts

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Supplementary Information

*2,3-diphenylquinoxaline (**3a**, Table 3, Entry 1).* M.p.: 127-128°C (126-127°C [36-37]); ^{1}H NMR (300 MHz, DMSO-d6): δ (ppm): 7.32-7.36 (m, 6H); 7.42-7.46 (m, 4H); 7.86-7.88 (m, 2H); 8.14-8.16 (m, 2H). ^{13}C NMR (300 MHz, DMSO-d6): δ(ppm) : 128.50; 129.22; 129.26; 130.16; 130.84; 139.23; 140.93; 153.49.

*6-methyl-2,3-diphenylquinoxaline (**3b**, Table 3, Entry 2).* M.p.: 121-122°C (120-122°C [36-37]); ^{1}H NMR (300 MHz, DMSO-d6): δ (ppm): 2.47 (s, 3H); 7.30-7.47 (m, 6H); 7.68-7.71 (m, 4H); 7.92 (m, 1H); 8.01 (m, 1H); 8.04 (m, 1H). ^{13}C NMR (300 MHz, DMSO-d6): δ (ppm): 21.83; 127.96; 128.82; 129.15; 130.13; 133.02; 139.42; 141.00; 152.56; 153.30.

*6-nitro-2,3-diphenylquinoxaline (**3c**, Table 3, Entry 3).* M.p.: 141-142°C (140-142°C [37]); ^{1}H NMR (300 MHz, DMSO-d6): δ (ppm): 7.36-7.46 (m, 6H); 7.47-7.54 (m, 4H); 8.38 (m, 1H); 8.58 (m, 1H); 8.93 (m, 1H). ^{13}C NMR (300 MHz, DMSO-d6): δ (ppm): 124.05; 129.87; 130.29; 138.45; 139.69; 143.46; 148.11; 155.86; 156.51.

*2,3-Diphenyl-5,6,7,8-tetrahydroquinoxaline (**3d**, Table 3, Entry 4).* M.p.: 153–154°C (152–155°C [37]); ^{1}H NMR (300 MHz, DMSO-d6): δ (ppm): 1.99–2.03 (m, 4H), 3.11 (m, 4H), 7.30–7.33 (m, 6H), 7.44–7.49 (m, 4H). ^{13}C NMR (300 MHz, DMSO-d6): δ (ppm): 22.9, 32.0, 128.2, 128.4, 129.9, 139.2, 149.8, 151.1.

*2,3-Diphenylpyrazine (**3e**, Table 3, Entry 5).* M.p.: 119–120°C (121–122°C [37]); ^{1}H NMR (300 MHz, DMSO-d6): δ (ppm): 7.30–7.37 (m, 6H), 7.43–7.48 (m, 4H), 8.62 (s, 2H). ^{13}C NMR (300 MHz, DMSO-d6): δ (ppm): 128.6, 128.9, 129.8, 139.0, 142.4, 153.1.

*2,3-di(furan-2-yl)quinoxaline (**3f**, Table 3, Entry 6).* M.p.: 133–135°C (134–136°C [36-37]); ^{1}H NMR (300 MHz, DMSO-d6): δ (ppm): 6.59 (m, 2H), 6.68 (m, 2H), 7.65 (m, 2H), 7.79 (m, 2H), 8.17 (m, 2H). ^{13}C NMR (300 MHz, DMSO-d6): δ (ppm): 112.00, 112.93, 129.06, 130.67, 140.71, 142.85, 144.22.

