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Research Article

A New approach for the synthesis of Quinoxalines through Oxidative-cyclization catalyzed by Mesityl imidazolium salt as an Organo-N-heterocyclic Carbene

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ABSTRACT

A fast and convenient oxidative-cyclization reaction between phenacyl bromide and 1, 2-diamines catalyzed by *in situ* generated organo-N-heterocyclic carbene (NHC) at room temperature provided a range of quinoxalines in high yields. The organo-NHC catalyst, 1, 3-dimesityl imidazol-2-ylidene, was generated *in situ* by the deprotonation of 1, 3-dimesityl imidazolium chloride salt (IMes.HCl) with a mild base 1, 8-diazabicyclo (5.4.0) undec-7-ene (DBU). Further, the influence of a base and solvent on catalytic performance of organo-NHC was assessed. Addition of two drops of dimethylsulfoxide (DMSO) found to be highly beneficial to accomplish the above oxidative-cyclization in one minute. Finally, a reasonable mechanism for organo-NHC involved oxidative-cyclization was also proposed.

Keywords: Quinoxaline, NHC, 1, 2-diamine and oxidative-cyclization.

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CHEMISTRY RESEARCH ARTICLE

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ABSTRACT

A fast and convenient oxidative-cyclization reaction between phenacyl bromide and 1, 2-diamines catalyzed by *in situ* generated organo-N-heterocyclic carbene (NHC) at room temperature provided a range of quinoxalines in high yields. The organo-NHC catalyst, 1, 3-dimesityl imidazol-2-ylidene, was generated *in situ* by the deprotonation of 1, 3-dimesityl imidazolium chloride salt (IMes.HCl) with a mild base 1, 8-diazabicyclo (5.4.0) undec-7-ene (DBU). Further, the influence of a base and solvent on catalytic performance of organo-NHC was assessed. Addition of two drops of dimethylsulfoxide (DMSO) found to be highly beneficial to accomplish the above oxidative-cyclization in one minute. Finally, a reasonable mechanism for organo-NHC involved oxidative-cyclization was also proposed.

Keywords: Quinoxaline, NHC, 1, 2-diamine and oxidative-cyclization.

1. INTRODUCTION

Quinoxalines are N-containing Benzo-fused heterocycles and first reported by Korner and Hinsberg in 1884.[1,2] Quinoxalines and their derivatives have several biological/pharmaceutical applications.[3,4] They have been used in anticancer,[5] antibiotic viz. echinomycin, leromycin & actinomycin,[6] anti-HIV,[7] anti-inflammatory,[8] kinase inhibition activities[9] and antiviral.[10] Besides, Quinoxalines are also used in preparing dyes, electroluminescent materials, chemically controllable switches and organic semiconductors.[11-14] Interestingly, quinoxaline ring can be found in many drug molecules like quinacillin, triostin, varenicline as shown in Figure 1.

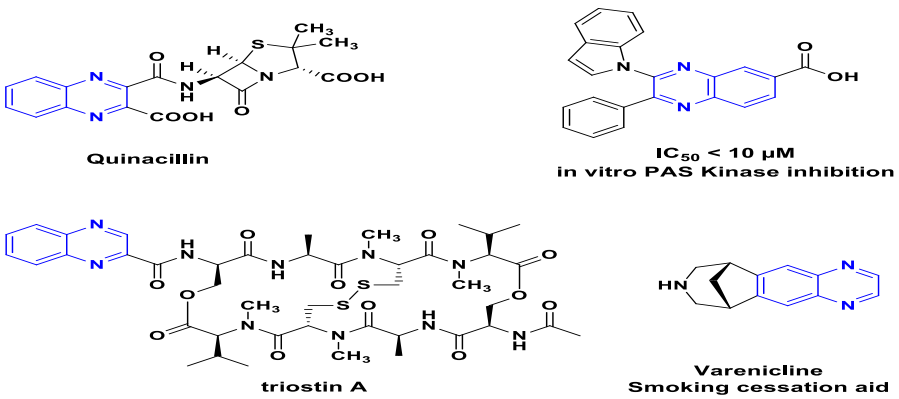


Figure 1. Some of the biologically active compounds containing quinoxaline ring moiety

