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A Simple and efficient protocol for the synthesis of quinoxalines catalyzed by pyridine

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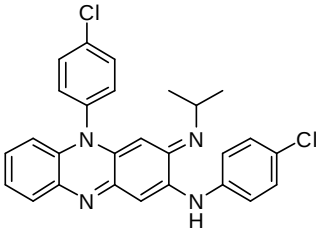
Abstract: A simple and efficient protocol has been developed for the synthesis of quinoxalines. In the synthesis, the reaction of 1,2-phenylenediamines and phenacyl bromide were carried out using pyridine as a catalyst in THF at room temperature to give quinoxalines. This method is applicable to a variety of substrates to afford the corresponding derivatives in excellent yields.

Keywords: Phenacyl bromide; *1,2*-phenylenediamines; pyridine; quinoxalines.

1. Introduction

Quinoxalines are a versatile class of nitrogen containing heterocyclic compounds and they constitute useful intermediates in organic synthesis and medicinal chemistry. Quinoxaline derivatives possess a broad spectrum of biological activities including anti-bacterial, anti-viral, anti-inflammatory, anti-cancer, and kinase inhibitors.[1] In addition, quinoxaline derivatives have been evaluated as anthelmintic agents, semiconductors, dyes and biocides.[2,3]

Therefore, a variety of synthetic strategies have been developed for the preparation of substituted quinoxalines. Conventionally, quinoxaline synthesis can be achieved by the reaction of 1,2-phenylenediamine with two-carbon synthones such as α-dicarbonyls,[4-7] α-halogeno carbonyls, α-hydroxycarbonyls, α-azocarbonyls, epoxides, and α, β-dihalides.[8-15]



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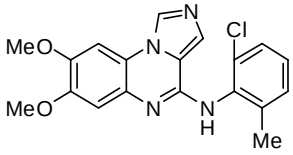

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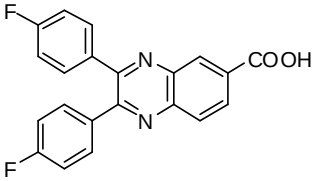

Hit-2-anti-HCV

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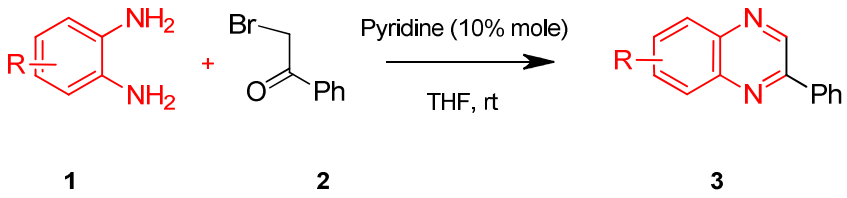
Among the reported procedures, the most common method is the condensation of an aryl-1,2-diamine with 1,2-diketone compounds in refluxing ethanol or acetic acid[16-21] or using different catalysts and reaction conditions.[22-28] The reactions of phenacyl halides with phenylene 1,2-diamines were also reported to give quinoxalines via condensation-oxidation process in different catalyst and/or medium. Recently, for this purpose, sodium hexafluorophosphate-Amberlite[29], KF-alumina[30], CeCl3.7H2O[31], Polyethylene glycol (PEG-400)[32], cetyltrimethyl ammonium bromide (CTAB)[33], Sodium tetrachloroaurate(III) dehydrate[34], TMSCl-water[35], beta-cyclodextrine-water[36], tetrabutylammonium bromide in basic media[37], DMSO in solvent free conditions[38,39], microwave irradiation[40], $HClO_4$-SiO2[9] were successfully used.
Herein, we present a simple and an efficient methodology for preparation of quinoxalines from phenacyl bromide and phenylene-1,2-diamines using pyridine as a catalyst.

2. Results and discussion

In a typical experiment, an equimolar amount of 1,2-diaminobenzene (**1**) and phenacyl bromide (**2**) were reacted in tetrahydrofuran in presence of pyridine at room temperature. The reaction was completed within 2 hours to afford the corresponding derivative, 2-phenylquinoxaline (**3a**) in excellent yields as shown in the general **Scheme 1**. To optimize the reaction conditions, we have studied the role of the catalyst pyridine using in different mole ratio. The observation shows that 10% mole equivalent of pyridine is sufficient for the completion of reaction.

