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Molecular iodine: a powerful catalyst for the easy and efficient synthesis of quinoxalines

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Abstract—Various biologically important quinoxaline derivatives were efficiently synthesized in excellent yields using inexpensive, nontoxic, and readily available bench top chemical, iodine in catalytic amount (10 mol%). Besides this, a systematic study was carried out to evaluate parameters such as solvent and catalyst loading. Several aromatic as well as aliphatic 1,2-diketones and aromatic 1,2-diamines, such as substituted phenylene diamines, tetra amines were further subjected to condensation using catalytic amounts of iodine to afford the products in excellent yield.

1. Introduction

Among the various classes of nitrogen containing heterocyclic compounds, quinoxaline derivatives are important components of several pharmacologically active compounds.[1] Although rarely described in nature, synthetic quinoxaline ring is a part of a number of antibiotics such as echinomycin, leromycin, and actinomycin, which are known to inhibit the growth of Gram-positive bacteria and are also active against various transplantable tumors.[2] Besides this, it has been reported for their application in dyes,[3] efficient electroluminescent materials,[4] organic semiconductors,[5] building blocks for the synthesis of anion receptor,[6] cavitands,[7] dehydroannulenes,[8] and DNA cleaving agents.[9] A number of synthetic strategies have been developed for the synthesis of substituted quinoxalines and the most common method is the condensation of an aryl 1,2-diamine with 1,2-dicarbonyl compounds in refluxing ethanol or acetic acid.[10] However, many improved methods have been reported for the synthesis of quinoxalines using catalytic amounts of various metal precursors, acids, and zeolites.[11] In addition to the above catalytic methods, reports were also known with microwave[12] and solid phase synthesis.[13] Nevertheless, most of these methods suffer from unsatisfactory product yields, critical product isolation procedures, expensive and detrimental metal precursors, and harsh reaction conditions, which limit their use under the aspect of environmentally benign processes.

The use of molecular iodine in organic synthesis has been known for a long time. In recent years, molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations[14] under mild and convenient conditions to afford the corresponding products in excellent yields with high selectivity. However, there is no example of quinoxaline synthesis using molecular iodine as a catalyst. As part of our on going interest, in the use of cheap and ecofriendly materials as catalysts for various organic transformations, we had the opportunity to look into the synthesis of quinoxalines using molecular iodine.

2. Results and discussion

In the beginning, a systematic study was carried out for the catalytic evaluation of iodine toward the synthesis of quinoxalines. Initially, a blank reaction was conducted using benzil and *o*-phenylenediamine in boiling ethanol, which resulted in the formation of a condensation product after 45 min (60% Y). With the same substrates, the reaction in ethanol, using catalytic amount of iodine at room temperature afforded the products in

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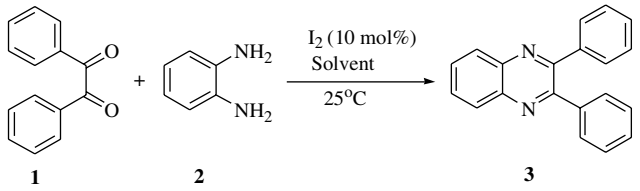


1 2 3

Scheme 1.

quantitative yield during 15 min. Thus, in the absence of iodine, the reaction was slow and also requires refluxing conditions with unsatisfactory yields. We next investigated the effect of different solvents on the reaction rate as well as the yields of products. Almost all the solvents afforded the products in excellent yield with a variation in time period. Protic solvents like methanol and ethanol afforded the products in high yield within 15–20 min.

After screening different solvents, acetonitrile came out as the solvent of choice, which not only afforded the products in good yield, but also with higher reaction rates. In general, for polar solvents the reaction rate is high, whereas for nonpolar solvents it is little low (Scheme 1 and Table 1).

The method of iodine catalyzed synthesis of quinoxalines is very simple, efficient, clean, and without any other side products. We also evaluated the amount of iodine required for this transformation. As less as, 5 mol% of iodine can catalyze the reaction to the same extent, but needs a little longer reaction times (>1 h). In the absence of iodine, the reaction takes more than 24 h to complete. In an optimized reaction condition, 1,2-diketone (1 mmol) and 1,2-diamine (1.2 mmol) in acetonitrile (0.5 mL) were mixed with iodine (0.10 mmol) and stirred at room temperature for 3–30 min. After the completion of the reaction (monitored by TLC), a simple work up affords the products in excellent yield[15] (Scheme 2).

