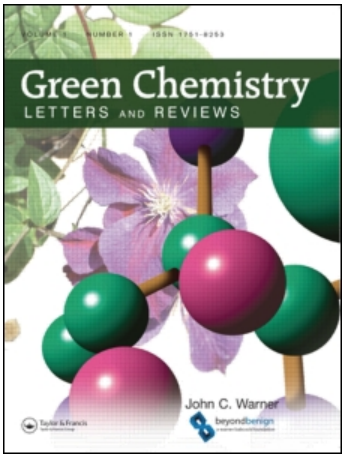


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# Lithium bromide as an efficient, green, and inexpensive catalyst for the synthesis of quinoxaline derivatives at room temperature

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## RESEARCH LETTER

# Lithium bromide as an efficient, green, and inexpensive catalyst for the synthesis of quinoxaline derivatives at room temperature

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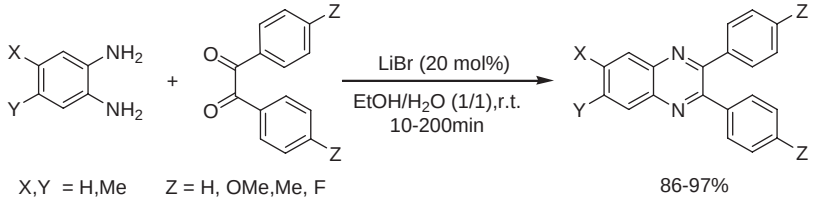
An efficient, simple, and green procedure for the synthesis of quinoxaline derivatives is described. The condensation of 1,2-diamines with 1,2-diketones using lithium bromide (LiBr) in $H_2O$/EtOH as a green reaction media at room temperature affords the title compounds in high to excellent yields and in short reaction times.




**Keywords:** lithium bromide (LiBr); quinoxaline; 1,2-diamine; 1,2-diketone; green chemistry



## Introduction

Quinoxaline derivatives are an important class of nitrogen-containing heterocycles in medicinal chemistry as they have various biological activities, such as antimycobacterial (*1,2*), antibacterial (*3*), antifungal (*4*), antihelmintic (*4*), antidepressant (*5*), and antitumor properties (*6,7*). Moreover, these compounds have been applied for the preparation of various dyes (*8*). The condensation of 1,2-diamines with 1,2-diketones has been used as a useful protocol for the synthesis of quinoxalines. For this transformation, several catalysts and reagents have been reported, including *o*-iodoxybenzoic acid (*9*), ceric(IV) ammonium nitrate (*10*), zirconium tetrakis (dodecyl sulfate) (*11*), $Yb(OTf)_3$ (*12*), $(NH_4)_6Mo_7O_{24}.4H_2O$ (*13*), sulfamic acid (*14*), $H_6P_2W_{18}O_{62}.24H_2O$ (*15*), oxalic acid (*16*), iodine in DMSO (*17*), polyaniline-sulfate salt (*18*), and $KHSO_4$ (*19*). Other methods which have been applied for the synthesis of quinoxaline derivatives include heteroannulation of nitroketene *N,S*-arylimino acetals with $POCl_3$ (*20*), bi-catalyzed oxidative coupling of epoxides with ene-1,2-diamines (*21*), and cyclization of α-arylimino oximes of α-dicarbonyl compounds (*22*). However, many of the reported protocols are associated with one or more of the following disadvantages: need for anhydrous conditions; harsh reaction conditions; the use of expensive reagents; prolonged reaction times; moderate yields; and no agreement with the green chemistry protocols. Therefore, development of an efficient, cheap, simple, and environmentally friendly method for the preparation of quinoxaline derivatives is desirable.

Lewis acid-catalyzed reactions are currently of great interest because of their unique reactivity, selectivity, and need for mild conditions, but most of them are unusable in water (*23,24*). Lithium bromide (LiBr) is a mild Lewis acid, which has been employed as catalyst in several organic transformations (*25–34*). The strong oxophilicity of $Li^+$ activates oxygen-containing electrophiles to accept nucleophilic attack (*35,36*). In most of the reported reactions, LiBr has been introduced as almost neutral Lewis acid catalyst.