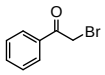
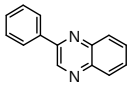
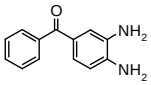
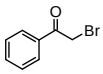
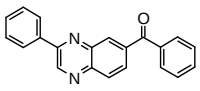
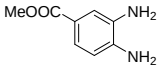
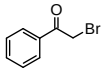
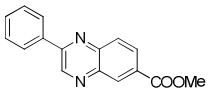
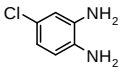
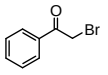
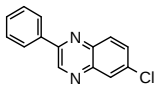
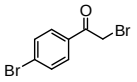
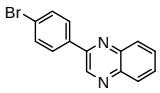
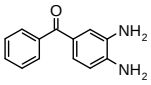
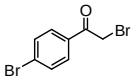
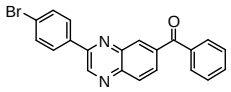
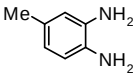
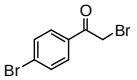
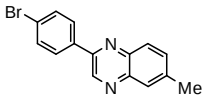
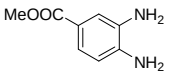
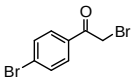
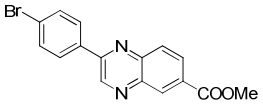
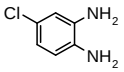
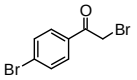
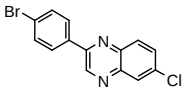
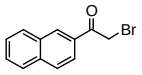
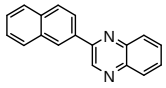
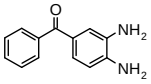
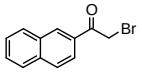
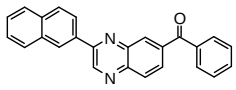
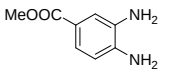
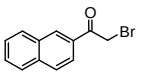
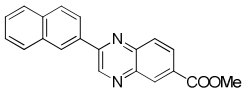


Scheme 1. The reaction of 1,2-diaminobenzene with pheacyl bromide

In a similar manner, 3,4-diaminobenzophenone and phenacyl bromide were reacted in presence of pyridine at room temperature in tetrahydrofuran to afford the corresponding product, phenyl-(3-phenylquinoxalin-6-yl)-methanone (**3b**) in very good yields. The reaction was very clean and completed within 2 hours. In another experiment, phenacyl bromide was tested with 1,2-diamino-4-benzoic acid methyl ester and 1,2-di amino-4-chlorobenzene to yield the corresponding products, methyl-2-phenyl quinoxaline-6-carboxylate (**3c**) and 6-chloro-2-phenylquinoxaline (**3d**) respectively in very good yields.

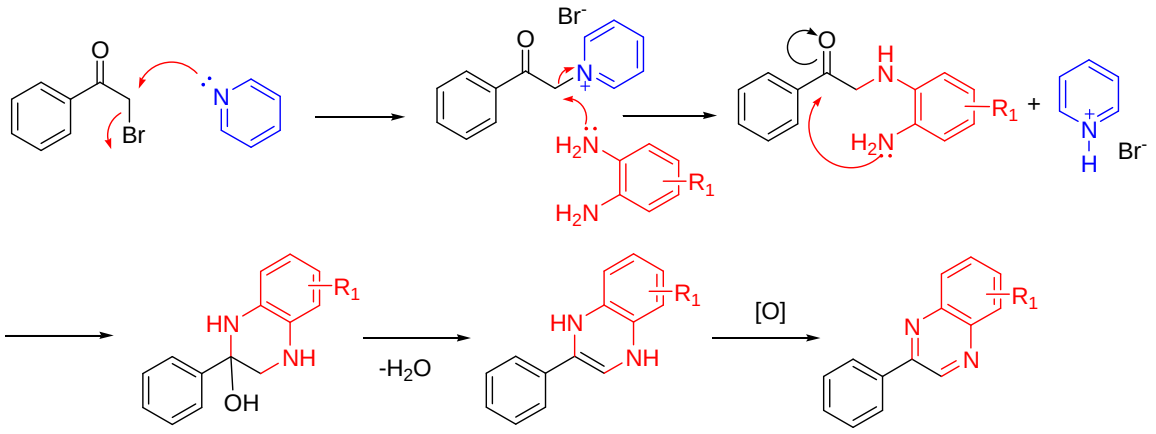
Encouraged by the results obtained with phenacyl bromide and various substituted 1,2-diamino benzenes, we have extended this reaction with substituted phenacyl bromides such as 4-bromophencyl bromides and 2-bromoacetyl-2-naphthalene to afford the corresponding products in very good yields and the results were summarized in the table-1.