Table 1. Effect of solvents for the iodine catalyzed synthesis of quinoxalines

Entry[a]	Solvent	Time	Yield[b] (%)
1	CH_2Cl_2	15 min	95
2	MeOH	20 min	92
3	EtOH	15 min	90
4	Et_2O	30 min	91
5	THF	30 min	94
6	DMF	15 min	89
7	CH_3CN	2–3 min	98
8	EtOAc	30 min	85
9	$PhCH_3$	3 h	93
10	PhH	4.5 h	91

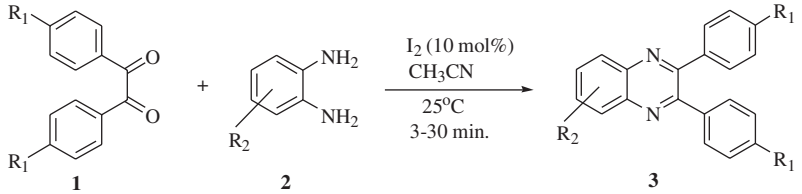
[a] All reactions were performed at 1 mmol scale using 10 mol% of iodine in 0.5 mL of solvent.
[b] Column isolated yields.

In order to evaluate the efficiency of this methodology, a number of 1,2-diketones and 1,2-diamines were further subjected to condensation using catalytic amount of iodine (Table 2).

With symmetrical aromatic diamines the reaction showed good product yields. Diamine, such as naphthalene-1,2-diamine, steric factors played a key role in affecting the rate of reaction and the reaction requires a longer time. With electron donating substituents in the amine part, increased yields of products were obtained, whereas the effect is reverse with electron with drawing substituents. On the other hand, electron donating substituents associated with aromatic 1,2-diketone decreased the product yields and the effect is reverse with electron with drawing groups. However, the variations in the yields were very little and both substituted aromatic diamines such as 4-chloro and 3-methyl gave the condensed products in excellent yields with different substituted 1,2-diketones. To check the versatility of this method, we have also subjected other than symmetrical 1,2-diketones, such as furil and 1-phenyl-1,2-propanedione, and obtained the products in excellent yields. In the case of unsymmetrical 1,2-diketones such as 1-phenyl-1,2-propanedione, different aromatic diamines delivered a 1:1 ratio of regioisomers in almost quantitative yield (Table 3, entries 7 and 8). In another variation, tetra amines such as 3,3′,4,4′-tetraamino-1,1′-biphenyl underwent condensation with diketone (benzil) in the presence of catalytic amount of iodine (10 mol%) and afforded the product **5** in 85% yield[16] (Scheme 3).

This methodology is very useful for the synthesis of a sterically hindered amine such as 2,3,2′,3′-tetraphenyl-[6,6′] biquinoxalinyl **5**.

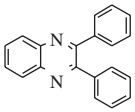
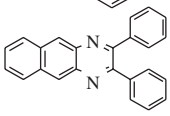
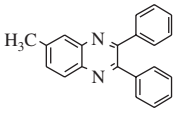
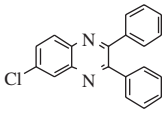
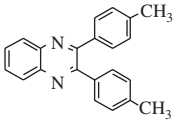
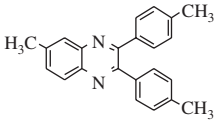
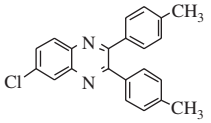
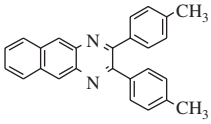
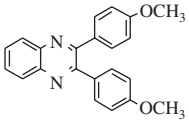
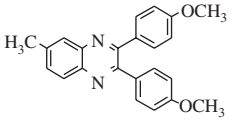
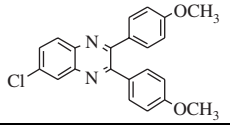
Though the role of iodine is not clearly known, but it can act as a mild Lewis acid. A part from its acidity iodine plays a complex role in accelerating the dehydrative steps, and thus promotes the formation of products.[17]



1 2 3

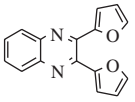
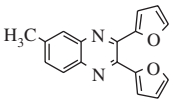
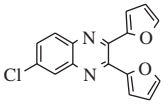
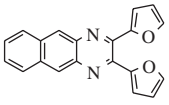
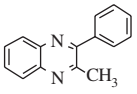
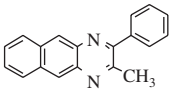
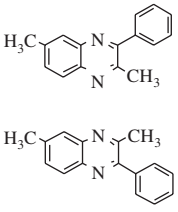
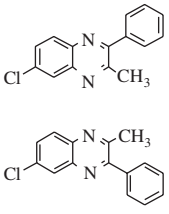
Scheme 2.