With reference to the aforementioned significant properties, since the last two decades variety of classical and catalyzed cyclo-condensation methods have been developed for the synthesis of quinoxalines. Few intriguing contributions include (i) dodecatungstocobaltate catalyzed condensation of phenacyl bromides with *o*-phenylenediamine (OPD)[15] (i) condensation of OPD with 1,2-dicarbonyl

compounds,[16] (iii) WO_3/ZrO_2 catalyzed α, β-unsaturated ketones with OPD,[17] (iv) (K10 clay) catalyzed of condensation 1,2-diamines with phenacyl bromides,[18] (v) pyridine or HPF_6^- catalyzed coupling of phenacylbromides with 1, 2-diamines.[19,20] (vi) imidazolium ionic liquid catalyzed condensation of phenacyl bromides with OPD,[21] (vii) all water strategy based tandem aroyl methylation - nitro reduction-cyclo condensation[22] and (viii) thiamine catalyzed cyclization-oxidation of phenacylbromide with phenylenediamine.[23] However, most of the above reported methods have some generally considered drawbacks such as the use of toxic metal catalysts, strong base, extended reaction times and low yields, tedious work-up process, low solubility of starting materials in water and incompatibility for the construction functionalized quinoxalines.

On other hand, nowadays the use of metal free catalyst, specifically the use of organo-catalysis process has been receiving much attention in the synthetic organic chemistry due to green chemistry regulations. Among the organo-catalysts, NHCs are diverse Lewis base (nucleophilic) organo catalysts that have both strong σ-basicity and π-acidity features.[24-31] Indeed the concept of NHCs has been first proposed by Breslow, wherein the involvement of thiamine as thiazol-2-ylidiene carbene found in benzoin,[32] latter Stetter reactions[33] and thereafter the legacy has been in a continuous process for plethora of organic transformations. and recently for the synthesis of quinoxalines.[23] The mechanistic variety of NHCs depending on their properties has led to the development of several unprecedented C–C and C–X (X = heteroatom) bond formations. In this context, the first stable NHC isolated by Arduengo in 1991 from imidazolium salts[34] disclosed their tunable steric and electronic properties by varying the N-substituents on the imidazole ring. It is considerable that the imidazolium salts are precursors to NHCs, cheap, stable and easy to use.

In this context, we wish to describe our research work on *in situ* generated organo-NHC (1, 3-dimesityl imidazol-2-ylidene) catalyzed oxidative cyclo-condensation between phenacyl bromide and 1, 2-diamines to furnish a range of quinoxalines in high yields at room temperature. The influence of solvent, DBU and DMSO as an additive for the fast accomplishment the above reaction in one minute is highly considerable as compared to previous reports.

2. RESULTS AND DISCUSSION

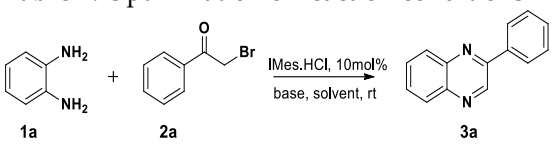
In our work, at first we have investigated the intermolecular oxidative cyclization reaction (Table 1) between phenacyl bromide 1a (1 equiv) and o-phenylenediamine 2a (1 equiv) using an *in situ* generated organo-NHC 1, 3-dimesityl imidazol-2-ylidene catalyst to obtain the quinoxaline (3a) in dichloromethane. Previously, a report by S. Singh[23] used a strong base NaOH to generate the organo-NHC from the corresponding azolium salt and used in the synthesis of quinoxaline via oxidative-cyclization. Indeed, the use of strong base possibly leads to the decomposition of organo-NHC when similar acidic protons are present on NHC precursors. Furthermore, the presence of strong base may direct unwanted side reactions. In this respect we intended to use mild bases to generate organo-NHC catalysts.

As shown Table 1, at first we have used Et_3N as mild base to deprotonate IMes.HCl salt to generate organo-NHC 1, 3-dimesityl imidazol-2-ylidene catalyst in *situ* in dichloromethane (DCM). Under this condition, the above condensation reaction yielded the quinoxaline (3a) in 53% in a reaction period of 20 minutes at room temperature (entry 1, Table 1). The reaction was monitored by TLC. After TLC monitoring, this quinoxaline (3a) product formation was confirmed by analyzing spectral data (Experimental). These observations prompted us to monitor the effect of different bases and solvents as shown in Table 1 (entries 2-8) to see the product yields variation and reaction times. The results are summarized in Table 1 indicates that the NHC generated in tetrahydrofuran (THF) by DBU/DMSO combination performed advantageously to accomplish the above condensation in one minutes to produce quinoxaline (3a) in maximum yield of 81%.