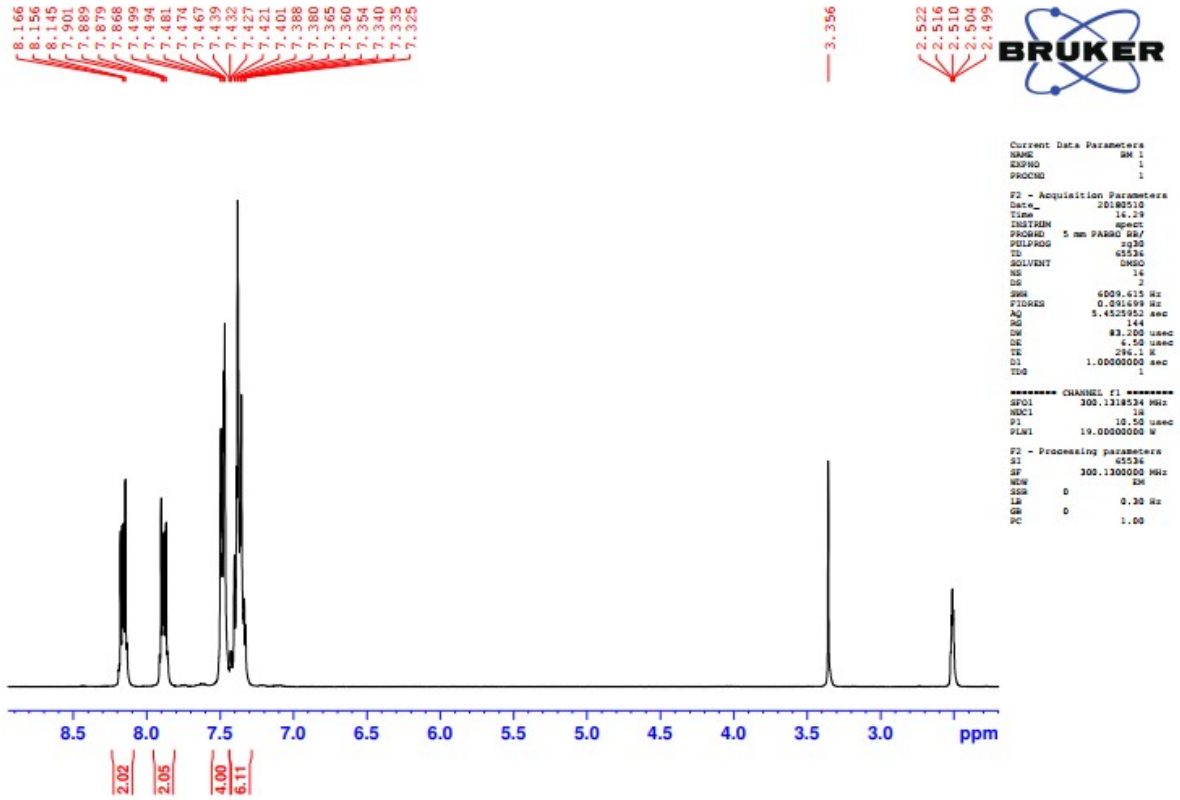
*2,3-di(furan-2-yl)-6-methylquinoxaline (**3g**, Table 3, Entry 7).* M.p.: 124–125°C (122–124°C [36-37]); ^{1}H NMR (300 MHz, DMSO-d6): δ (ppm): 6.71 (m, 4H), 7.68 (m, 3H), 7.99 (s, 1H), 7.99 (m, 1H). ^{13}C NMR (300 MHz, DMSO-d6): δ (ppm): 21.46, 111.42, 111.97, 112.40, 127.30, 127.88, 132.21, 138.53, 139.98, 140.65, 141.12, 141.92, 143.35, 143.52, 150.40.

*2,3-di(furan-2-yl)-6-nitroquinoxaline (**3h**, Table 3, Entry 8).* M.p.: 154–156°C (152–154°C [36-37]); ^{1}H NMR (300 MHz, DMSO-d6): δ (ppm): 6.62-6.65 (m, 2H), 6.97 (m, 2H), 7.68 (m, 2H), 8.32 (m, 1H), 8.59 (m, 1H), 9.04 (m, 1H). ^{13}C NMR (300 MHz, DMSO-d6): δ (ppm): 111.38, 111.52, 113.55, 114.38, 122.49, 123.98, 129.47, 137.98, 141.88, 142.98, 143.45, 143.95, 144.41, 146.64, 148.89, 148.98.

