



One-pot synthesis of 2-substituted quinoxalines using K10-montmorillonite as heterogeneous catalyst



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ABSTRACT

An efficient one-pot synthesis of 2-substituted quinoxalines from 1,2-diamines and phenacyl bromides is developed using K10-montmorillonite (K10 clay) as a catalyst at 50 °C in acetonitrile medium. This method offers an easy route for the synthesis of substituted quinoxalines in high yields. A plausible mechanism is proposed in which quinoxalines are formed via dehydration–dehydrohalogenation–cyclization sequence. Further, the K10 clay catalyst is recovered by simple filtration and reused six times without any loss in its catalytic activity.

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Synthesis of quinoxalines and their derivatives is receiving considerable attention due to their biological activities and pharmaceutical applications.¹ Quinoxalines have been used in anticancer,² antiviral,³ antibiotic (echinomycin, leromycin and actinomycin) anti-inflammatory, and kinase inhibition activities.⁴ Furthermore, they are also used as potential building blocks for the synthesis of organic semiconductors,⁵ electroluminescent materials,⁶ cavitands,⁷ dehydroannulenes,⁸ and dyes.⁹

A number of methods have been developed for the synthesis of quinoxalines. One such method involves the condensation of a 1,2-diketone with aryl-1,2-diamine to give the corresponding quinoxaline at refluxing temperature in ethanol, benzene, or acetic acid.¹⁰ This reaction is catalyzed by iodine,¹¹ indium(III) chloride,¹² copper(II) sulfate,¹³ ceric ammonium nitrate,¹⁴ *o*-iodoxybenzoic acid,¹⁵ phosphorus oxychloride,¹⁶ silica gel,¹⁷ gallium(III) triflate,^{18a} and clayzic.^{18b} On the other hand, 1,4-addition of the 1,2-diamines to diazenylbutenes¹⁹ and oxidation of α -hydroxyketones with 1,2-diamines²⁰ have also been reported for the synthesis of the corresponding quinoxalines. Also, the synthesis of quinoxaline has been reported by the reaction of 1,2-diamines with substituted phenacyl bromides in solid phase,²¹ and using catalysts like perchloric acid supported on silica,^{22a} trimethylsilyl chloride,^{22b} KF-alumina,^{22c} β -cyclodextrin,²³ and 1,4-diazabicyclo [2,2,2]octane.²⁴ However, these reported procedures suffer from limitations such as the need of excess catalyst loading, toxic

reagents, and the requirement of high temperature to conduct the reaction. In particular, acetic acid and perchloric acid are more hazardous and the current trend is to develop green and sustainable protocols toward the same.

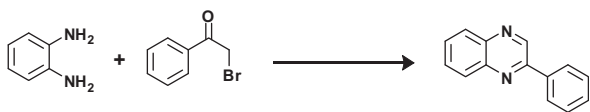
In this context, considerable attention has been devoted to perform organic transformations using solid acids as heterogeneous catalysts.²⁵ In the present work, we report a new synthetic strategy for the synthesis of quinoxaline derivatives catalyzed by K10 clay under mild reaction conditions. K10 clay is a layered alumina-silicate clay with a dioctahedral layer sandwiched between two tetrahedral layers.²⁶ K10 clay with a moderate acid strength and a surface area of 250 m²/g can be used as heterogeneous catalyst for various organic transformations due to their tunable Bronsted and Lewis acidities^{27a,b} and is considered to be an environmentally benign solid acid catalyst that offers several advantages, such as ease of handling, non-corrosiveness, low cost, and reusability.

The reaction conditions were optimized²⁸ for the synthesis of 2-phenylquinoxaline using *o*-phenylenediamine and phenacyl bromide as model substrates and the observed results are given in Table 1. Blank control experiments in the absence of catalyst showed 8% and 17% of product at room temperature and 50 °C in 8 and 3 h respectively in acetonitrile medium (Table 1, entries 1 and 2). In the absence of solvent, K 10 clay gave 13% and 69% yields at room temperature and 50 °C respectively in 3 h (Table 1, entries 3 and 4). Further increasing the reaction time to 6 h at 50 °C improved the yield to 77% (Table 1, entry 5) and it can be considered as an encouraging result, from the green and sustainable process since it does not require any solvent in the reaction

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Table 1
Optimization of reaction conditions for the synthesis of 2-phenylquinoxaline^a



| Entry | Catalyst | Solvent | Time (h) | Temp (°C) | Yield ^b (%) |
|-------|----------|-----------------|----------|-----------|------------------------|
| 1 | — | ACN | 8 | rt | 8 |
| 2 | — | ACN | 3 | 50 | 17 |
| 3 | K10 clay | None | 3 | rt | 13 |
| 4 | K10 clay | None | 3 | 50 | 69 |
| 5 | K10 clay | None | 6 | 50 | 77 |
| 6 | K10 clay | ACN | 3 | rt | 33 |
| 7 | K10 clay | ACN | 8 | rt | 90 |
| 8 | K10 clay | ACN | 0.5 | 50 | 18 |
| 9 | K10 clay | ACN | 1 | 50 | 40 |
| 10 | K10 clay | ACN | 2 | 50 | 71 |
| 11 | K10 clay | ACN | 3 | 50 | 92 |
| 12 | K10 clay | Methanol | 0.5 | 50 | 10 |
| 13 | K10 clay | Methanol | 1 | 50 | 29 |
| 14 | K10 clay | Methanol | 2 | 50 | 56 |
| 15 | K10 clay | Methanol | 3 | 50 | 80 |
| 16 | K10 clay | Methanol | 6 | 50 | 82 |
| 17 | K10 clay | THF | 3 | 50 | 85 |
| 18 | K10 clay | Chloroform | 3 | 50 | 75 |
| 19 | K10 clay | Acetone | 3 | 50 | 70 |
| 20 | K10 clay | Dichloromethane | 3 | 50 | 68 |
| 21 | K10 clay | DMF | 3 | 50 | 59 |
| 22 | K10 clay | Benzene | 3 | 50 | 60 |
| 23 | K10 clay | Toluene | 3 | 50 | 62 |

^a Reaction conditions: *o*-phenylenediamine (1 mmol), phenacyl bromide (1 mmol), K10 clay (50 mg), solvent (5 mL).

