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Green and selective protocol for the synthesis of quinoxalines

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ABSTRACT

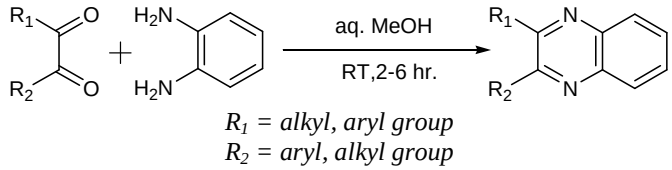
An efficient and eco-friend method has been developed for the synthesis of quinoxaline derivatives via the condensation of aryl 1, 2-diamines with 1, 2-dicarbonyl compounds in MeOH at room temperature.

Key words: Eco-friend, Quinoxaline, Low cost method.

INTRODUCTION

Quinoxaline and its derivatives are an important class of benzoheterocycles displaying a broad spectrum of biological activities which have made them privileged structures in pharmacologically active compounds [1–4]. They are used as dyes, pharmaceuticals and antibiotics such as echinomycin, levomycin and actinoleutin. Some studies were carried out in order to explore the antitumoral properties of quinoxaline compounds [5]. Recently, quinoxalin and its analogues have been investigated as the catalyst's ligands [6]. On the other hand quinoxalines constitute the basis of many insecticides, fungicides, herbicides and anthelmintics, as well as being important in human health and as receptor antagonists [2, 3 and 7]. Because of wide variety of applications associated with the quinoxaline moieties, their synthesis has remained the goal of many research groups over the years. Recently, the synthesis of quinoxaline derivatives via the condensation of aryl 1, 2-diamines with 1, 2-dicarbonyl compounds in MeOH/AcOH [8] under microwave irradiation at 100 ^{o}C has been reported, but the process requires special instrumentation. In addition, improved methods have been developed for the synthesis of quinoxaline derivatives, using *o*-iodoxybenzoic acid [9], ceric(IV)ammonimnitrate [10], $Yb(OTf)_3$ [11], $H_6P_2W_{18}O_{62,}$ $2H_2O$ [12] and oxone [13]. However, most of the traditional processes suffer from a variety of disadvantages, such as pollution, high cost, poor chemical yields, requirements for long reaction time, and tedious work-up procedures, which limit their use under the aspect of environmentally benign processes. Recently, a microwave-induced iodine-catalyzed synthesis of different types of quinoxalines via condensation of 1, 2-diamines with 1, 2-dicarbonyl compounds has been reported [14].

Considering the above and in continuation of our research to develop cost effective and eco-friend protocol for the synthesis of nitrogen heterocycles [15 and 16], we report herein the synthesis of quinoxaline derivatives via the condensation of aryl 1, 2-diamines with 1, 2-dicarbonyl compounds in MeOH at room temperature in absence of acid, base or catalytic support.



Scheme 1: Synthesis of quinoxaline derivatives.

MATERIALS AND METHODS

All the melting points were determined in an open capillary method, UV spectra were recorded in JASCO V-530 UV/VIS spectrophotometer; IR was recorded in Perkin-Elmer FT-IR spectrophotometer; NMR was recorded in Bruker-Avance 300 MHz FT-NMR instrument using TMS as the internal standard. NMR spectra were recorded in $CDCl_3$. The chemicals used were purchased from Merck, Fluka and SRL and were used as received (Merck, Fluka) or after purification (SRL) following the standard methodology.

Preparation of quinoxaline derivatives

In a typical reaction procedure, 2 mmol of recrystallised benzil, taken in a 50 ml round bottom flask was dissolved in 3 ml of wet methanol and was made homogeneous by stirring with a magnetic spinning bar. To this 2 mmol of *o*-phenylenediamine was added. Stirring was continued until the reaction is completed (checked by tlc). Methanol was evaporated under reduced pressure and the crude product was purified by chromatography using silica gel. Petroleum ether-ethyl acetate (PE - EA) mixtures were used as eluent.

RESULT AND DISCUSSION

To cope up with the growing demand of *N*-heterocycles, our laboratory has devoted a significant effort to develop efficient protocols for the preparation of a diverse collection of substituted heterocyclic scaffolds from common intermediates [15, 16]. The present investigation has developed a clean method for a one-pot synthesis of quinoxaline derivatives at room temperature without any side products.