Table 2. Synthesis of different quinoxalines using symmetrical aromatic 1,2-diketones

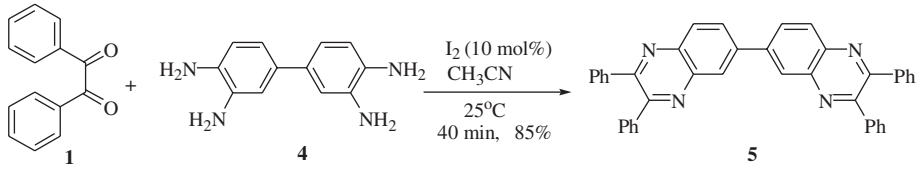
Entry[a]	Product[b]		Time (min)	Yield[c] (%)
1		**3a**	3	98
2		**3b**	20	96
3		**3c**	5	95
4		**3d**	10	90
5		**3e**	4	94
6		**3f**	5	92
7		**3g**	15	90
8		**3h**	30	90
9		**3i**	3	94
10		**3j**	5	96
11		**3k**	10	92

[a] All reactions were performed at 1 mmol scale using 10 mol% of iodine in 0.5 mL of CH_3CN.
[b] All products were well characterized using ^1H, ^{13}C NMR, and elemental analysis.
[c] Isolated yields of pure products after passing through a small bed of silica.

Table 3. Synthesis of different quinoxalines using heterocyclic and unsymmetrical 1,2-diketones

Entry[a]	Product[b]		Time (min)	Yield[c] (%)
1		**3l**	5	95
2		**3m**	10	96
3		**3n**	20	92
4		**3o**	30	92
5		**3p**	3	95
6		**3q**	10	93
7		**3r**	5	93[d]
8		**3s**	15	90[d]

[a] All reactions were performed at 1 mmol scale using 10 mol% of iodine in 0.5 mL of CH_3CN.
[b] All products were well characterized using ^1H, ^{13}C NMR, and elemental analysis.
[c] Isolated yields of pure products after passing through a small bed of silica.
[d] The yield belongs to the overall yield of two regioisomers which are formed in 1:1 ratio.



1 4 5

Scheme 3.

3. Conclusion

In summary, we describe a simple, efficient, and eco-friendly method for the synthesis of quinoxalines from various 1,2-diketones and 1,2-diamines using cheap and readily available molecular iodine as a catalyst. The ambient conditions, high reaction rates, excellent product yields, and easy workup procedure not only make this methodology an alternative platform to the conventional acid/base catalyzed thermal processes, but also makes it significant under the umbrella of environmentally greener and safer processes.

Acknowledgments

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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.2005.07.026.

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15. Typical experimental procedure for the synthesis of 2,3-diphenyl-quinoxaline (**3a**): a mixture containing 1,2-diketone **1** (1 mmol), 1,2-diamine **2** (1.2 mmol) and iodine (10 mol%) in acetonitrile (0.5 mL) was stirred at room temperature for 3 min (monitored by TLC). After completion of the reaction, solvent was removed under reduced pressure and the crude product was subjected to flash column chromatography using silica gel (eluent, 95:5 hexane–EtOAc) which afforded quinoxaline **3a**. Or the crude reaction mixture was diluted with EtOAc (15 mL) washed with aqueous sodiumthiosulfate (2×10 mL, 10%) followed by water (2×10 mL). The organic layer was dried over anhydrous $MgSO_4$, followed by the evaporation of the solvent to obtain the crude product, which was purified as above, to afford pure **3a** as a white solid (0.276 g 98% Y). Mp 126–127 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (m, 2H), 7.76 (m, 2H), 7.56 (m, 4H), 7.35 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 153.50, 141.29, 139.15, 130.01, 129.93, 129.27, 128.87, 128.33. Anal. Calcd for $C_{20}H_{14}N_2$: C, 85.08; H, 5.00; N, 9.92. Found: C, 84.98; H, 5.12; N, 9.90.
16. 2,3,2′,3′-Tetraphenyl-[6,6′] biquinoxalinyl (**5**): yellow color solid, mp >295 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.6 (s, 2H), 8.33 (d, $J = 8.6$ Hz, 2H), 8.2 (dd, $J = 8.7$ Hz, $J = 1.7$ Hz, 2H), 7.58 (m, 8H), 7.41 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): 154.19, 153.75, 141.48, 141.28, 140.98, 139.00, 129.98, 129.92, 129.55, 129.01, 128.35, 127.50. Anal. Calcd for $C_{40}H_{26}N_4$: C, 85.38; H, 4.66; N, 9.96. Found: C, 85.02; H, 4.79; N, 10.19.
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