The results are tabulated in Table 1 which highlights that it would be convenient to generate organo-NHC in a controlled mode in the presence of base/DMSO as described by Arduengo.[34] It was noticed in many previous reports that the DMSO acts as a catalyst/promoter in the generation of NHC. Indeed we observed that IMes.HCl was sparingly soluble in THF. In order to increase the conversion rates, a catalytic amount of DMSO added to this reaction, a slight yellow colour clear solution was observed. It indicates solubility of NHC increased and provided lower activation energy and improved the rate of the reaction.[35-37] indeed the use of DMSO found to

multiple also in organic syntheses. DMSO may also act a co-catalyst and co-solvent to accelerate the organic syntheses in a selected procedure apart from the generation of NHC.

Table 1. Optimization of reaction conditions

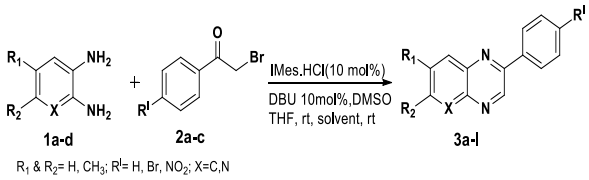


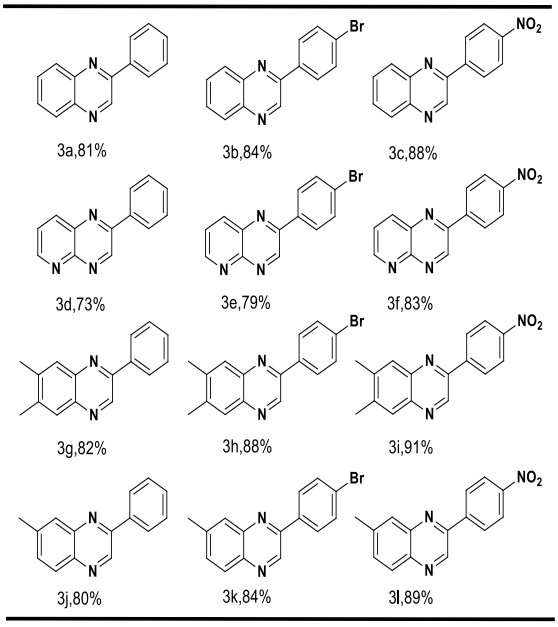
S. No.	Base	Mol% of IMes	Solvent	Time (min)	Yield (%)
1	Et_3N	10	DCM	20	53
2	DBU	10	DCM	10	69
3	K_2CO_3	10	DCM	30	47
4	KO*t*Bu	10	DCM	10	63
5	DBU	10	MeOH	10	42
6	DBU	10	H_2O	60	-
7	DBU	10	THF	10	72
8	DBU	10	THF-DMSO	01	81
9	NaOH	10	THF	20	65

Reaction conditions: phenacyl bromide 1a (1 equiv) and o-phenylenediamine 2a (1 equiv), IMes.HCl (10 mol %), base (10 mol %), 5 ml of solvent at room temperature.

Further, the optimized conditions were extended to test the ability of organo-NHC catalyst on the condensation of various phenacyl bromides and diamines. Here electron donating groups on diamine ring and electron withdrawing groups on phenacyl bromide ring produce a slight excess of product formation. We have also observed that the pyridine ring-containing diamine produce 2-phenylpyrido [2, 3-b] pyrazine was the major product, whereas another isomer 3-phenylpyrido [2, 3-b] pyrazine was obtained the minor product (below 5%) because pyridine ring directed the formation of the product. In addition, ring deactivated groups on phenacyl bromide accomplished high yields for the reason that NHC attacks on carbonyl much faster than others.

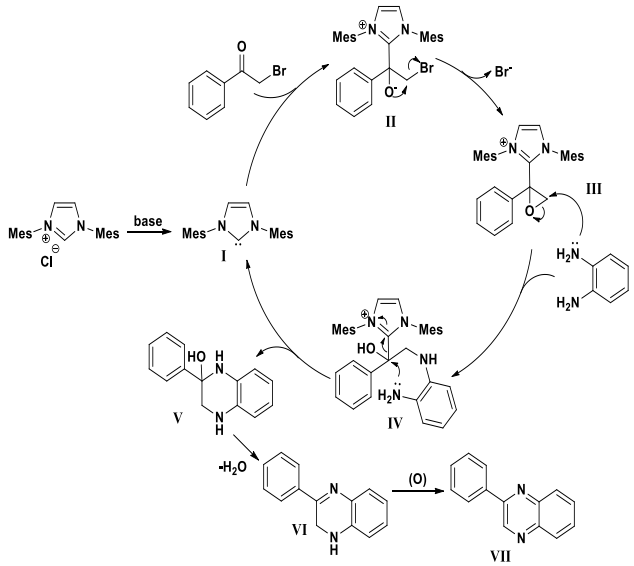
Table 2. Quinoxaline derivatives from diamines and phenacyl bromides