Encouraged by the findings of the model study with benzil and *o*-phenylenediamine in methanol (vide infra), several experiments were carried out to optimize the newly developed general protocol for synthesis of quinoxalines (Table 1). In deciding the best solvent for the above transformation, a series of polar protic and polar aprotic solvents were tried in the above model reaction and methanol was found to be the best (Table 1).

The study also indicated that a 3:2 (v/v ratio) of (MeOH + H_2O) mixture is equally effective as a reaction solvent and this observation established this greener protocol to be very effective and

acceptable for commercial production of this important class of derivatives. Solvents like, acetonitrile, DMSO, DMF and even ethanol were not found encouraging (Table 1).

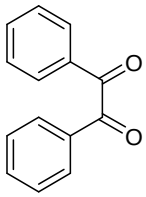
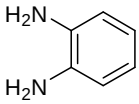
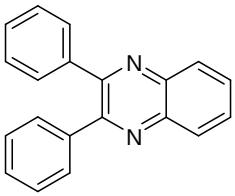
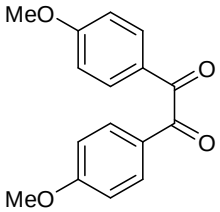
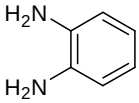
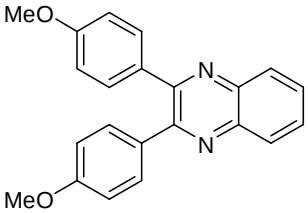
Table 1 Variation of solvent / reaction time / temperature / % yield of quinoxaline in the reaction of benzil and *o*-phenylenediamine

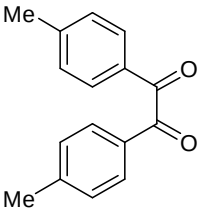
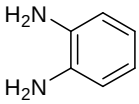
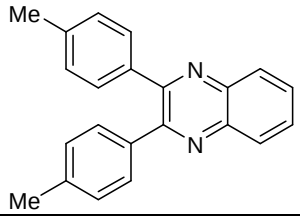
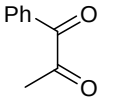
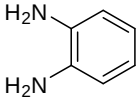
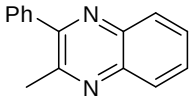
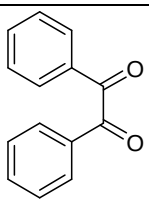
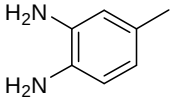
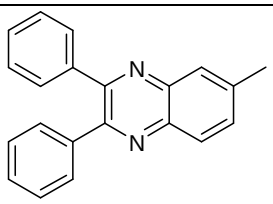
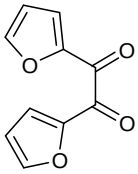
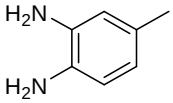
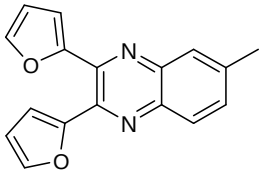
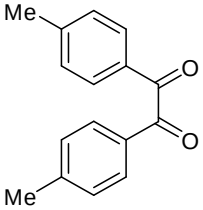
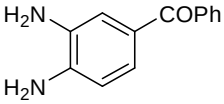
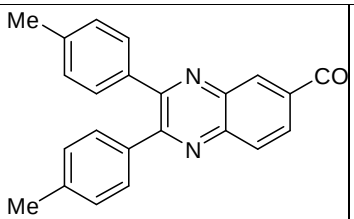
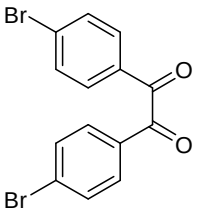
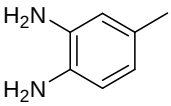
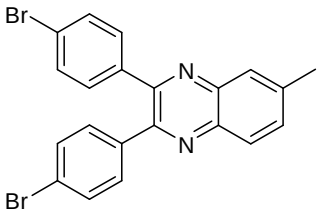
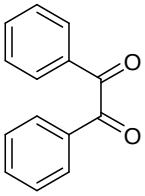
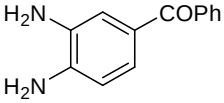
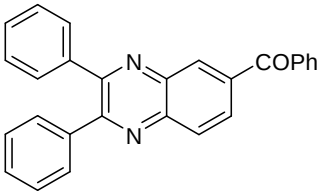
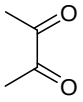
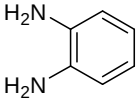
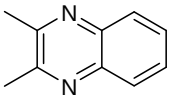
Entry	Solvent[a]	Time (h)	Temperature (^oC)	% Yield[b]
1	Water	2	RT	nil
2	Water	18	RT	nil
3	Water	10	70	nil
3	Methanol	2	RT	88
4	Acetonitrile	18	RT	25
5	DCM	18	RT	10
6	DMSO	18	RT	15
7	DMF	48	RT	25
8	Acetonitrile	10	70	30
9	DMF	10	70	25
10	Isopropanol	18	RT	36
11	Isopropanol	10	70	45

