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N-heterocyclic carbene (thiamine) promoted eco-friendly synthesis of quinoxalines under mild reaction conditions

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An efficient and convenient protocol of broad scope for the synthesis of quinoxaline by cyclization-oxidation of phenacyl bromide with equimolar amount of phenylenediamine at room temperature catalyzed by thiamine in the form of N-heterocyclic carbene (NHC). High efficiency, inexpensiveness, and non-toxicity are the interesting features of the catalyst, which make it eco-friendly and highly attractive.

Keywords: quinoxaline; phenacyl bromide; phenylenediamine; thiamine; N-heterocyclic carbene

Introduction

Quinoxaline and its derivatives have attracted the interest of chemists due to their interesting biological, pharmacological, and agrochemical uses. They display a broad spectrum of biological activities such as antibacterial (1, 2), antifungal (3), anticancer (4, 5), antinflammatoryatory (6), antiviral (7), and also act as kinase inhibitor (8–10). Besides these pharmacological activities, quinoxaline derivatives are potential building blocks for the synthesis of organic semiconductor (11, 12), electroluminescent material (13, 14), DNA cleaving agents (15), dehydroannulenes (16), dyes (17), pesticides (18), corrosion inhibitor (19), chemically controllable switches (20) as well as practical applications such as copper(I) sensor (21), building blocks for dendrimers (22), ligands in metal complexes of supramolecular devices or DNA probes (23–26).

Therefore, these compounds have distinguished themselves as heterocycles with chemical and biological significance. As a result, synthesis of these molecules attracted considerable attention. Consequently, many methods have been developed for the synthesis of quinoxaline derivatives, which include condensation of 1,2-diamines and 1,2-dicarbonyl compounds (27–32), oxidative cyclization of α-hydroxy ketones with 1,2-diamines (33–36), oxidative coupling of epoxides with ene-1,2-diamines (37), 1,4-addition of 1,2-diamines to diazenylbutenes (38), cyclization-oxidation of phenacyl bromides with 1,2-diamines by HClO₄·SiO₂ (39), β-cyclodextrin (β-CD) (40), DABCO (41), and by using solid phase synthesis (42, 43).

However, many of these reported methods have many drawbacks such as longer reaction time, unsatisfactory yield, use of toxic organic solvents, use of expensive metal salt as catalyst, drastic reaction condition, tedious work-up procedures, and unsuitable for functionalized quinoxaline formation. In view of these, we have attempted to develop a new procedure for the synthesis of quinoxaline derivatives which should be easy and efficient. In this context we report, herein, an efficient and mild reaction catalyzed by thiamine as N-heterocyclic carbene (NHC) for synthesis of quinoxaline derivatives by phenacyl bromide and o-phenylenediamine.

Recently, the use of non-metallic reagent and organocatalytic process is an area of growing interest because of environmental regulations. In this context, thiamine has achieved considerable attention because thiamine is inexpensive, nontoxic, and reusable eco-friendly specie. The structure of thiamine contains a pyrimidinering and thiazole ring linked by methylene bridge (44–46). In current study, thiamine (thiazolium ion) formed by deprotonation of thiamine hydrochloride (VB₁), a natural thiazolium salt at its most acidic position (position-2 of thiazole ring), is an actual catalyst (Scheme 1).

Thiamine as NHC has just the right balance of nucleophilicity, the ability to stabilize the intermediate and good leaving group (47). It has broad application in synthetic organic chemistry which

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includes benzoin condensation (48), azabenzoin condensation (49), Stetter reaction (50–52), intramolecular Stetter reaction (53, 54), Stetter pall-knorr reactions (55), and coupling reaction of aldehyde–ketones (56), etc.

Results and discussion

Considering the aforementioned valid point we have developed organocatalyzed synthesis of biologically and pharmacologically important quinoxaline. The present protocol involves stirring an equimolar mixture of phenacyl bromide (1) and phenylenediamine (2) using thiamine (20 mol%) as an organocatalyst in ethanol at room temperature to provide the corresponding quinoxaline in 88–96% yield. (Table 1, Scheme 2)

It was observed that the reaction preceded efficiently using thiamine and resulted in a high yield of the desired product in short reaction time (15 min). We have attempted different ratios of thiamine (0, 5, 10, 15, 20, and 25 mol%) and observed that 20 mol% of the catalyst was found suitable for the optimum conversion. The increase in the mole ratio of thiamine did not improve the yield (Figure 1). Further to optimize the reaction conditions; the reaction was studied in various solvents such as dichloromethane (DCM), methyl alcohol (MeOH), ethyl acetate (EtOAc), tetrahydrofuran (THF) and dimethylformamide (DMF). The reaction proceeded in all solvents with different degrees of conversion (Figure 2). However, ethyl alcohol (EtOH) was the solvent of choice in terms of reaction time and yield.

