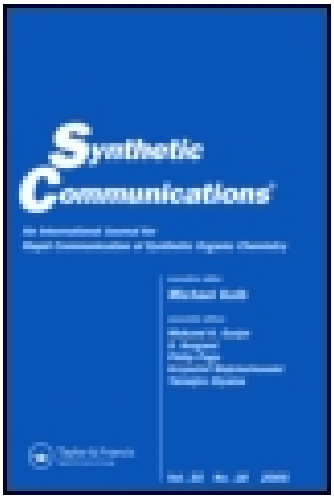

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Efficient and Green Method for the Synthesis of 1,5-Benzodiazepine and Quinoxaline Derivatives in Water

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Efficient and Green Method for the Synthesis of 1,5-Benzodiazepine and Quinoxaline Derivatives in Water

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Abstract: Various 1,5-benzodiazepine and quinoxaline derivatives have been synthesized in water with excellent yields using a catalytic amount of indium chloride at room temperature. This synthetic protocol is nontoxic, safe, and environmentally benign.

Keywords: 1,5-benzodiazepine, indium chloride, Lewis acid, quinoxaline, water media

The development of simple and efficient chemical processes or methodologies for the synthesis of biologically active compounds in water is one of the major challenges for chemists, because water is a safe, readily available, and environmentally benign solvent.[1] 1,5-Benzodiazepine and quinoxaline units are important because they are found in many biologically active compounds.[2] In clinical practice, 1,5-benzodiazepine derivatives are used as anticonvulsant, antianxiety, and hypnotic agents.[2] In organic synthesis, they are used as valuable synthons for the preparation of fused ring compounds such as triazolo-, oxadiazolo-, oxazino, and furano-benzodiazepines.[3] On the other hand, functionalized quinoxalines are useful intermediates in organic

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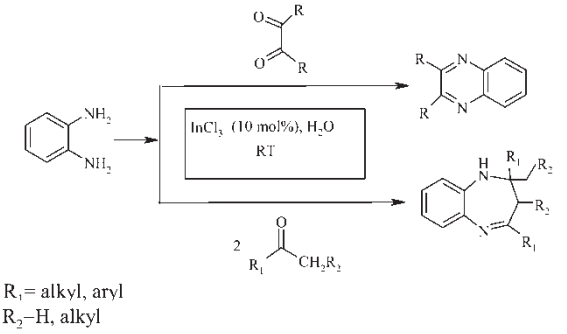
synthesis; they are found in various synthetic pharmaceuticals displaying a broad spectrum of biological activity including antiviral, antibacterial, and anti-inflammatory properties and as kinase inhibitors.[2] Quinoxaline and 1,5-benzodiazepine derivatives are also used for the preparation of various dyes.[4]

The condensation of 1,2-diamine with ketones or 1,2-dicarbonyl compounds gives 1,5-benzodiazepine and quinoxaline derivatives, respectively. A number of synthetic strategies have been reported for the synthesis of these two derivatives in the literature. For the synthesis of 1,5-benzodiazepine, BF_3-OEt_2,[5] $NaBH_4$,[6] polyphosphoric acid,[7] SiO_2,[7] MgO and $POCl_3$,[8] $Sc(OTf)_3$,[9] $Yb(OTf)_3$,[10] AcOH under microwave irradiation,[11] and ionic liquid[12] may be mentioned. On the other hand, ceric(IV) ammonium nitrate,[13] iodine,[14] zeolite,[15] microwave,[16] and solid-phase synthesis[17] are used for the synthesis of quinoxaline; other reagents such as $Pd(OAc)_2$ or $RuCl_2$-$(PPh_3)_3$-2,6,6-tetramethyl-1-peperidinyloxyl (TEMPO)[18] and MnO_2[19] are used for the synthesis of quinoxaline via a tandem oxidation process. However, many of the synthetic protocols reported so far suffer from disadvantages such as anhydrous conditions, use of organic solvents, drastic reaction conditions, prolonged reaction time, and use of transition metals. Therefore, development of an efficient, safe, and environmentally friendly reagent system is desirable.

