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Quinoxaline synthesis in novel tandem one-pot protocol

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ABSTRACT

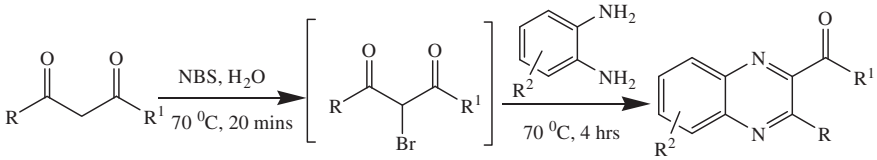
A variety of quinoxalines were synthesized via tandem one-pot procedure for the first time in water medium. The key strategy was the in situ preparation of α-halo-β-keto esters by the reaction of *N*-bromo succinimide with β-keto esters and further condensation with phenylene diamines. This novel eco-friendly approach offers an easy, efficient, and mild synthesis of highly substituted quinoxalines in good yields.

Quinoxaline and its derivatives represent one of the most biologically active classes of compounds,[1] possessing a wide and diverse spectrum of pharmacological properties[2], such as anticancer[3], antiviral,[4] antibiotic (echinomycin), and anti-inflammatory activities.[5] The quinoxaline nucleus is also associated with applications in dyes,[6] organic semiconductors,[7] dehydroannulenes,[8] and cavitands.[9]

Consequently a number of synthetic strategies have been developed for the synthesis of various substituted quinoxalines involving the condensation of 1,2-diamines with α-diketones,[10] oxidation of α-hydroxy ketones followed by the condensation with 1,2-diamines,[11] and oxidative cyclization of phenacyl bromides with 1,2-diamines.[12] These compounds were also synthesized using other non-conventional synthetic protocols like solid phase synthesis,[13] microwaves,[14] and zeolites.[15] Recently Meshram et al. described the preparation of quinoxaline derivatives from 1,2-diamines and α-halo-β-ketoesters using ionic liquids.[16]

However, most of the reported methods suffer from drawbacks such as the use of expensive reagents/additives, metal catalysts, inflammable organic solvents or harsh reaction conditions, as well as the difficult experimental/work-up procedures. In view of the above shortcomings, development of a mild and eco-friendly one-pot synthetic protocol for these highly significant classes of compounds is desirable.

Recently, there has been increasing recognition for the development of green synthetic protocols, such as reactions in aqueous



R = Me. Et, Ph, CF_3; R^1= Me, Et, Ph, OEt, OBn;
R^2 = H, 4,5-Dimethyl, 4-Nitro, 4-Methyl;

Scheme 1.

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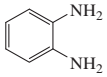
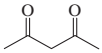
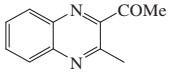
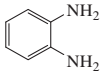
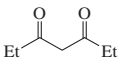
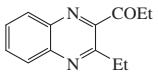
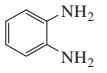
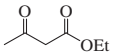
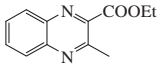
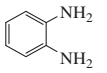
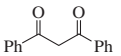
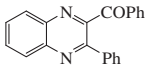
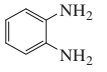
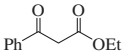
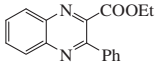
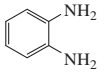
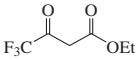
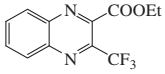
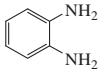
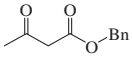
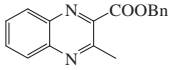
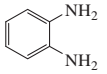
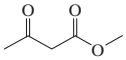
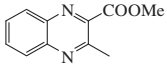
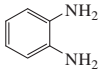
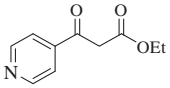
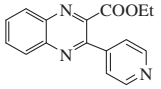
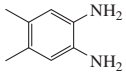
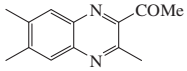
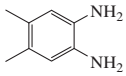
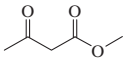
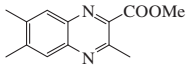
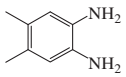
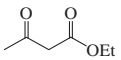
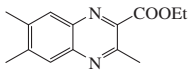
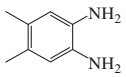
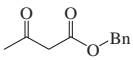
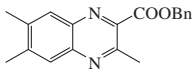
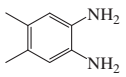
Table 1
Investigation of various solvents in the synthesis of quinoxalines.

Entry	Solvent	Temperature	Yield (%)
1	H_2O	rt	20
2	H_2O	70	85
3	H_2O	90	85
4	PEG-400	80	55
5	DCM	Reflux	25
6	CH_3CN	Reflux	15
7	MeOH	Reflux	62

medium or catalyst/solvent-free conditions. These protocols have been replacing the conventional methodologies. Organic reactions in aqueous medium acquired prominence since the pioneering studies on Diels–Alder reactions by Breslow.[17] Water is a preferred solvent medium[18] compared to the other organic solvents, due to its associated advantages, such as safety, non-toxicity, easy availability, affordability, and environmental acceptability.

In continuation of our on-going research program on the exploration of novel environment friendly approaches in synthetic organic chemistry,[19] we describe herein a tandem one-pot procedure for the preparation of quinoxalines directly from readily available and inexpensive β-diketones/β-ketoesters and 1,2-phenylene diamines (Scheme 1). The in situ preparation of α-halo-β-ketone/α-halo-β-ketoester as the main reactant reduces the steps and time involved in the reaction strategy. The advantages of the present protocol are the shorter reaction pathway and the use of aqueous medium for the conduct of the reaction. The present one-pot approach also helps us to simplify reaction handling and product

Table 2
Synthesis of quinoxalines In aqueous medium[a].