Table 1. Pyridine catalyzed synthesis of quinoxalines

SNo	Diamine	1-Bromo ketone	Product[a] (3a-3o)	Reaction Time (h)	Yield[b] (%)
a				2.0	92
b				2.0	89
c				2.5	86
d				2.5	88
e				2.0	90
f				2.5	88
g				2.0	89
h				3.0	85
i				3.0	85
j				2.0	90
k				2.0	88
l				3.0	86

[a]All the products were identified by their ^{1}H NMR, IR and mass
[b]Yields were isolated and unoptimized

All the reactions were completed within 2 to 3 hours of reaction time at room temperature and the obtained products yields were in 85 to 92 %. The structures of the products were identified by their ^{1}H NMR, IR and mass spectral analysis.



Scheme 2. Estimated reaction mechanism

The reaction may be explained by the probable mechanism in Scheme 2. The initial step involves the pyridine attack on active methylene carbon to form a pyridine bromonium salt. The second step involves the nucleophilic attack of one of the amine from *ortho*-phenylene substrate on active methylene carbon to weaken the pyridine bond. The third step involves the nucleophilic attack of another amine group from *ortho*-phenylene substrate on carbonyl carbon and followed by water elimination and a following oxidation to yield the desired product of quinoxaline derivative.
In 4-substituted-1,2-phenylenediamines, the priority in the attack of different amine groups may lead to the both of the formation of 6-substituted-2-phenylquinoxalines or 7-substituted-2-phenylquinoxalines. Therefore we assigned the known compounds comparing with physical data reported in the literature. The structures of unknown compounds were also assigned by comparing the direction in similar compounds.

3. Conclusion

In conclusion, we have demonstrated a simple and efficient protocol for the synthesis of quinoxalines using pyridine as catalyst *via* coupling of phenacyl bromides with 1, 2-diamines compounds successfully. The method is very simple, clean and applicable to a variety of reactants.

4. Experimental

Melting points were recorded on Buchi R-535 apparatus. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr disk. ^{1}HNMR-Spectra were recorded on Gemini-spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnegan MAT 1020 mass spectrometer operating at 70 eV.

4.1.General procedure for the preparation of quinoxalines: To a stirred mixture of phenacyl bromide (1 mmol) and pyridine (0.1 mmol) in THF (2 mL) was added 1,2-diamine (1 mmol) slowly at room temperature and continued for a period of specific time (Table 1). Progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, as indicated by TLC, the reaction mixture was poured in water and extracted with EtOAc (2x10 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude products, which were purified by column chromatography using silica-gel (60-120 mesh) by eluting with EtOAc-hexane mixture in 2:8 ratio. All the pure products were identified by their IR, ^{1}H NMR and mass spectrometry data.

4.2. Spectral data for compounds:

4.2.1. 2-Phenylquinoxaline (3a): Yellow Solid. Mp. 78 ^{o}C (Lit[14] 75-76 ^{o}C). IR (neat): ῡ 3448, 3059, 2922, 2852, 1631, 1544, 1487, 1313, 1224, 1027, 956, 768 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 7.49-7.59 (m, 3H), 7.70-7.80 (m, 2H), 8.05-8.30 (m, 4H), 9.30 (s, 1H).; EIMS: *m/z* (%): 207 (M+1, 100), 195 (20), 130 (15), 102 (10), 89 (10).