The current environmental concerns encourage development of "greener" conditions, where possible, and the tight legislation on the maintenance of green conditions in synthetic processes that insists on preventing generation of waste, avoiding the use of non-green organic solvents, and minimizing the energy requirements (*11,13,16,37–41*). The use of aqueous

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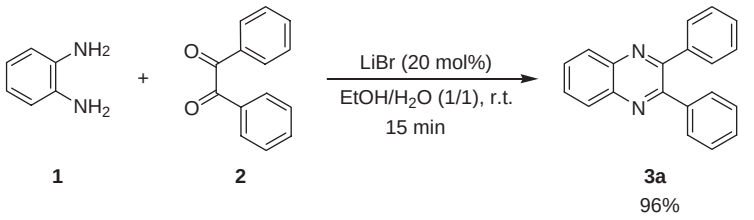



Scheme 1. Condensation of benzene-1,2-diamine with benzil.

reaction media has received considerable attention in the context of green chemistry for several reasons: (1) it is cheap, safe, and environmentally benign; (2) performing reactions in aqueous medium eliminate the additional efforts to dry substrates and reagents before use, and thus reduce/eliminate the consumption of drying agents, energy, and time; and (3) the unique physical and chemical properties of water can be utilized to realize reactivity or selectivity that cannot be attained in organic solvents (*11,13,16,37–41*).

As part of our researches to develop efficient and environmentally benign synthetic methods in organic chemistry (*11,13,16,42–48*), we report here an efficient, extremely mild, green, and simple method for the preparation of quinoxalines from aryl/alkyl 1,2-diamines and different 1,2-diketones using LiBr as an inexpensive, commercially available, and water-tolerant Lewis acid catalyst in $H_2O$/EtOH mixture (Scheme 1).

## Results and discussion

At first, effects of different proportions of LiBr to substrate, and also solvents were investigated on the condensation of benzene-1,2-diamine with benzil at room temperature (Scheme 1). The results are summarized in Table 1. As shown in Table 1, reasonable results were obtained when the reaction was carried out in the presence of 20 mol% of LiBr in EtOH/$H_2O$ (1/1, v/v).

Table 1. Effect of different proportions of LiBr to substrate, and also solvents on the condensation of benzene-1,2-diamine with benzil at room temperature.

| Mol% of catalyst | Solvent | Time (min) | Yield[a] (%) |
|---|---|---|---|
| 10 | EtOH/$H_2O$ (1/1) | 60 | 67 |
| 20 | EtOH/$H_2O$ (1/1) | 15 | 96 |
| 30[b] | EtOH/$H_2O$ (1/1) | 12 | 96 |
| 20 | EtOH | 60 | 64 |
| 20 | $H_2O$ | 120 | Trace |
| 20 | THF | 60 | 28 |
| 20 | $CHCl_3$ | 60 | 42 |
| 20 | MeCN | 60 | 54 |

[a]Isolated yield.
[b]Increasing the amount of the catalyst didn't efficiently improve the reaction results.

To show the influence of oxophilicity of $Li^+$ on activation of the carbonyl group of 1,2-diketones to accept nucleophilic attack of the amine group of 1,2-diamines, the reaction of benzene-1,2-diamine with benzil was examined in the presence of NaBr, KBr, and CsBr (20 mol%) in EtOH/$H_2O$ (1/1) at room temperature (Table 2); however, in these cases, the product was produced in low yields and in long reaction times. Thus, $Li^+$ efficiently activates 1,2-diketones to progress the reaction (*35,36*).

To recognize the generality and the scope of our method, different aromatic and aliphatic 1,2-diamines were reacted with structurally diverse 1,2-diketones. The results are displayed in Table 3. As Table 3 indicates, when aromatic 1,2-diamines were used, all reactions proceeded efficiently and the desired quinoxalines were obtained in excellent yields and in short reaction times (Table 3, entries 1–13). However, aliphatic 1,2-diamines afforded the corresponding quinoxaline derivatives in slightly lower yields and longer reaction times (Table 3, entries 14–16). Furthermore, it was observed that the kind of 1,2-diketone had no significant effect on the reaction results.

