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A new efficient method for the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazines via iodocyclization

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ABSTRACT

An efficient approach for the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazine derivatives is described by molecular iodine- mediated cyclization. The reaction condition is very simple, offers easy isolation, and affords good to excellent yields of the products.

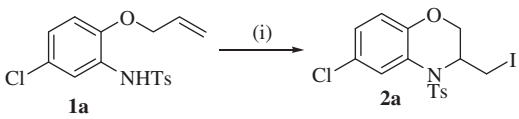
Recently organic compounds containing 1,4-benzoxazine derivatives have received great attention in chemical and medicinal research because of their natural occurrence and important biological activities. Several 3,4-dihydro-2*H*-1,4-benzoxazine derivatives have been reported as potassium channel openers (PCOs) in vascular smooth muscle.[1] Some 1,4-benzoxazine derivatives are known to be central nervous system depressants, antipsychotic agents, calcium antagonists, and antibacterial agents while some other derivatives are potential drugs for treating neurodegenerative, inflammatory, autoimmune, cardiovascular, and diabetic disorders.[2] For example, levofloxacin used as antibiotics exhibits excellent activities against gram-positive and gram-negative bacteria contains 3,4-dihydro-2*H*-1,4-benzoxazine moiety.[3] 1,4-Benzoxazine derivatives have also been used as intermediates for the synthesis of other heterocyclic structures of biological importance.[4,5]

As a consequence several methods have been developed so far for the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazine derivatives.[2a,6] However, most of the methods reported were multistep procedures and lacked generality, needed use of toxic and expensive reagents, and suffered from complex workup and purification procedures. These difficulties have limited their wider applicability. Moreover recent publications[7] rely on the use of different metal catalysts for the construction of the 3,4-dihydro-2*H*-1,4-benzoxazine derivatives (using palladium or copper catalysts). The reaction condition also requires the presence of ligands and proceeds under thermal conditions. So there is always a demand for more general, more economic, environment friendly reaction pathways that proceed under mild conditions.

In recent years, molecular iodine has received considerable attention as an inexpensive, non-toxic, readily available reagent to effect the iodocyclization reactions. The halocyclization of an unsaturated C–C bond with an intramolecular nucleophilic center plays an important role in the stereo selective construction of cyclic compounds and functionalization of double bonds.[8] Synthesis of various heterocyclic compounds of biological importance by iodocyclization has been explored with a wide variety of nucleophiles, including N, O, S, Se etc., and it has become a powerful tool for the construction of different heterocycles.[9]

As a part of our ongoing research interest toward the development of new methodologies to construct various biologically active heterocycles,[10] we have undertaken a study to synthesize different 3,4-dihydro-2*H*-1,4-benzoxazines via iodocyclization reactions and the results are reported here.

We have initiated our investigation with the substrate **1a**. Under usual reaction conditions (1.5 equiv I_2–2.5 equiv $NaHCO_3$–CH_3CN) the iodocyclization of **1a** afforded the desired cyclized product **2a** in 65% yield and the reaction took 10 h to completion. Increasing the amount of iodine or base did not improve the yield



1a 2a

Scheme 1. Reagents and conditions: (i) I_2 (1.5 equiv), base (2.5 equiv), CH_3CN, rt.

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Table 1
Optimization of iodine mediated reaction[a]

Entry	I_2 (equiv)	Base[b]	Time (h)	Solvent	Yield[c] (%)
1	1.5	—	24	CH_3CN	NR
2	**1.5**	**K_2CO_3**	**6**	**CH_3CN**	**88**
3	6	K_2CO_3	6	CH_3CN	85
4	1.5	$NaHCO_3$	10	CH_3CN	65
5	1.5	Cs_2CO_3	6	CH_3CN	82
6	1.5	Na_2CO_3	6	CH_3CN	75
7	1.5	K_2CO_3	6	Toluene	25
8	1.5	K_2CO_3	6	THF	<20

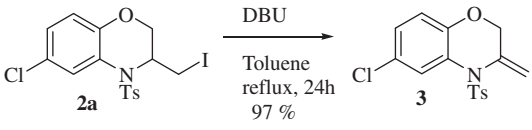
[a] All the reactions are carried out at room temperature.
[b] In all cases 2.5 equiv base is used.
[c] Isolated yield of products.

of the product. After a survey of basic reagents to improve the nucleophilicity of the nitrogen atom we found that the reaction of **1a** with a relatively strong base such as K_2CO_3, Cs_2CO_3, or Na_2CO_3 proceeds to give **2a**[11] in good yields (Scheme 1). Among various bases used K_2CO_3 was found to produce the highest yield and also reduced the reaction time (6 h) (Table 1, entry 2).

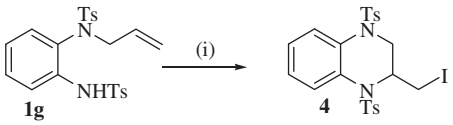
We have also examined the effect of various solvents regarding the yield of the reaction and CH_3CN was found to give the highest yield (entry 2). Thus the optimal reaction conditions developed so far include stirring of the substrate with 1.5 equiv of iodine, 2.5 equiv K_2CO_3 in CH_3CN at room temperature for 6 h.

