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An efficient protocol for the synthesis of quinoxaline derivatives at room temperature using molecular iodine as the catalyst

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Abstract—The use of molecular iodine as the catalyst for a one-pot synthesis of quinoxaline derivatives at room temperature is reported.

Functionalized quinoxalines represent an important class of nitrogen-containing heterocycles as they constitute useful intermediates in organic synthesis and are useful dyes.[1] Quinoxaline derivatives are well known in the pharmaceutical industry and have been shown to possess a broad spectrum of biological activities including antiviral, antibacterial, anti-inflammatory and as kinase inhibitors.[2] In addition, quinoxaline derivatives have been evaluated as anticancer and anthelmintic agents.[3] A number of synthetic strategies have been developed for the preparation of substituted quinoxalines.[4] By far, the most common method relies on the condensation of an aryl 1,2-diamine with a 1,2-dicarbonyl compound in refluxing ethanol or acetic acid for 2–12 h giving 34–85% yields.[5] Recently, improved methods have been reported for the synthesis of quinoxaline derivatives including the Bi-catalyzed oxidative coupling of epoxides and ene-1,2-diamines,[6] from α-hydroxy ketones via a tandem oxidation process using Pd $(OAc)_2$ or $RuCl_2$-$(PPh_3)_3$-TEMPO[7] and MnO_2,[8] a solid-phase synthesis on Synphase™ Lanterns,[9] cyclization of α-arylimino oximes of α-dicarbonyl compounds under reflux in acetic anhydride[10] and the condensation of *o*-phenylene diamines and 1,2-dicarbonyl compounds in MeOH/AcOH under microwave irradiation.[11]

In recent years, the use of molecular iodine in organic synthesis has received considerable attention as an inexpensive, non-toxic, readily available mild Lewis acid catalyst for organic transformations such as dehydration of tertiary alcohols to alkenes,[12] synthesis of benzyl alkyl ethers,[13] synthesis of mixed ethers under hydrogen pressure,[14] synthesis of benzothiophenes,[15] bis-indoles,[16] deprotection of acetals,[17] esterification,[18] transesterification[19] and Michael addition.[20] Recently, we reported the use of iodine for the synthesis of β-keto-enol ethers[21] and multicomponent dihydropyrimidinone synthesis.[22] In this letter, we report the synthesis of functionalized quinoxalines **3** by the iodine catalyzed cyclocondensation of 1,2-dicarbonyl compounds **1** and substituted *o*-phenylene diamines **2** in excellent yields (Scheme 1).

In a model condensation reaction, benzil **1a** and 1,2-diaminobenzene **2a** in DMSO were stirred at room temperature using a catalytic amount of molecular iodine. The progress of the reaction was monitored by TLC. After completion of the reaction after 35 min, an aqueous work-up afforded 2,3-diphenylquinoxaline **3a** (95% yield). To evaluate the use of this procedure, a variety of substituted *o*-phenylenediamines were condensed with 1,2-disubstituted 1,2-dicarbonyl compounds. The results are shown in Table 1. The reaction proceeds very cleanly at room temperature and no undesirable side-reactions were observed. In the absence of iodine, the reaction did not proceed, even after 10 h.

We have demonstrated an efficient and mild protocol for the condensation of 1,2-dicarbonyl compounds and

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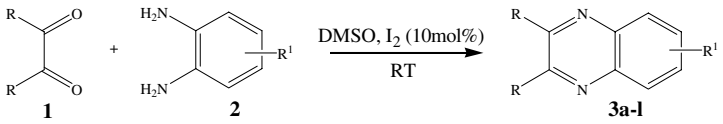
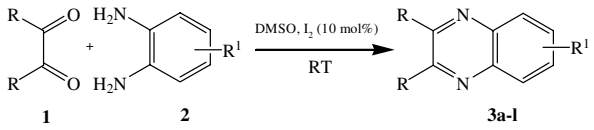


Scheme 1.

Table 1. Synthesis of quinoxaline derivatives **3a**–**l**



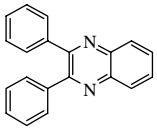
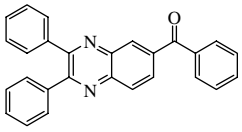
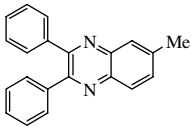
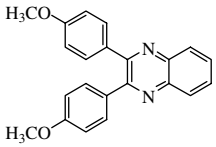
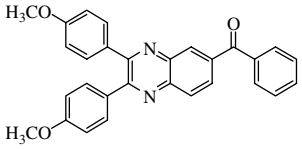
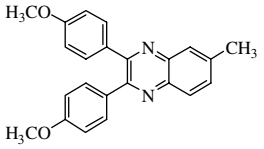
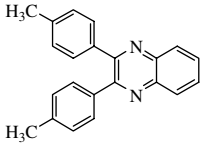
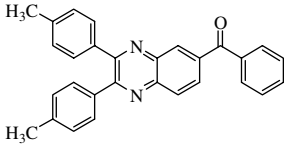
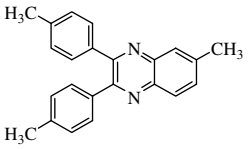
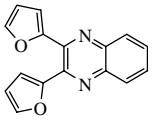
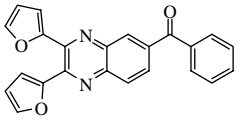
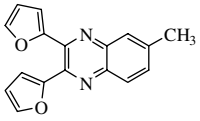
Entry	Products **3a**–**l**	Time (min)	Yields (%)[a]
a		35	95
b		70	85
c		50	90
d		40	92
e		75	88
f		60	90
g		40	90
h		70	86

Table 1 (*continued*)

Entry	Products **3a–l**	Time (min)	Yields (%)[a]
i		55	91
j		45	90
k		75	86
l		65	88

[a] Refers to isolated yield.

different substituted *o*-phenylenediamines to give functionalized quinoxalines at room temperature in DMSO using a catalytic amount of molecular iodine in excellent yields.

General experimental procedure: A mixture of the 1,2-diketone **1** (10 mmol), 1,2-diamino arene **2** (10 mmol) and molecular iodine (10 mol %) in DMSO (10 ml) was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured onto crushed ice and stirred for 10–15 min. The solid which separated was filtered, washed with aqueous sodium thiosulfate solution to remove iodine and subsequently with water, and then recrystallized from ethanol to afford pure quinoxaline **3**.

The products **3a–l** obtained were identified by comparison with authentic samples by TLC and ^{1}H NMR and IR spectroscopy.

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