## Experimental

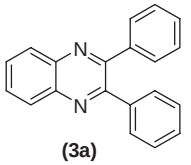
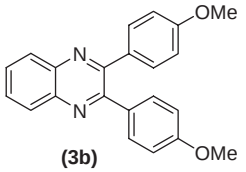
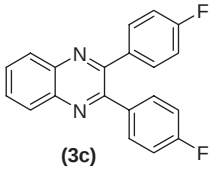
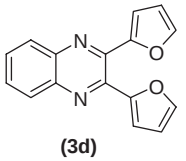
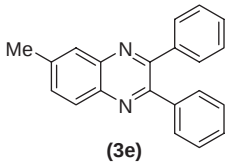
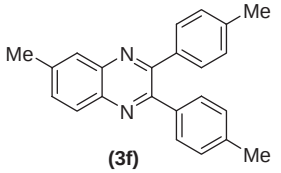
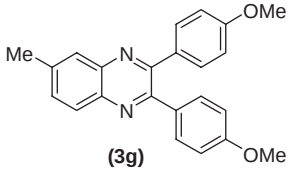
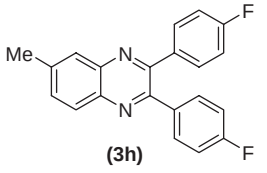
All chemicals were purchased from Merck or Fluka Chemical Companies. The progress of the reactions was followed by TLC using silica gel SILG/UV 254 plates. The $^1$H NMR (250 or 500 MHz) and $^{13}$C NMR (62.9 or 125 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer (δ in ppm). Microanalyses were performed on a Perkin-Elmer 240-B microanalyzer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

Table 2. The reaction of benzene-1,2-diamine with benzil in the presence of various alkaline metals bromides.

| Catalyst | Solvent | Time (min) | Yield[a] (%) |
|---|---|---|---|
| LiBr | EtOH/$H_2O$ (1/1) | 15 | 96 |
| NaBr | EtOH/$H_2O$ (1/1) | 120 | 35 |
| KBr | EtOH/$H_2O$ (1/1) | 120 | 23 |
| CsBr | EtOH/$H_2O$ (1/1) | 120 | 17 |

[a]Isolated yield.

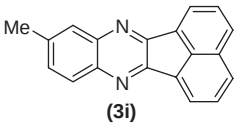
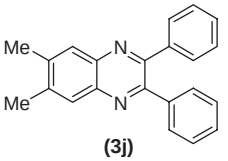
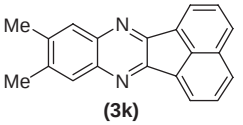
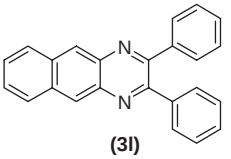
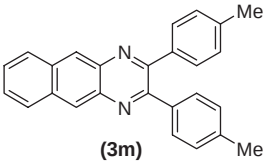
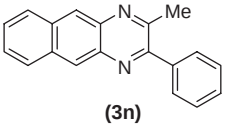
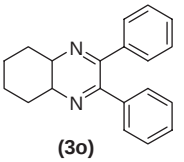
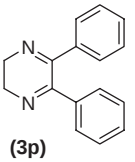
Table 3. The green preparation of quinoxaline derivatives from 1,2-diamines and 1,2-diketones using LiBr in EtOH/$H_2O$ (1/1) at room temperature.

| Entry | Product[a] | Time (min) | Yield[b] (%) | M.p.°C (Lit.) |
|---|---|---|---|---|
| 1 |  **(3a)** | 15 | 96 | 130–131 (128–129) *(9)* |
| 2 |  **(3b)** | 15 | 93 | 147–149 (151–152.5) (*9*) |
| 3 |  **(3c)** | 15 | 95 | 134–136 (135–137) (*9*) |
| 4 |  **(3d)** | 15 | 91 | 127–129 (127–129) (*11*) |
| 5 |  **(3e)** | 15 | 94 | 115–117 (117–118) (*9*) |
| 6 |  **(3f)** | 15 | 96 | 139–140 (137) (*10*) |
| 7 |  **(3g)** | 15 | 95 | 128–130 (125–127) (*9*) |
| 8 |  **(3h)** | 15 | 97 | 163–165 (165–167) (*9*) |

(continued)

[a]The structure of known compounds was identified by comparison of their melting points and spectral data with those in the authentic samples.
[b]Isolated yield.