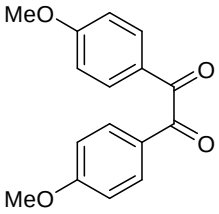
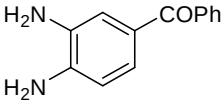
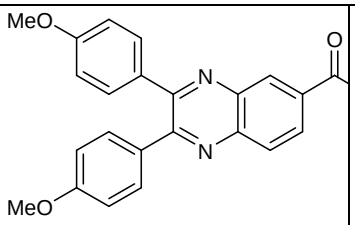
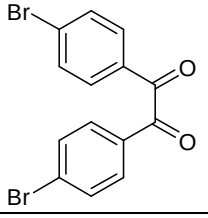
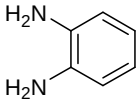
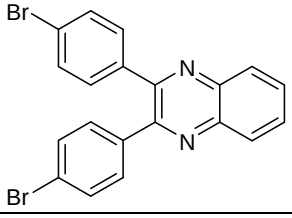
a; freshly distilled 2 ml solvent, b; isolated by column chromatography

In order to show the general applicability, we attempted the resent procedure to a number of both structurally and chemically diversified 1, 2-dicarbonyls and 1, 2-diamines to synthesize quinoxaline derivatives (Table 2) and could able to get the identical results in each case. It was found that the developed method was very much effective for aromatic as well as aliphatic diketones. The amines and diketones with electron donating (Entry 3, 6 of Table 2) as well as with electron withdrawing groups (Entry 2 and 8 of Table 2) participated uniformly in the reaction. Apparently, the nature and position of substituents on the aryl ring did not make much difference in reactivity of the protocol.

Table 2 Synthesis of quinoxaline derivatives using different diketo and diamines

Entry	1, 2-diketone	1,2-diamine	Time h)	Pyrazine	% Yield
1			2.5		88
2			3		86

3			3		87
4			5		82
5			5		85
6			4		82
7			4		86
8			3.5		78
9			3		88
10			5		84

11			4.5		78
12			3		82

% Yield refers to the isolated yield of all the compounds of all the compounds.

Phenyl-(2, 3-diphenylquinoxalin-6-yl) methanone (Table 2, entry 9)
Pale yellow crystalline solid, M. P: 145-147 ^{o}C
^{1}H NMR ($CDCl_3$, 300MHz): δ 7.25-7.63 (m, 12H), 7.84-7.95 (m, 2H), 8.23-8.29 (m, 2H), 8.53 (s, 1H); ^{13}C NMR ($CDCl_3$, 75MHz): δ128.3, 128.5, 129.1, 129.2, 129.6, 129.7, 129.9, 130.1, 132.4, 132.8, 137.1, 138.2, 138.5, 138.6, 140.1, 142.9, 154.5, 155.1, 195.7.
IR (KBr) ν_{max} cm^{-1}: 3058, 1658, 1598, 1541, 1446, 1398.

2, 3-Di (furan-2-yl)-6-methylquinoxaline (Table 2, entry 6)
Pale yellow crystals, M. P: 116-118 ^{o}C
^{1}H NMR ($CDCl_3$, 300MHz): δ 2.29 (s, 3H), 2.59 (s, 2H), 6.55-6.70 (m, 4H), 7.47-7.62 (m, 3H), 7.92-8.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 21.6, 21.9, 111.9, 112.6, 112.8, 117.2, 118.9, 124.6, 127.9, 128.6, 132.8, 141.2, 150.9.
IR (KBr) ν_{max} cm^{-1}: 2923, 1616, 1559, 1488.

CONCLUSION

A mild, efficient and environmentally benign method has been developed for the synthesis of quinoxalines and is established as superior in every respect in comparison to the already reported methods. The method is tested suitable for aliphatic, aromatic and heterocyclic 1, 2 diketones.

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