3. MECHANISM

The plausible mechanistic explanation reveals the formation of quinoxaline (VII) as depicted in Scheme. At first, Mesityl Imidazolium salt reacts with base and produce organo-NHC (I). Then this NHC interacted with phenacyl bromide to form oxirane ring (III). Further, oxirane ring nucleophilic attack of phenylenediamine gives intermediate (IV), which will undergo cyclization followed by dehydrogenation to furnish the desired quinoxaline product (VII).



Scheme 1. Plausible mechanistic pathway for the formation of quinoxalines.

4. EXPERIMENTAL SECTION

To phenacyl bromide 1a-d (1 equiv) and NHC precursor (10 mol %) in dry THF (5 ml) under nitrogen atmosphere was added DBU (10 mol %) and 2 to 3 drops of DMSO. The mixture was stirred for 5 min. NHC generated *in situ* and reacted with 1a-d. Then added drop wise to a solution of diamine 2a-c (1 equiv) in THF, the reaction mass was allowed to attain room temperature and stirring was continued up to completion of reaction. The progress of the reaction was monitored by TLC. After completion of reaction, diluted with water and aqueous layer extracted with ethyl acetate 2-3 times. The combined organic layers washed with brine solution and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the organic layer was evaporated under reduced pressure to afford a crude product. The crude product was purified with column chromatography (silica gel, 60–120 mesh, eluent; n-hexane/EtOAc gradient) to afford pure products (3a-l). Analytical data of products (**3a-l)** are given below.

2-phenylquinoxaline (3a): Yellow solid, mp 76-78 ^oC, 81%; ^1H-NMR ($CDCl_3$, 500 MHz):δ 9.31 (s, 1H), 8.35 – 8.01 (m, 4H), 7.85 – 7.60 (m, 2H), 7.53 (dt, *J* = 23.5, 7.0 Hz, 3H) ppm;^{13}C-NMR ($CDCl_3$, 125 MHz) :δ 148.8, 143.3, 142.3, 141.5, 136.7, 130.2, 130.2, 129.6, 129.5, 129.1, 129.1, 127.5 ppm; FT-IR (KBr): υ 3059, 2963, 2851, 1627, 1543, 1228, 1026, 956 cm^{-1}; ESI-MS: m/z = 207.12 $[M+1]^+$;EA calcd (%): calcd. C 81.53, H 4.89, N 13.58; found C 83.26, H 4.72, N 13.59.

2-(4-bromophenyl)quinoxaline (3b): Pale Yellow solid, mp 136-139 ^oC, 84%; ^1H-NMR ($CDCl_3$, 400 MHz): δ 9.32 (s, 1H), 8.10 – 8.06 (m, 4H), 7.83 – 7.76 (m, 2H), 7.66 (d, *J* = 8.4 Hz, 2H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz) : δ 149.3, 142.6, 141.9, 141.4, 136.2, 132.4, 131.2, 130.1, 129.8, 129.6, 129.0, 126.0 ppm; FT-IR (KBr): υ 3422, 2931, 1586, 1528, 1421, 1076, 958 cm^{-1}; Mass (ESI-MS) : m/z = 285.2 $[M+1]^+$; EA calcd (%): calcd. C 58.97, H 3.18, N 9.82; found C 58.93, H 3.32, N 9.93.

2-(4-nitrophenyl)quinoxaline (3c): Yellow solid, mp 189-193 ^oC, 88%; ^1H-NMR ($CDCl_3$, 400 MHz): δ 9.14 (s, 1H), 8.46 – 8.33 (m, 4H), 8.29 – 7.88 (m, 2H), 7.78 (d, *J* = 8.0 Hz, 2H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 156.3, 155.2, 152.3, 147.3, 142.1, 133.1, 131.8, 129.8, 129.6, 129.3, 127.7, 115.3 ppm; FT-IR (KBr): υ 3056, 2933, 1648, 1532, 1483, 1356, 1093, 945, 856 cm^{-1}; Mass (ESI-MS): m/z = 252.13 $[M+1]^+$; EA calcd (%): calcd. C 66.93, H 3.61, N 16.73; found C 67.23, H 3.58, N 16.83.