The scope of this thiamine catalyzed quinoxaline formation was explored under optimal condition, and the results are summarized in Table 1. In order to demonstrate the versatility of the thiamine promoted synthesis of quinoxalines, a series of α-bromoketones were treated with various 1, 2-diamines. It was observed that electron-rich substituents on the diamine influence the reaction. For example, the presence of highly electron-rich substituent (entry 4) on the diamine ring activates the substrate. This phenomenon was not observed with weak electron-donating substituents like methyl (entry 3). Further it was observed that electron withdrawing substituents (entry 2) on the diamine ring deactivate the substrate. We have also examined phenacyl bromide having different substituents such as NO2, CN, Br, and CH3. The electron deficient functionalities (entries 5, 8, and 17) influence the reaction and furnish the corresponding quinoxaline in good yield, whereas the electron-rich substituents (entry 13) on phenacyl bromide gave comparatively low yield of quinoxaline under identical conditions.

A plausible mechanism for the formation of quinoxaline (6) is depicted in Scheme 3. It is presumed that initially NHC (4) would be formed from thiazolium ion (3); this persistent carbene couple with phenacyl bromide (1) and form oxirane ring (5), a highly reactive intermediate which after reacting with phenylenediamine (2) and subsequent cyclization followed by dehydrogenation results in the expected product (6).

Experimental process

Preparation of catalyst

A total of 0.5 g thiamine hydrochloride was dissolved in 1.6 ml of water and 6 ml of 95% ethanol was added. The solution was cooled in an ice bath and then 1 ml of 3 M NaOH was added dropwise, stirring in a manner such that the temperature does not rise above 20 °C. Intense yellow colored solution changed to pale yellow solution of thiamine (thiazolium ion).

Procedure

A mixture of phenacyl bromide (1 mmol) and thiamine (20 mol%) in ethanol (5 mL) was stirred at room temperature for 2 min. Then, phenylenediamine (1 mmol) was added slowly, and the mixture was stirred at room temperature until the reaction was completed (as monitored by TLC) (Table 3). The reaction mixture was then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na2SO4, the solvent was removed under reduced pressure, and the resulting product 2-phenylquinoxaline was further purified by column chromatography (ethyl acetate; Hexane, 1:4 v/v). All compounds were characterized by their melting point: 1H NMR, 13C NMR, and mass spectral data.
| Entry | Phenacyl bromide | 1,2-diamine | Product | Time (min) | Yield \(^{b}\) (%) |
|-------|------------------|-------------|---------|------------|-------------------|
| 1     | Br               | H\_2N\_2H\_2N\_a | 1a      | 15         | 92                |
| 2     |                 | H\_2N\_2H\_2N\_b COOMe | 1b      | 19         | 88                |
| 3     |                 | H\_2N\_2H\_2N\_c | 1c      | 14         | 93                |
| 4     |                 | H\_2N\_2H\_2N\_d OMe | 1d      | 13         | 96                |
| 5     | Br\_2           | H\_2N\_2H\_2N\_a | 2a      | 15         | 94                |
| 6     |                 | H\_2N\_2H\_2N\_b | 2b      | 13         | 94                |
| 7     |                 | H\_2N\_2H\_2N\_c COOMe | 2c      | 20         | 93                |
| 8     | Br\_3           | H\_2N\_2H\_2N\_a | 3a      | 14         | 90                |
| 9     |                 | H\_2N\_2H\_2N\_b | 3b      | 15         | 92                |
| 10    |                 | H\_2N\_2H\_2N\_c | 3c      | 12         | 95                |
Table 1 (Continued).

| Entry | Phenacyl bromide | 1,2-diamine | Product | Time (min) | Yield\(^b\) (%) |
|-------|------------------|-------------|---------|------------|-----------------|
| 11    |                 |             | 3d      | 13         | 92              |
| 12    |                 |             | 3e      | 15         | 90              |
| 13    |                 |             | 4a      | 18         | 90              |
| 14    |                 |             | 4b      | 18         | 91              |
| 15    |                 |             | 4c      | 15         | 92              |
| 16    |                 |             | 4d      | 18         | 88              |
| 17    |                 |             | 5a      | 15         | 90              |

\(^a\)Reaction condition: phenacyl bromide (1 mmol), phenylenediamine (1 mmol), thiamine (20 mol%), and ethanol (5 mL).
\(^b\)Yield of the isolated products.