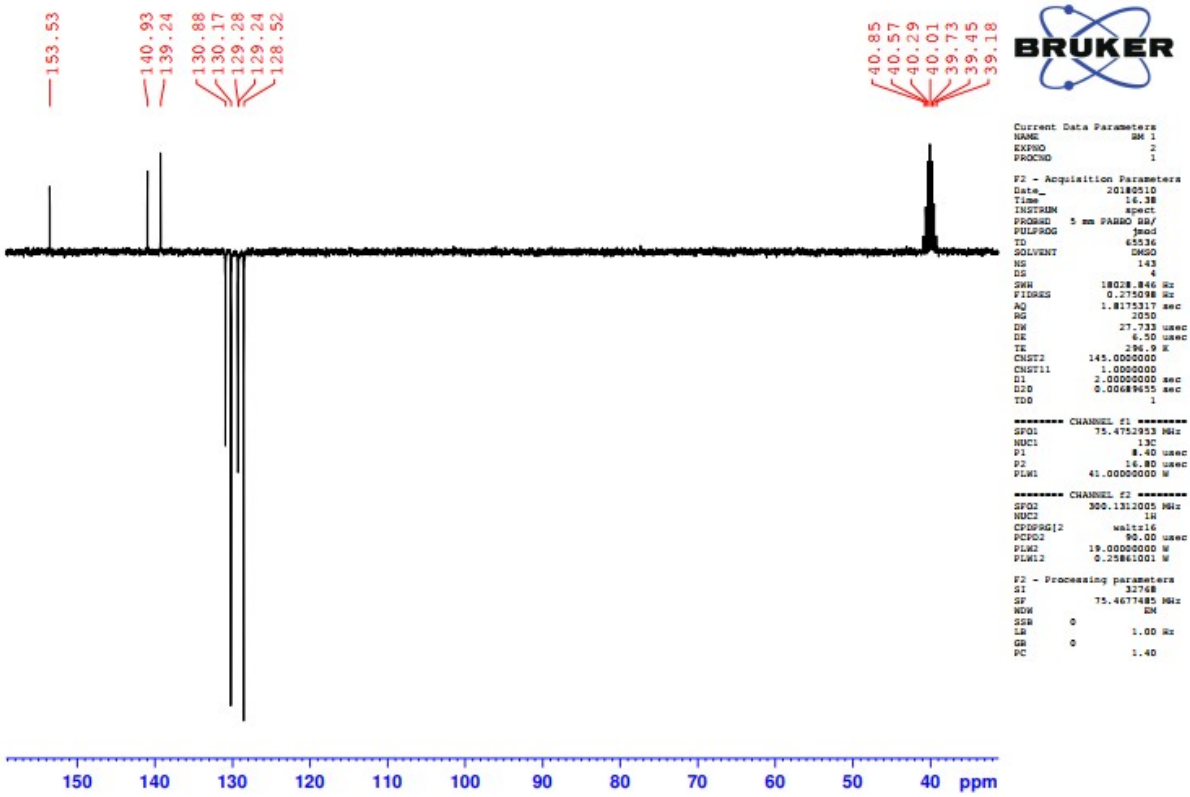
*2,3-Di(2-furyl)-5,6,7,8-tetrahydroquinoxaline (**3i**, Table 3, Entry 9).* M.p.: 150°C (150–151°C [37]); ^{1}H NMR (300 MHz, DMSO-d6): δ (ppm): 1.91–1.97 (m, 4H), 2.99–3.04 (m, 4H), 6.45–6.51 (m, 4H), 7.50 7.51 (m, 2H). ^{13}C NMR (300 MHz, DMSO-d6): δ (ppm): 22.65, 31.87, 111.34, 111.63, 139.22, 143.35, 150.77, 150.81.