3-phenylpyrido[2,3-b]pyrazine (3d): Brown solid, mp 95-99 ^oC, 73%; ^1H-NMR ($CDCl_3$, 400 MHz): δ 9.32 (s, 1H), 8.93 (d, *J* = 5.4 Hz, 1H), 8.38 (d, *J* = 10.8 Hz, 1H), 8.33 – 8.24 (m, 2H), 7.69 (dd, *J* = 10.8 *&* 5.4 Hz, 1H), 7.48 – 7.63 (m, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz) : δ 153.21, 151.12, 148.32, 144.26, 139.36, 134.23, 133.92, 130.62, 128.96, 128.12, 123.26 ppm; FT-IR (KBr): υ 3053, 1586, 1461, 1323, 1236, 963, 847, 756, 687 cm^{-1}; Mass (ESI-MS): m/z = 208.23 $[M+1]^+$; EA calcd (%): calcd. C 75.35, H 4.38, N 20.28; found C 75.43, H 4.39, N 20.15.

3-(4-bromophenyl)pyrido[2,3-b]pyrazine (3e): Brown solid, mp 192-195 ^oC, 79%; ^1H-NMR ($CDCl_3$, 400 MHz): δ 9.39 (s, 1H), 9.11 (d, *J* = 8.1 Hz, 1H), 8.39 – 8.53 (m, 3H), 7.62 – 7.71 (m, 1H), 7.53 – 7.60 (m, 2H) ppm**;** ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 152.23, 151.62, 147.82, 144.53, 137.72, 134.34, 132.82, 130.71, 128.21, 126.63, 123.12 ppm; FT-IR (KBr): υ 3056, 1586, 1573, 1463, 1337, 1203, 1063, 997, 832 cm^{-1}; Mass (ESI-MS): m/z = 287.42 $[M+2]^+$; EA calcd (%): calcd. C 54.57, H 2.82, N 14.69; found C 54.62, H 2.76, N 14.66.

3-(4-nitrophenyl)pyrido[2,3-b]pyrazine (3f): Brown solid, mp 210-214 °C, 83%; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 9.42 (s, 1H), 9.15 (d, *J* = 7.6 Hz, 1H), 8.43 – 8.61 (m, 3H), 8.32 (d, *J* = 8.0 Hz, 2H), 7.61 – 7.82 (m, 1H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 153.21, 151.62, 148.13, 147.21, 141.62, 139.46, 137.32, 135.46, 127.92, 124.63, 123.86 ppm; FT-IR (KBr): υ 3068, 1596, 1537, 1483, 1353, 1326, 1298, 853 cm^{-1}; Mass (ESI-MS): m/z = 252 $[M]^+$; EA calcd (%): calcd. C 61.90, H 3.20, N 22.21; found C 62.12, H 3.24, N 20.16.

6,7-dimethyl-2-phenylquinoxaline (3g): Yellow solid, mp 118-122 °C, 82%; ^{1}H-NMR ($CDCl_3$, 500 MHz) : δ 9.26 (s, 1H), 8.21 (d, *J* = 8.0 Hz, 2H), 7.93 (s, 1H), 7.88 (s, 1H), 7.62 – 7.48 (m, 3H), 2.53 (s, 6H) ppm; ^{13}C-NMR ($CDCl_3$, 125 MHz) : δ 148.6, 143.2, 141.9, 141.4, 140.6, 138.1, 137.7, 131.5, 129.8, 129.3, 128.8, 127.3, 21.6, 20.9 ppm; FT-IR (KBr): υ 3053, 2931, 2876, 1589, 1493, 1326, 1225, 1035, 786 cm-1; Mass (ESI-MS): m/z = 234.29 $[M+]^+$;EA calcd (%): calcd. C 82.02, H 6.02, N 11.96; found C 81.73, H 6.21, N 12.02.