**Characterization data for synthesized compounds**

**Compound 1a:** mp 75–78 °C; \(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 7.52–7.61 (m, 3 H), 7.73–7.83 (m, 2 H), 8.13–8.22 (m, 4 H), 9.33 (s, 1 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 127.3, 129.0, 129.1, 129.5, 129.6, 130.1, 130.2, 136.7, 141.5, 142.2, 143.3, 151.7; MS (ESI): \(m/z\) 207 (M\(^{+}\)1).

**Compound 1b:** mp 152–154 °C; \(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 4.0 (s, 3 H), 7.58 (m, 3 H), 8.16 (d, 1 H, \(J = 8.309\) Hz), 8.24 (d, 2 H, \(J = 8.309\) Hz), 8.35 (d, 1 H, \(J = 2.26\) Hz), 8.78 (s, 1 H), 9.38 (s, 1 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 52.5, 127.6, 129.1, 129.6, 129.7, 130.7, 131.5, 135.9, 140.4, 144.2, 153.1, 166.1; MS (ESI): \(m/z\) 265 (M\(^{+}\)1).

**Compound 1c:** mp 72–74 °C; \(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 2.62 (s, 3 H), 7.52–7.61 (m, 3 H), 7.73–7.83 (m, 2 H), 7.98 (d, 1 H), 8.1 (d, 2 H), 9.33 (s, 1 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 21.8, 127.3, 129.0,
Compound 1d: mp 73–76 °C; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 3.75 (s, 3 H), 7.52–7.61 (m, 3 H), 7.73–7.83 (m, 2 H), 7.8 (s, 1 H), 8.0 (s, 1 H), 8.6 (s, 1 H), 9.33 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 66.1, 107.1, 122.6, 127.3, 129.0, 129.1, 131.2, 136.7, 143.0, 144.3, 149.5, 151.7, 161.5; MS (ESI): m/z 237 (M$^+$1).

Compound 2a: mp 138–140 °C; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 7.64–7.85 (m, 4 H), 8.03–8.2 (m, 4 H), 9.32 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 125.0, 129.0, 129.6, 129.9, 130.5, 132.4, 135.5, 141.4, 142.2, 142.6, 150.6; MS (ESI): m/z 285 (M$^+$1).

Compound 2b: mp 118–120 °C; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 2.62 (s, 3 H), 7.58 (d, 1 H, $J$ = 8.49 Hz), 7.68 (d, 3 H, $J$ = 8.49 Hz), 7.88 (d, 1 H, $J$ = 7.74 Hz), 7.98 (d, 1 H, $J$ = 8.49 Hz), 8.10 (d, 2 H, $J$ = 8.49 Hz), 9.2 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 21.8, 124.8, 126.1, 127.6, 129.0, 132.2, 132.7, 135.5, 140.7, 141.2, 141.5, 142.1, 150.5; MS (ESI): m/z 299 (M$^+$).

Compound 2c: mp 159–161 °C; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 2.62 (s, 3 H), 7.6 (t, 1 H, $J$ = 8.39 Hz), 7.82 (d, 2 H, $J$ = 8.39 Hz), 7.86 (d, 1 H, $J$ = 4.34 Hz), 8.0 (d, 1 H, $J$ = 2.63 Hz), 8.34 (d, 2 H, $J$ = 8.39 Hz), 9.25 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 20.3, 113.3, 117.4, 126.5, 132.0, 133.6, 139.5, 140.4, 140.8, 142.5, 148.2; MS (ESI): m/z 232 (M$^+$1).

Compound 3a: mp 209–211 °C; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 2.55 (s, 6 H), 7.8 (s, 1 H), 7.85 (s, 1 H), 8.05 (d, 2 H, $J$ = 8.39 Hz), 8.33 (d, 2 H, $J$ = 8.309 Hz), 9.2 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 20.3, 113.3, 117.7, 127.6, 132.3, 132.6, 139.7, 140.6, 140.9, 141.5, 148.4; MS (ESI): m/z 276 (M$^+$).

Scheme 2.
Conclusion

In summary, thiamine is shown to be an effective and useful alternative catalyst, in the form of NHC, for the preparation of quinoxaline and its derivatives. The present procedure offers several unique advantages like enhanced yield, shorter reaction times, operational simplicity, mild reaction conditions, and eco-friendly approach by minimizing the chemical waste.

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References

1. Badran, M.M.; Abonzid, K.A.; Hussein, M.H. Arch. Pharm. Res. 2003, 26, 107–113.
2. Seitz, L.E.; Suling, W.J.; Reynolds, R.C. J. Med. Chem. 2002, 45, 5604–5606.
3. Kerr, J.R.; Taylor, G.W.; Rutman, A.; Hoiby, N.; Cole, P.J.; Wilson, R. J. Clin. Pathol. 1999, 52, 385–387.