*2,3-Di(2-furyl)pyrazine (**3j**, Table 3, Entry 10).* M.p.: 77–78°C (78–80°C [37]); ^{1}H NMR (300 MHz, DMSO-d6): δ (ppm): 6.53–6.72 (m, 4H), 7.56–7.57 (m, 2H), 8.53 (m, 2H). ^{13}C NMR (300 MHz, DMSO-d6): δ (ppm): 111.82, 112.15, 112.33, 141.76, 143.84, 150.40.

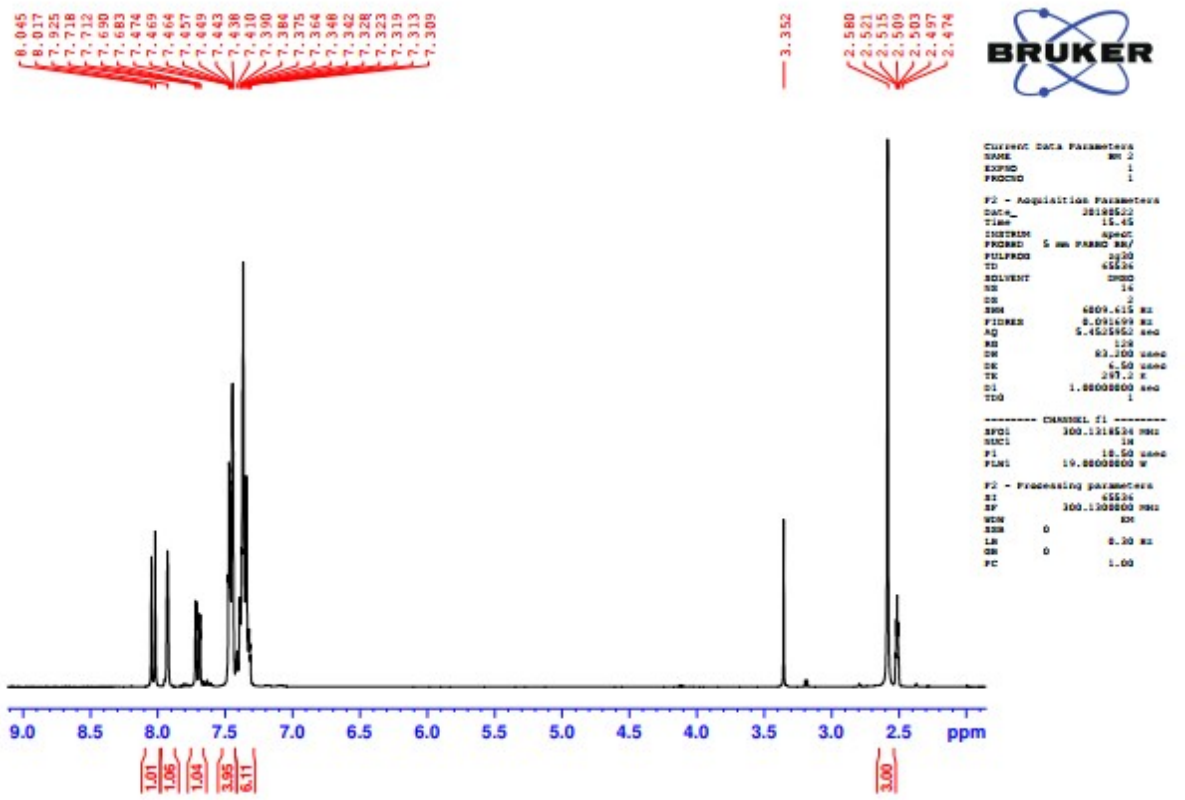
^{1}H and ^{13}C NMR spectra of Quinoxalines:



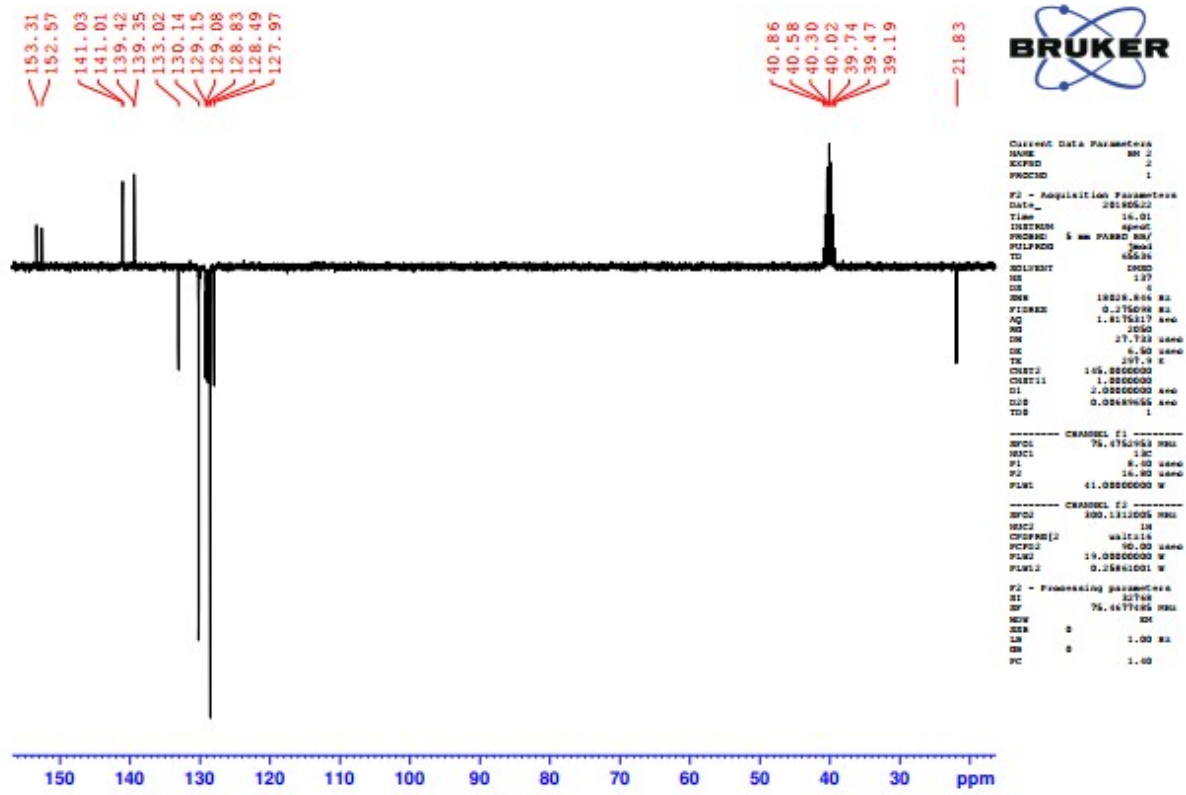
^{1}H NMR spectrum of 2,3-diphenylquinoxaline (DMSO-d6).