Entry	Substrate (1)	Substrate (2)	Product	Yield (%)[b]
1				85
2				84
3				84
4				83
5				79
6				80
7				83
8				82
9				78
10				88
11				82
12				86
13				84
14				85
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16				88

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Table 2 (*continued*)

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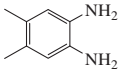
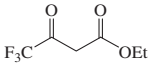
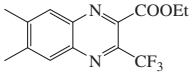
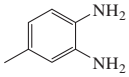
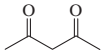
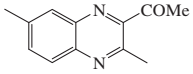
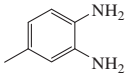
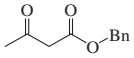
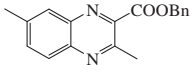
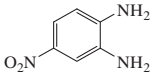
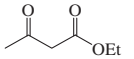
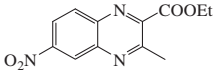
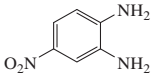
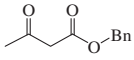
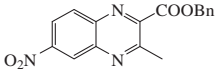
17				80
18				70
19				72
20				70
21				72

[a] Reaction conditions: β ketones/β keto esters (1 equiv), NBS (1.2 equiv), phenylene diamine (1 equiv), H_2O (15 ml).
[b] Yields of the isolated product.

purification, improve synthetic efficiency, and reduce solvent consumption as well as disposal, thereby minimizing the harmful impact of various chemicals on environment.[20] More over this novel methodology offers an improvement over the recent report of quinoxaline synthesis in ionic liquids by Meshram et al.[16] and our earlier report on quinoxaline synthesis by supramolecular catalysis using β-cyclodextrin.[21] Meshram et al. used α-halo-β-ketoesters as reactants, which in turn are to be prepared by additional reactions, whereas the present facile novel work minimized the number of steps to synthesise the desired quinoxalines, offering a faster, simpler, and atom-economic one-pot direct methodology.

Initially a reaction was attempted between benzene 1,2-diamine and 3-bromopentane-2,4-dione (prepared in situ) as a model reaction in aqueous medium. 3-Bromopentane-2,4-dione was prepared by adding *N*-bromosuccinamide (1.2 equiv) to acetyl acetone in water at 70 °C and stirring for 20 min. 1,2-Phenylene diamine was added to the reaction mixture and heated for 4 h to obtain the desired quinoxaline in 85% yield. In these reactions succinimide was obtained as the by-product. This has been recycled to NBS as described in the general procedure.[22] The reaction is envisaged to proceed in the proposed mechanistic pathway (Scheme 1) involving the in situ formation of α-halo-β-ketone/α-halo-β-ketoester, followed by further cyclizations to yield the expected product. In order to evaluate the effect of solvent on the reaction, various solvents, such as PEG-400, methanol, acetonitrile, dichloromethane and water were examined. Among different solvents, water proved to be the best medium for this reaction (Table 1).

On the basis of the preliminary results, various 1,2-phenylene diamines and 1,3-diketones were subjected to the present reaction conditions to investigate the scope and limitation of the reaction, the results of which were represented in Table 2. In view of the interesting results obtained with 1,3-diketones, the scope of the reaction was extended further to β keto esters (Scheme 1) and the results were incorporated in Table 2. The reactions proceeded well to obtain encouraging yields in the case of both 1,3-diketones as well as β-keto esters.

As replacing *N*-bromo succinimide with *N*-iodo succinimide did not improve the yields further, reaction studies were conducted only with *N*-bromo succinimide (Scheme 1). Unsymmetrical 1,2-diamine (4 methyl 1,2-phenylene diamine) yielded isomeric products with 75:25 ratio (entries 18 and 19). CF_3 substituent on 1,3-diketone as well as β-keto ester had less effect on the reaction progress and yields the products (entry 6 and 17). 4-Nitro benzene 1,2-diamine had also reacted in the present reaction conditions resulting in lower yield of the product (entries 20 and 21).

In conclusion, a novel, tandem, mild, and environ friendly, one pot synthetic protocol was developed for obtaining quinoxalines directly from the corresponding 1,2-phenylene diamines and 1,3-dicarbonyl compounds for the first time in aqueous medium, in the absence of any catalyst which will contribute for the growth of green chemistry.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.110.

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22. *General procedure for the synthesis of substituted quinoxalines*: To a round bottom flask of water (15 mL) acetyl acetone (1 mmol) was added followed by NBS (1.2 mmol) and stirred for 20 min at 70 °C. To this reaction mixture, 1,2-phenylene diamine (1.0 mmol) was added and stirred until completion of the reaction as indicated by TLC. The reaction mixture was extracted with ethyl acetate (3 × 10 mL) .The organic layers were washed with water, saturated brine solution and dried over anhydrous Na_2SO_4. The combined organic layers were evaporated under reduced pressure and the resulting crude product was purified by column chromatography. To the filtrate, which contained succinimide and HBr was added $NaBrO_3$ and concd H_2SO_4 as already reported[23] and the mixture stirred for 30 min, extraction with ethyl acetate giving NBS in an isolated yield of 70–80%.
Data of representative example: 1-(3-methylquinoxalin-2-yl)ethanone (Table 2, entry1): Solid. Mp 78–80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.82 (3H, s), 2.96 (3H, s), 7.70–7.83 (2H, m), 8.00–8.13 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.96, 28.50, 29.58, 95.93, 126.84, 128.94, 132.15, 133.78, 143.94. ESI-MS: *m*/*z* 187 $(M+H)^+$. HRMS calcd for 187.1123, found 187.1232.
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