4.2.2. Phenyl-(3-phenylquinoxalin-6-yl)-methanone (3b): White Solid. Mp. 145-146 ^{o}C (Lit[41] 144-145 ^{o}C). IR (neat): ῡ 3448, 3058, 2925, 1651, 1596, 1451, 1296, 1173, 1112, 1027, 972, 920, 761, 717 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 7.50-7.70 (m, 6H), 7.85-7.95 (m, 2H), 8.20-8.30 (m, 4H), 8.50 (s, 1H), 9.40 (s, 1H).; EIMS: *m/z* (%): 311 (M+1, 100), 151 (10).

4.2.3. Methyl-2-phenylquinoxaline-6-carboxylate (3c): White Solid. Mp. 155-157 ^{o}C (Lit[28] 152-154 ^{o}C). IR (neat): ῡ 3051, 2967, 2855, 1634, 1591, 1523, 1476, 1412, 1369, 1304, 1271, 1208, 1136, 1081, 1015, 956, 842, 751 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 4.02 (s, 3H), 7.50-7.60 (m, 3H), 8.10-8.40 (m, 4H), 8.80 (s, 1H), 9.40 (s, 1H). EIMS: *m/z* (%): 265 (M+1, 100), 282 (10), 287 (15).

4.2.4. 6-Chloro-2-phenylquinoxaline (3d): Gray Solid. Mp. 135-137 ^{o}C (Lit[42] 136-138 ^{o}C). IR (neat): ῡ 3428, 3059, 2961, 2847, 1605, 1542, 1481, 1323, 1246, 1041, 973, 741 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 7.50-7.65 (m, 3H), 7.75-7.85 (m, 2H), 7.88 (d, 2H, *J* = 7.5 Hz), 7.99 (t, 1H, *J* = 7.5 Hz), 9.30 (s, 1H). EIMS: *m/z* (%): 241 (M+1, 10), 258 (60), 263 (100).

4.2.5. 2-(4-Bromophenyl)-Quinoxaline (3e): Yellow Solid. Mp. 133-134 ^{o}C (Lit[36] 138 ^{o}C). IR (neat): ῡ 3421, 2927, 1633, 1583, 1534, 1475, 1418, 1101, 1073, 955, 830, 759 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 7.70-7.80 (m, 4H), 8.10-8.20 (m, 4H), 9.30 (s, 1H).; EIMS: *m/z* (%): 287 (M+1, 40), 285 (M+1, 60), 263 (100), 247 (90), 225 (25), 209 (30), 139 (15), 97 (10), 74 (10), 69 (10).

4.2.6. [3-(4-Bromophenyl)-quinoxalin-6-yl]-(phenyl)-methanone (3f): White Solid. Mp. 158-160 ^{o}C. IR (neat): ῡ 3448, 3061, 2922, 2852, 1648, 1574, 1537, 1461, 1409, 1311, 1288, 1246, 1173, 1113, 1072, 1005, 971, 940, 880, 827, 726, 692 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 7.55 (t, 2H, *J* = 7.0 Hz), 7.62 (d, 1H, *J* = 7.0 Hz), 7.75 (d, 2H, *J* = 7.0 Hz), 7.90 (d, 2H, *J* = 7.0 Hz), 8.18 (d, 2H, *J* = 7.0 Hz), 8.20-8.30 (m, 2H), 8.45 (s, 1H), 9.40 (s, 1H).; EIMS: *m/z* (%): 389 (M+1, 48), 358 (100), 352 (15), 318 (10), 301 (10), 291 (10), 277 (12), 240 (10), 186 (10), 131 (10), 102 (18), 57 (12).

4.2.7. 2-(4-Bromophenyl)-6-methylquinoxaline (3g): Yellow Solid. Mp. 138-140 ^{o}C (Lit[43] 134-135 ^{o}C). IR (neat): ῡ 2962, 2933, 2875, 1623, 1586, 1540, 1489, 1437, 1384, 1308, 1264, 1202, 1132, 1072, 1044, 1008, 960, 832, 777 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 2.18 (s, 3H), 7.50-7.62 (m, 3H), 8.18-8.30 (m, 4H), 9.30 (s, 1H).; EIMS: *m/z* (%): 299 (M+1, 10), 281 (15), 279 (20), 260 (25), 237 (15), 201 (45), 185 (100), 175 (10), 155 (15), 149 (10), 128 (10), 111 (10), 93 (10).