^{13}C NMR spectrum of 2,3-diphenylquinoxaline (DMSO-d6).



^{1}H NMR spectrum of 6-methyl-2,3-diphenylquinoxaline (DMSO-d6).



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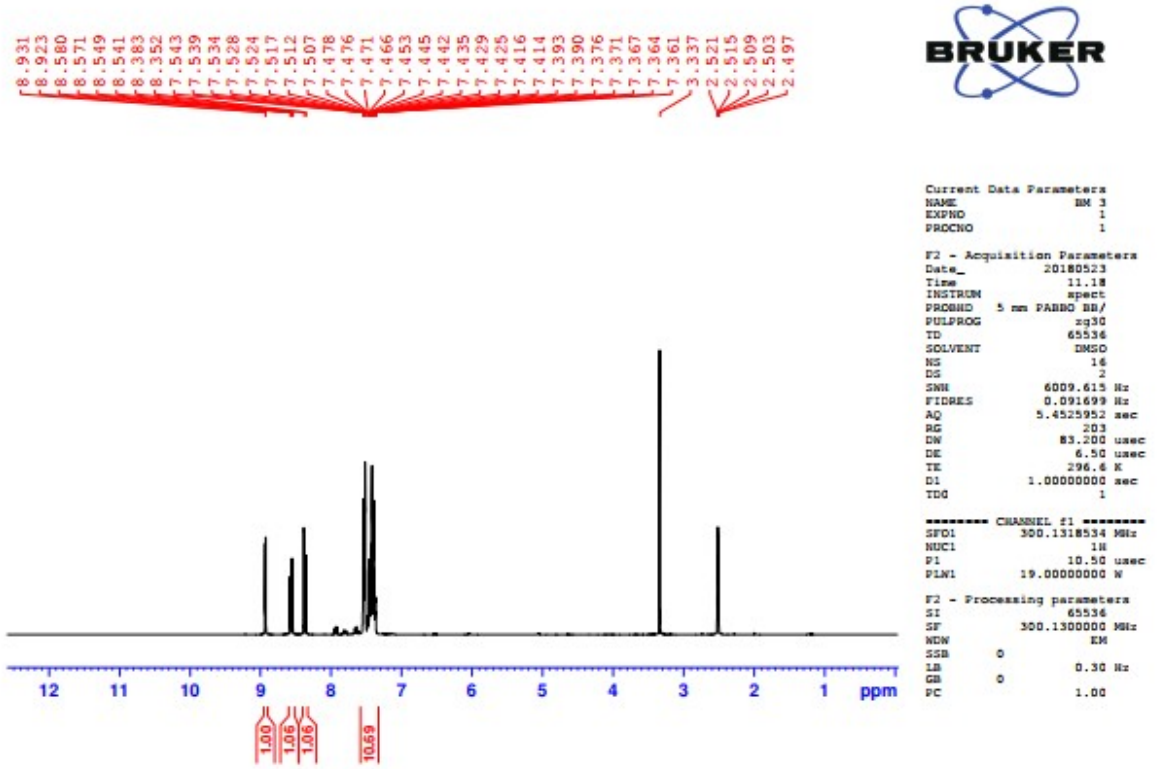
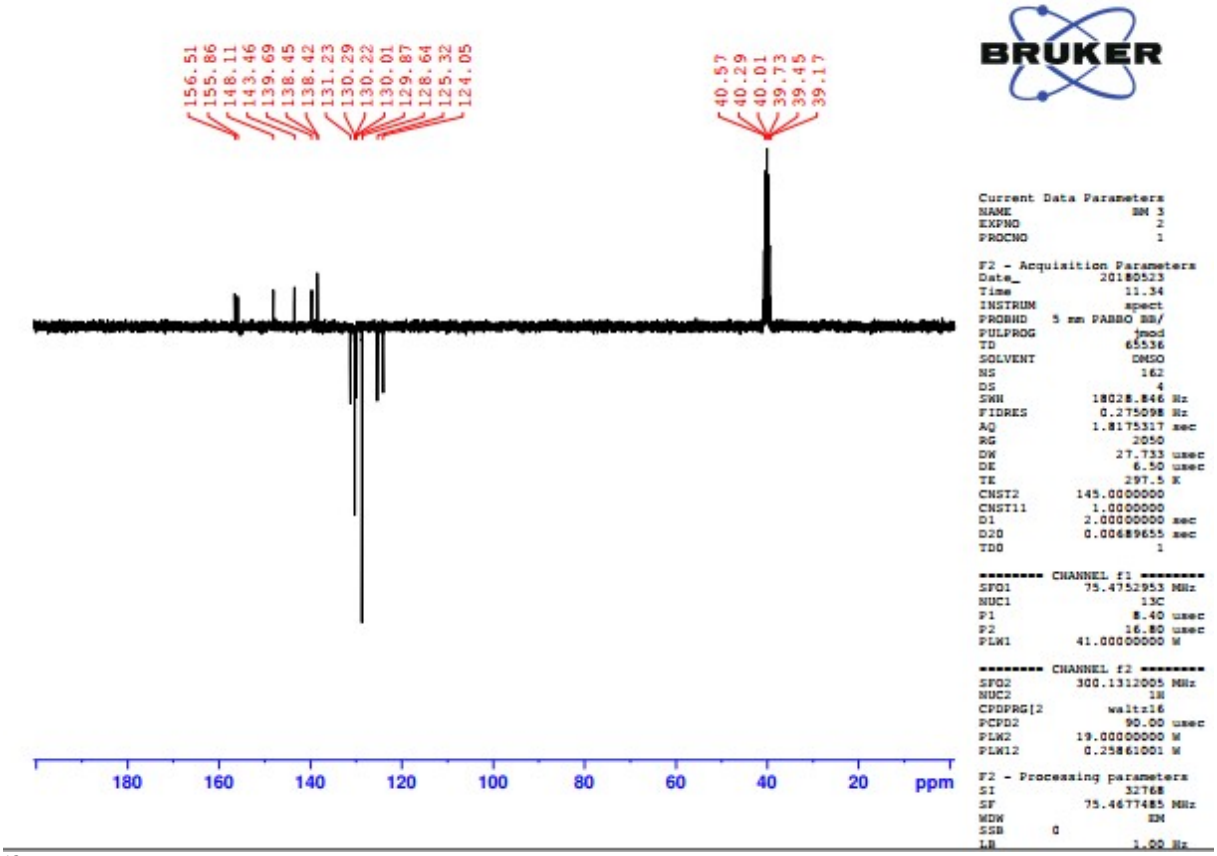