Table 3. (*Continued*)

| Entry | Product[a] | Time (min) | Yield[b] (%) | M.p.°C (Lit.) |
|---|---|---|---|---|
| 9 |  (3i) | 10 | 95 | 233–235 |
| 10 |  (3j) | 15 | 94 | 175–177 (172) (*14*) |
| 11 |  (3k) | 10 | 96 | 303–305 (304–306) (*16*) |
| 12 |  (3l) | 15 | 91 | 186–188 187–188 (*10*) |
| 13 |  (3m) | 15 | 92 | 196–198 (198) (*10*) |
| 14 |  (3n) | 40 | 87 | 133–135 (134) (*10*) |
| 15 |  (3o) | 200 | 86 | 169–171 (167) (*14*) |
| 16 |  (3p) | 200 | 87 | 159–161 (158) (*14*) |

[a]The structure of known compounds was identified by comparison of their melting points and spectral data with those in the authentic samples.
[b]Isolated yield.

### *General procedure for the preparation of quinoxalines from 1,2-diamines and 1,2-diketones*

To a mixture of 1,2-diketone (1 mmol), LiBr (0.017 g, 0.2 mmol), and EtOH/$H_2O$ [20 mL, 1/1 (v/v)] in a 50 mL round-bottomed flask was added 1,2-diamine (1 mmol), and the resulting mixture was stirred at room temperature for the appropriate time (Table 3). Afterward, $H_2O$ (20 mL) was added to the reaction mixture,

and was allowed to stand at room temperature for 1 h. During this time, crystals of the pure product formed which were collected by filtration, and dried.

### *Selected spectral data of the products*

2,3-Diphenylquinoxaline (3a). White solid; m.p. 130–131°C (Lit. (*9*) 128–129°C); $^1$H NMR ($CDCl_3$): δ 7.29–7.33 (m, 6H), 7.51 (m, 4H), 7.77 (m, 2H), 8.21 (m, 2H); $^{13}$C NMR ($CDCl_3$): δ 128.1, 128.7, 129.1, 129.9, 131.0, 139.6, 141.7, 153.2; Anal. calcd. for $C_{20}H_{14}N_2$: C, 85.08; H, 5.00; N, 9.92; Found: C, 85.29; H, 4.82; N, 10.13.

9-Methylacenaphtho[1,2-b]quinoxaline (3i). Pale yellow solid; m.p. 233–235°C; $^1$H NMR (500 MHz): δ 2.60 (s, 3H), 7.55 (d, $J = 8.2$ Hz, 1H), 7.79 (t, 2H, $J = 7.5$ Hz), 7.95 (s, 1H), 8.03–8.07 (m, 3H), 8.35 (t, 2H, $J = 6.3$ Hz); $^{13}$C NMR (125 MHz): δ 22.2, 121.9, 122.1, 129.0, 129.2, 129.5, 129.6, 129.8, 130.4, 131.7, 132.4, 136.7, 140.0, 140.1, 141.7, 153.8, 154.5; Anal. calcd. for $C_{19}H_{12}N_2$: C, 85.05; H, 4.51; N, 10.44; Found: C, 84.73; H, 4.69; N, 10.29.

9,10-Dimethylacenaphtho[1,2-b]quinoxaline (3k). Yellow solid; m.p. 303–305°C (Lit. (*16*) 304–306°C); $^1$H NMR ($CDCl_3$): δ 2.51 (s, 6H), 7.78 (m, 2H), 7.89 (s, 2H), 8.03 (m, 2H), 8.34 (m, 2H); $^{13}$C NMR ($CDCl_3$): δ 20.3, 121.5, 127.8, 128.0, 128.6, 128.9, 129.1, 139.5, 140.00, 148.5, 153.3; Anal. calcd. for $C_{20}H_{14}N_2$: C, 85.08; H, 5.00; N, 9.92; Found: C, 84.85; H, 5.19; N, 9.81.

## Conclusion

In summary, we have introduced a highly efficient catalyst for the condensation of 1,2-diamines with 1,2-diketones. The promising points for the presented method include high yield, ease of handling, low cost of the catalyst, simple procedure and work-up, cleaner reaction profile, short reaction time, and compliance with the green chemistry protocols which make it a useful and attractive process for the rapid synthesis quinoxaline derivatives as biologically interesting compounds.

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