4.2.8. Methyl 2-(4-bromophenyl)quinoxaline-6-carboxylate (3h): White Solid. Mp.135-137 ^{o}C (Lit[28] 134-136 ^{o}C). IR (neat): ῡ 2962, 2933, 2875, 1707, 1587, 1543, 1460, 1439, 1291, 1228, 1173, 1091, 953, 830, 781, 757 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 4.05 (s, 3H), 7.70 (d, 2H, *J* = 7.0 Hz), 8.10-8.20 (m, 3H), 8.38 (d, 1H, *J* = 7.0 Hz), 8.80 (s, 1H), 9.39 (s, 1H).; EIMS: *m/z* (%): 343 (m^{+} 40), 301 (45), 245 (20), 189 (100), 167 (10), 140 (15), 130 (20), 118 (60).

4.2.9. 2-(4-Bromophenyl)-6-chloroquinoxaline (3i): White Solid. Mp. 148-150 ^{o}C. IR (neat): ῡ 2962, 2933, 2875, 1587, 1543, 1460, 1412, 1382, 1291, 1228, 1173, 1091, 1006, 952, 830, 757 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 7.50-7.60 (m, 3H), 8.18-8.30 (m, 4H), 9.30 (s, 1H).; EIMS: *m/z* (%): 319 (M+1, 28), 305 (30), 302 (35), 276 (20), 260 (40), 237 (10), 201 (40), 185 (60), 175 (10), 155 (10), 128 (18), 111 (12), 93 (12).

4.2.10. 2-(Naphthalen-2-yl)-Quinoxaline (3j): Yellow Solid. Mp. 140-142 ^{o}C (Lit[36] 135 ^{o}C). IR (neat): ῡ 3448, 3056, 2925, 2855, 1631, 1594, 1543, 1485, 1302, 1265, 1190, 1124, 1034, 964, 855,

819, 746 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 7.50-7.60 (m, 2H), 7.70-7.82 (m, 2H), 7.84-8.01 (m, 3H), 8.10-8.20 (m, 2H), 8.40 (d, 1H, *J* = 8.0 Hz), 8.65 (s, 1H), 9.65 (s, 1H).; EIMS: *m/z* (%): 257 (m^{+1} 100), 247 (40), 242 (10), 209 (10), 122 (20), 100 (10).

4.2.11. [3-(Naphthalen-2-yl)-quinoxalin-6-yl]-(phenyl)-methanone (3k): White Solid. Mp. 150-152 ^{o}C. IR (neat): ῡ 3423, 3046, 2922, 2852, 1648, 1597, 1542, 1306, 1259, 1181, 1118, 1034, 972, 848, 820, 726 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 7.50-7.60 (m, 5H), 7.70-8.02 (m, 5H), 8.40 (s, 2H), 8.50-8.60 (m, 2H), 8.80 (s, 1H), 9.65 (s, 1H).; EIMS: *m/z* (%): 361 (M+1, 100), 330 (20), 250 (15), 197 (15), 118 (20), 103 (25).

***4.2.12. Methyl 2-(naphthalen-2-yl)quinoxaline-6-carboxylate (3l)*:** Pale Yellow Solid. Mp. 164-166 ^{o}C. IR (neat): ῡ 2961, 2931, 2860, 1710, 1544, 1461, 1331, 1292, 1233, 1174, 1091, 744 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 4.05 (s, 3H), 7.50-7.60 (m, 3H), 7.88-8.02 (m, 3H), 8.15-8.22 (m, 1H), 8.35-8.45 (m, 2H), 8.70 (s, 1H), 8.82 (d, 1H, *J* = 11.0 Hz), 9.58 (s, 1H).; EIMS: *m/z* (%): 315 (M+1, 10), 301 (40), 287 (100), 265 (65), 242 (10), 210 (10), 130 (20), 119 (15), 98 (10), 65 (10).

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