[1]H NMR spectrum of 6-nitro-2,3-diphenylquinoxaline (DMSO-d6).



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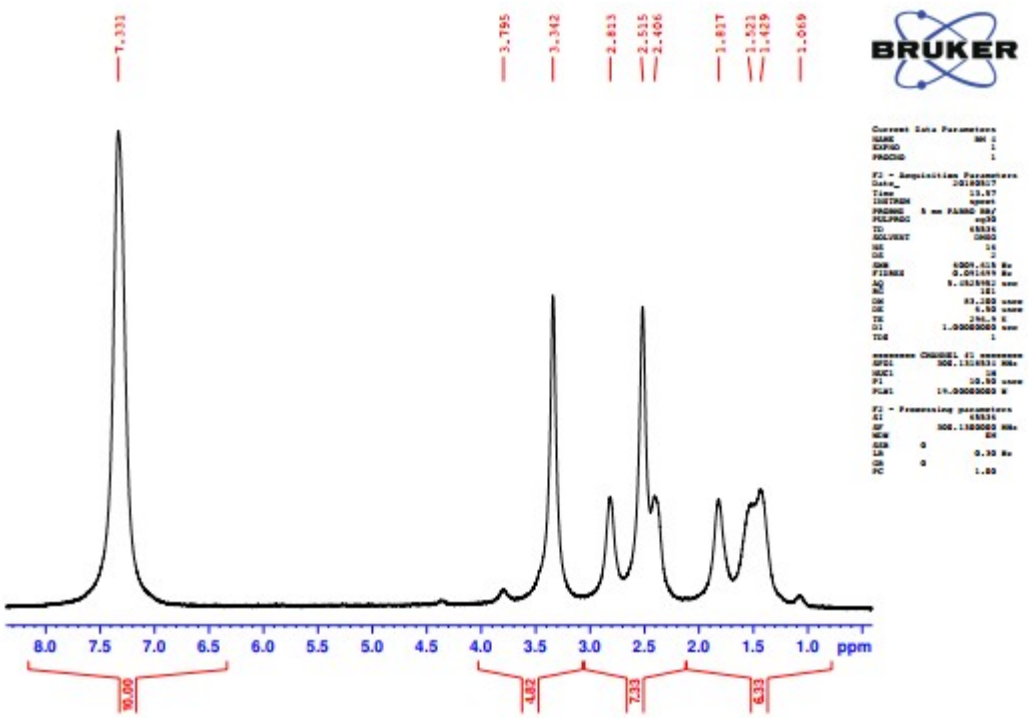
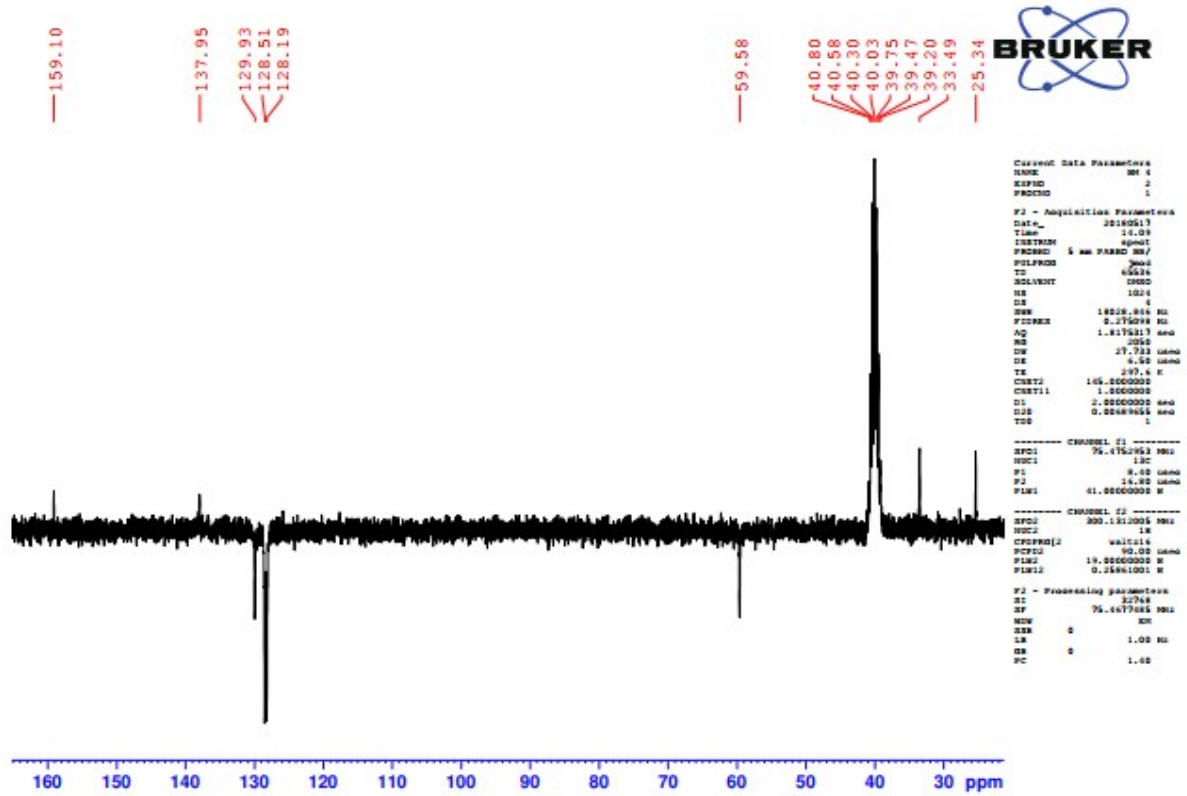


[1]H NMR spectrum of 2,3-Diphenyl-5,6,7,8-tetrahydroquinoxaline (DMSO-d6).