2-(4-bromophenyl)-6,7-dimethylquinoxaline (3h): Brown solid, mp 133-136 °C, 88%; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 9.29 (s, 1H), 9.15 (d, *J* = 8.4 Hz, 2H), 8.76 – 8.52 (m, 1H), 7.96 (d, *J* = 7.4 Hz, 2H), 7.63 (d, *J* = 7.4 Hz, 1H), 2.63(s, 6H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 152.1, 148.7, 147.4, 141.6, 141.8, 140.8, 137.8, 131.9, 128.6, 128.1, 125.2, 118.3, 29.8, 20.5 ppm; FT-IR (KBr): υ 3043, 2972, 2932, 1632, 1581, 1326, 1205, 1095, 964 cm^{-1}; Mass (ESI-MS): m/z = 270.32 $[M+1]^+$; EA calcd (%): calcd. C 61.36, H 4.18, N 8.94; found C 61.83, H 4.32, N 8.12.

6,7-dimethyl-2-(4-nitrophenyl)quinoxaline (3i): Yellow solid, mp 181-185 °C, 91%; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 9.36 (s, 1H), 8.83 (d, *J* = 8.0 Hz, 2H), 8.32– 7.93 (m, 3H), 7.88 (s, 1H), 2.55 (s, 6H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 154.3, 151.9, 148.5, 141.8, 140.9, 139.6, 132.8, 127.9, 118.3, 114.2, 21.3 ppm; FT-IR (KBr): υ 3062, 1596, 1482, 1437, 1356, 1326, 1296, 843, 791 cm^{-1}; Mass (ESI-MS): m/z = 279.12 $[M]^+$; EA calcd (%): calcd. C 68.81, H 4.69, N 15.05; found C 68.91, H 4.72, N 15.32.

7-methyl-2-phenylquinoxaline (3j): Brown solid, mp 76-78 °C, 80%, ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 9.26 (s, 1H), 8.28 – 8.12 (m, 3H), 7.91 (s, 1H), 7.63 – 7.51 (m, 5H), 2.53 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 151.8, 144.5, 142.6, 140.3, 136.3, 130.2, 129.8, 129.6, 129.5, 129.1, 127.6, 21.7 ppm; FT-IR (KBr): υ 3063, 2963, 2858, 1668, 1618, 1493, 1286, 1046, 956, 827 cm^{-1}; Mass (ESI-MS): m/z = 221.25 $[M+1]^+$; EA calcd (%): calcd. C 81.79, H 5.49, N 12.72; found C 81.63, H 5.53, N 12.78.

2-(4-bromophenyl)-7-methylquinoxaline (3k): Brown solid, mp 125-129 °C, 84%; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 9.35 (s, 1H), 8.56 – 8.32 (m, 2H), 8.25 – 8.11 (m, 2H), 8.01 – 7.83 (m, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 2.51 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 151.9, 143.2, 141.8, 140.4, 131.8, 130.4, 129.8, 129.5, 128.7, 21.3 ppm; FT-IR (KBr): υ 3055,2954, 2832, 1682, 1543, 1426, 965, 842, 753 cm^{-1};Mass (ESI-MS): m/z = 298.21 $[M]^+$; EA calcd (%): calcd. C 60.22, H 3.71, N 9.36; found C 61.83, H 3.76, N 9.26.

7-methyl-2-(4-nitrophenyl)quinoxaline (3l): Yellow solid, mp 151-154 °C, 89%; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 9.37 (s, 1H), 8.72 – 8.52 (m, 2H), 8.35 – 8.21 (m, 2H), 8.13 – 7.92 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 2.62 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 153.6, 144.3, 141.9, 140.2, 133.6, 131.5, 129.8, 129.3, 128.9, 22.4 ppm; FT-IR (KBr): υ 3061, 2962, 2863, 1671, 1542, 1431, 951, 856 cm^{-1}; Mass (ESI-MS): m/z = 266.23 $[M+1]^+$; EA calcd (%): Calcd. C 67.92, H 4.18, N 15.84; found C 68.12, H 4.06, N 15.53.

5. CONCLUSION

In conclusion we have developed a simple and rapid access to a range of quinoxalines *via* organo-NHC catalyzed oxidative-cyclization reaction conducted between phenacyl bromide and 1,2-diamines in THF at room temperature. The combination of DBU/DMSO was found to quite useful to accelerate the generation and performance of organo-NHC catalyst in the above synthetic reaction and thereby to improve the yields of quinoxalines. It is the first effort implemented the use of imidazol-2-ylidene based NHCs in the high yield synthesis of quinoxalines.

6. ACKNOWLEDGEMENTS

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