Lewis acid–catalyzed reactions are currently of great interest because of their unique reactivity, selectivity, and use of mild conditions, but they have been believed to be unusable in water.[20] Mostly lanthanide triflates such as $Sc(OTf)_3$ and $Yb(OTf)_3$ are used as water-tolerant Lewis acids for various organic transformations.[21] On the other hand, indium salts are extensively used in organic synthesis because of their low toxicity and stability in air and water.[22] Very recently, we have synthesized biologically active imidazoline and benzimidazole units from aldehyde and diamine via a condensation followed by oxidation process in water.[23] Now, we report here a green method for the synthesis of 1,5-benzodiazepine and quinoxaline derivatives from aldehyde and ketone/1,2-diketone using indium(III) chloride as a water-tolerant Lewis acid catalyst.

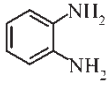
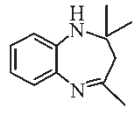
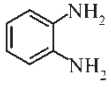
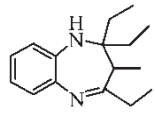
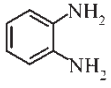
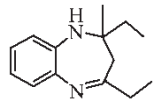
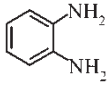
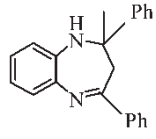
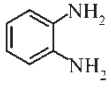
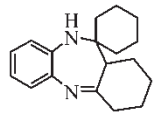
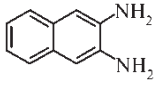
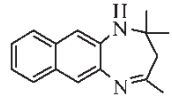
In a typical procedure, *O*-phenylenediamine (1.0 mmol), acetone (2 mmol) or 1,2-diketone (1 mmol), and indium chloride (10 mol%) were stirred in water (10 ml). After workup, the corresponding 1,5-benzodiazepine and quinoxaline were obtained with excellent yields (Scheme 1).

The formation of these two derivatives were not observed without any catalyst; the addition of indium chloride as a catalyst smoothly formed the desired products with excellent yields in water. The catalytic amount of indium chloride was optimized, and it was found that 10 mol% is sufficient for both the condensations. As shown in Table 1, both aliphatic (cyclic and acyclic) and aromatic ketones react with diamine to give their corresponding 1,5-benzodiazepines with excellent yields. The reaction of cyclic ketones with *O*-phenylinediamine gave fused-ring 1,5-benzodiazepine derivatives. When the 2-butanone was used as a substrate (entry 3), the cyclization occured



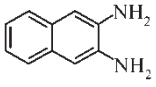
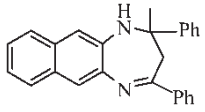
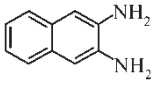
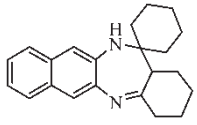
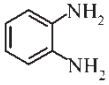
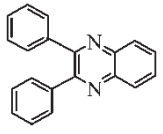
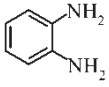
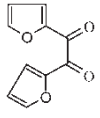
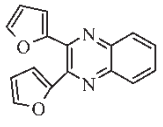
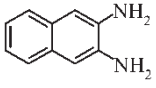
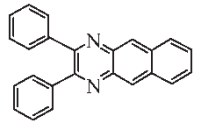
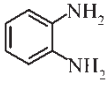
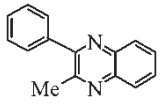
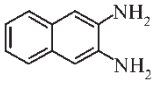
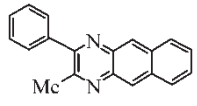
Scheme 1. Synthesis of 1,5-benzodiazepine and quinoxaline derivativeds.

Table 1. $InCl_3$-catalyzed syntheses of dihydro-1*H*-1,5-benzodiazepines and quinoxzline derivatives

Entry	Diamine	Ketone/1,2-diketone	Product	Yield (%)[a]
1		CH_3COCH_3		97
2		$CH_3CH_2COCH_2CH_3$		90
3		$CH_3COCH_2CH_3$		92
4		$PhCOCH_3$		90
5				85
6		CH_3COCH_3		85

(*continued*)