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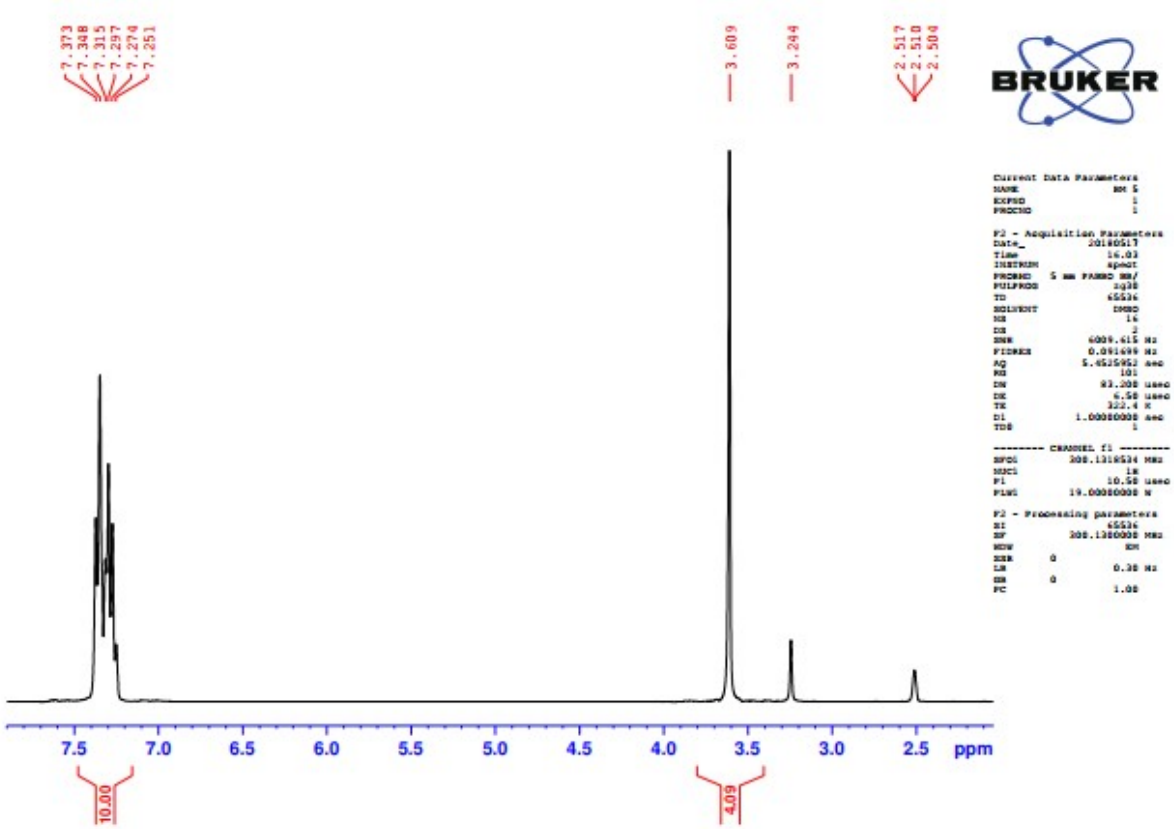
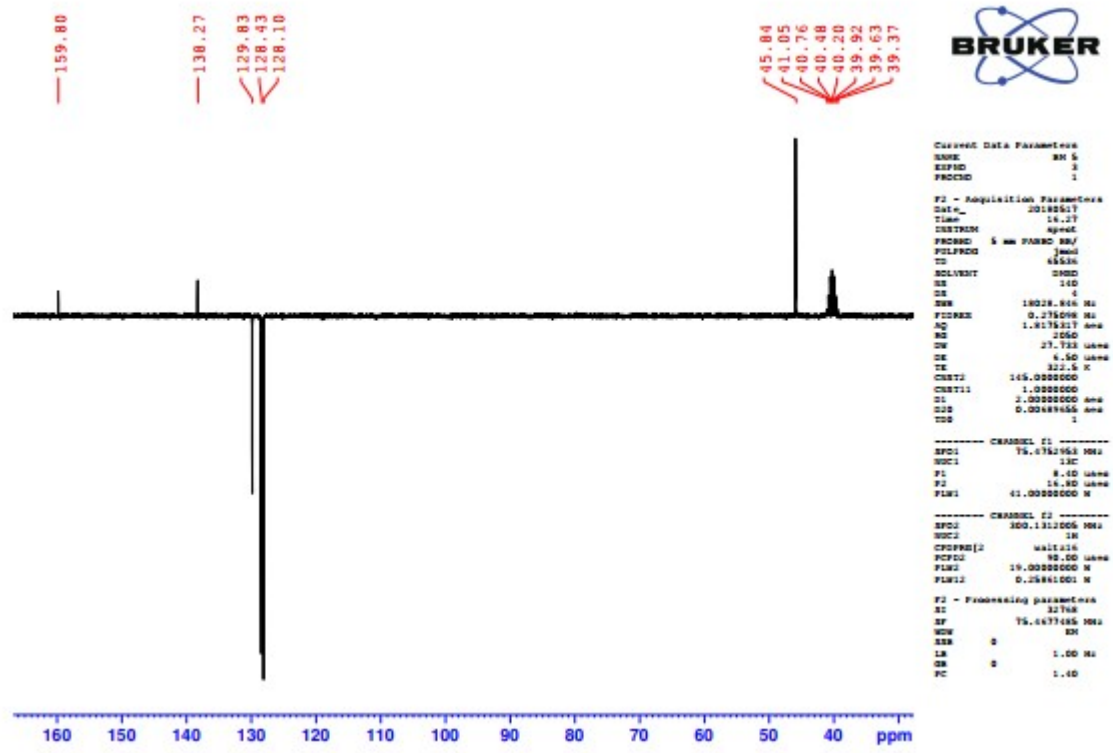


^{1}H NMR spectrum of 2,3-Diphenylpyrazine (DMSO-d6).



^{13}C NMR spectrum of 2,3-Diphenylpyrazine (DMSO-d6).