^b Isolated yield.

process. K10 clay showed highest yield of 92% in acetonitrile in 3 h while methanol gave 80% under identical conditions (Fig. 1) and no further increase in yield was noticed even after 6 h (Table 1, entries 8–16). Further, the reactions were performed using acetonitrile as a solvent only from the perspective of yield but however performing reactions in methanol or under solvent-less conditions is potentially more interesting from green and sustainable processes points of view. On the other hand, 90% yield (Table 1, entry 7) of the desired product was obtained in acetonitrile at room temperature in 8 h. Moderate to high yields were achieved with conventional organic solvents (Table 1, entries 17–23).

On the other hand, efforts were also made to optimize the catalyst loading in this reaction and the observed results are given in Fig. 2. It can be seen very clearly that the percentage yield gradually increased from 15 to 50 and reaches a maximum at 75 mg of

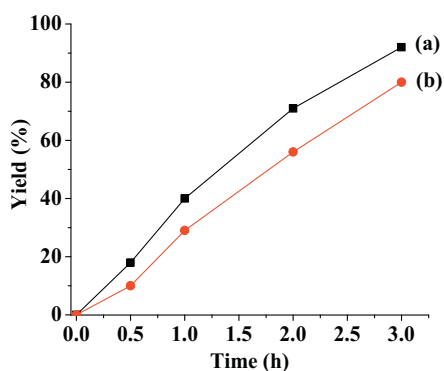


Figure 1. Time conversion plot for the synthesis of 2-phenylquinoxaline in acetonitrile (a) and methanol (b); reaction conditions: *o*-phenylenediamine (1 mmol), phenacyl bromide (1 mmol), K10 clay (50 mg), solvent (5 mL), 50 °C.

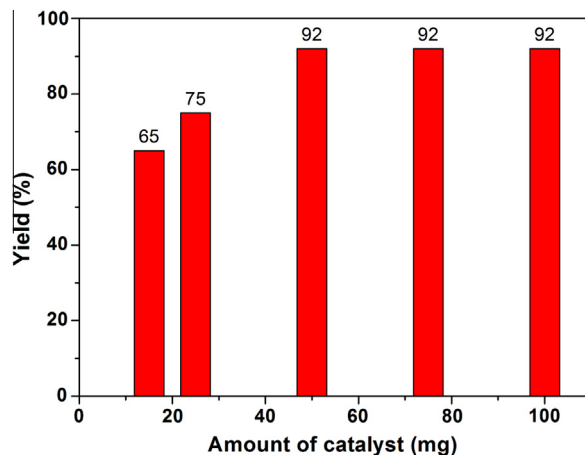


Figure 2. Effect of catalyst loading on the yield of 2-phenyl quinoxaline. Reaction conditions: *o*-phenylenediamine (1 mmol), phenacyl bromide (1 mmol), K10 clay, CH₃CN (5 mL), 50 °C, 3 h.

catalyst loading. Further increase of catalyst amount fails to increase the yield suggesting an optimal value of catalyst loading for this reaction under the present experimental conditions.

These interesting results observed in the synthesis of 2-phenylquinoxaline in high yield under mild reaction conditions encouraged us to check the generality of this methodology using a wide variety of 1,2-diamines and phenacyl bromides. Under the optimized conditions, both electron rich and electron deficient substituents on diamines and phenacyl bromides resulted in high yield of quinoxaline derivatives (Table 2). For example, the reaction of *o*-phenylenediamine with phenacyl bromide containing electron-donating (4-OMe) and electron-withdrawing (3-Br, 3-F, 4-NO₂) substituents resulted in high yields of substituted quinoxalines (Table 2, entries 2–5). On the other hand, substituted *o*-phenylenediamines also gave the corresponding 2-substituted quinoxalines with various phenacyl bromides in high yields (Table 2, entries 6–13). Increasing the molecular dimension of 1,2-diamine as in the case of 3,4-diaminobenzophenones, (Table 2, entries 14–17) with various phenacyl bromides has also resulted in very high yield of the desired products. It is also interesting to note that condensation between the ketone and the amino group is not observed under the present experimental conditions. It is very clear from the observed results that the nature of the substituents, steric hindrance, and molecular dimension of the reactants have a minimal role to play in determining the rate of reaction and as a result, most of the reactions afforded very high yields under mild reaction conditions. Thus, the operational simplicity of the process, achieving the desired products in high yields regardless of the kind of starting materials, low cost of the catalyst, and the use of acetonitrile as solvent make this protocol an alternative green chemical process for the already existing methodologies.

One of the main advantages of using heterogeneous catalysts such as K10 clay is that they can be recovered and reused efficiently. In this context, the reusability of K10 clay was checked in the synthesis of 2-phenylquinoxaline under optimized conditions, as given in Table 1. After completion of the reaction, the catalyst was recovered by filtration, washed thoroughly with acetonitrile and dried at 80 °C for 3 h. The recovered catalyst was used for consecutive runs under identical reaction conditions and the observed results are given in Table 3. Hence, the catalyst exhibited high activity up to six reuses with only a marginal decrease in the yield which may be caused from the loss of catalyst during recycling or adsorption of organic products over the catalyst by poisoning their active sites. In any case, this catalyst exhibited high potential by maintaining its activity while recycling experiments.

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