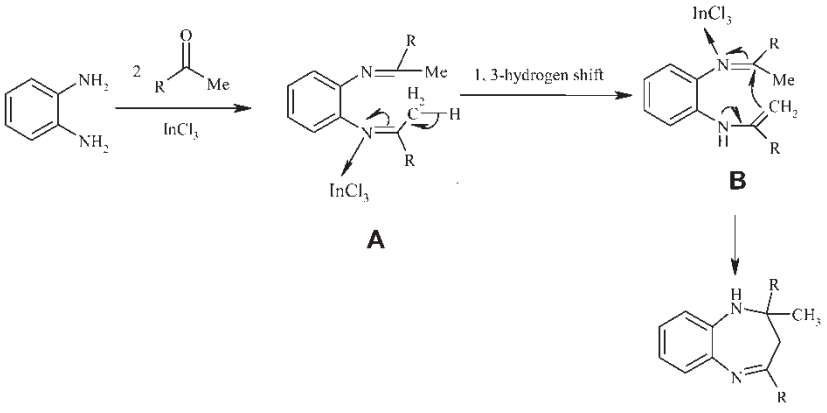
Table 1. Continued

Entry	Diamine	Ketone/1,2-diketone	Product	Yield (%)[a]
7		$PhCOCH_3$		80
8				79
9				98
10				95
11				94
12				91
13				88

[a]Yields are isolated pure products and were characterized by NMR and MS spectra.[10,13]

selectively from one side of the carbon skeleton to a single product. The condensation of diamine with an equimolar amount of 1,2-diketone gave quinoxaline with excellent yields. The products were separated by a simple filtration from the reaction mixture. These condensations occurred in water at room temperature, and the undesired products were not obtained in the reaction mixture.

Regarding the mechanism of the reaction, it is proposed that *O*-phenylenediamine forms diimine, **A**, with 2 equivalents of ketones. In the presence of indium(III) chloride, diimine undergoes a 1,3-shift of hydrogen to enamine, **B**, which undergoes intramolecular cyclazation to form a seven-membered ring (Scheme 2).



Scheme 2. Proposed mechanism and tentative intermediates.

We have demonstrated a simple, efficient, and green synthesis of biologically active 1,5-benzodiazepine and quinoxaline derivatives in the presence of a catalytic amount of indium(III) chloride in water. The advantages of the present reaction are the elimination of transition metals, organic solvents, and toxic reagents; operational simplicity; and high yield of the products.

EXPERIMENTAL

Typical Experimental Procedure for the Synthesis of 1,5-Benzodiazepine

A mixture of 1,2-diamine (1.0 mmol), ketone (2.0 mmol), and indium chloride (0.1 mmol) in water (5 ml) was stirred at room temperature for 3 h (monitored by thin-layer chromatography, TLC). After completion of the reaction, a solution of sodium bicarbonate (10 ml; 5% w/v) was added, and the product was extracted with ethyl acetate (15 ml × 3). The combined ethyl acetate layers dried over anhydrous sodium sulfate and were concentrated under reduced pressure to give the crude product, then purified by crystallization using a solvent mixture of hexane and ethyl acetate.

2,2,4-Trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (1): Yellow solid; mp 122–124°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.34 (s, 6H), 2.22 (s, 2H), 2.36 (s, 3H), 2.97 (s, 1H), 6.71–7.27 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.75, 31.37, 45.96, 69.30, 122.62, 122.99, 126.57, 126.76, 127.70, 138.77, 141.67, 173.31; FTIR (KBr): 3295.8 (NH), 2963.8 and 2911 (CH), 1637.2 (C═N) cm^{-1}; HRMS calcd. for $C_{12}H_{16}N_2$ (M^+) 188.131, found 188.25.

Typical Experimental Procedure for the Synthesis of Quinoxaline

To a mixture of 1,2-diamine (1.0 mmol), 1,2-diketone (1.0 mmol) and indium chloride (0.1 mmol) in water (5 ml) were stirred at room temperature for 30 min (monitored by TLC). After completion of the reaction, the crude product was filtered, washed with water (3 × 10 ml), and recrystallized from ethanol.

2,3-Diphenyl-quinoxaline (9): White solid; mp 125–128°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.24–8.19 (m, 14H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 129.14, 129.67, 130.08, 130.71, 130.83, 139.95, 142.10, 154.34; FTIR (KBr): 1682.7 and 1672.0 (C═N) cm^{-1}; HRMS calcd. for $C_{20}H_{14}N_2$ (M^+) 282.116; found 182.4.

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