Having demonstrated the optimal reaction condition, we explored the scope and generality of this cyclization protocol with the substrates **1b–f** and on similar treatment substrates **1b–f** afforded the products **2b–f** in excellent yields (Table 2).

The formation of the product **2a** via 6-*exo*-cyclization mode is in accordance with the Baldwin's rules. Initially the structure of 3,4-dihydro-2*H*-1,4-benzoxazines was determined from spectral data. Furthermore when **2a** was treated with DBU in toluene under refluxing condition it afforded product **3** which further supported the formation of the six-membered ring (Scheme 2).



Scheme 2.

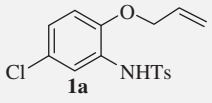
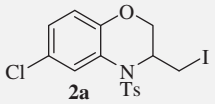
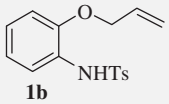
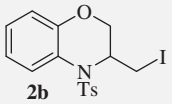
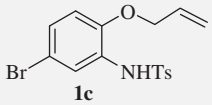
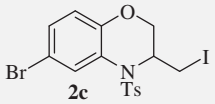
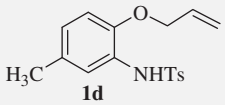
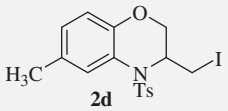
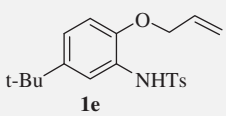
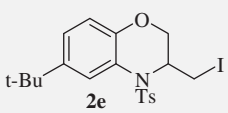
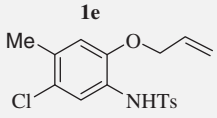
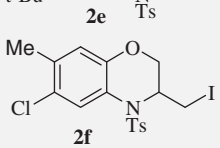


Scheme 3. Reagents and conditions: (i) I_2 (3 equiv), K_2CO_3 (1.5 equiv), CH_3CN, rt, 6h.

Compounds containing 1,2,3,4-tetrahydroquinoxaline moiety are found to possess a wide range of biological activities.[12,13] Therefore, we have extended the reaction for the synthesis of 1,2,3,4-tetrahydroquinoxaline derivative (**4**). Thus when **1g** was subjected to iodocyclization it afforded product **4** in 92% yield (Scheme 3).

In conclusion, we have achieved an efficient and straightforward method for the construction of 1,4-benzoxazines via iodocyclization. The procedure reported here is more economic than other applied methods and avoids separation problems. The applicability of this method for the synthesis of 1,2,3,4-tetrhydroquinoxaline is also described and further applications toward expanding the substrate scope are underway. Moreover, during the cyclization process iodine atom is incorporated in the final compounds, which

Table 2
Summarized results of iodocyclization

Entry[a]	Substrate	Time (h)	Product	Yield[b]
1	 **1a**	6	 **2a**	88
2	 **1b**	6	 **2b**	85
3	 **1c**	6	 **2c**	87
4	 **1d**	6	 **2d**	90
5	 **1e**	6	 **2e**	92
6	 **1f**	6	 **2f**	88

[a] All the reactions are carried out under optimized reaction conditions.
[b] Isolated yield of product.

are attractive for further transformation to other substituted compounds.

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11. *General procedure for the synthesis of the compounds* **2a**: To a solution of compound **1a** (200 mg, 0.57 mmol) in CH_3CN (5 mL), I_2 (108 mg, 0.85 mmol), and K_2CO_3 (196 mg, 1.42 mmol) were added. The reaction mixture was stirred at room temperature for 6 h. After completion of the reaction (monitored by TLC), CH_3CN was completely evaporated. The reaction mixture was then diluted with 40 mL of ether and washed with 20 mL of satd aq $Na_2S_2O_3$. The organic layer was separated and the aqueous layer was extracted with another 25 mL of ether. The combined organic layers were dried (Na_2SO_4) and filtered. The filtrate was concentrated and the crude product **2a** was purified by column-chromatography over silica-gel (60–120 mesh) using petroleum ether and ethyl acetate (9:1) as eluent. *Compound* **2a**: Yield: 88%, solid; mp 132–134 °C; IR(KBr): ν_{max} = 1595, 2935 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.95 (d, 1H, *J* = 2.0 Hz), 7.50 (d, 2H, *J* = 8.4 Hz), 7.26–7.32 (m, 2H), 7.03 (dd, 1H, *J* = 2.0, 8.4 Hz), 6.75 (d, 1H, *J* = 12.8 Hz), 4.47–4.48 (m, 1H), 4.38 (d, 1H, *J* = 11.6 Hz), 3.19–3.24 (m, 2H), 3.07 (t, 1H, *J* = 10.0 Hz), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = −0.01, 19.8, 51.7, 61.0, 111.5, 117.1, 120.9, 125.3, 125.7, 127.4, 128.3, 132.3, 142.7, 143.1. HRMS: *m*/*z* Calcd for $C_{16}H_{15}ClINO_3S$: 485.9404 [M^++Na]; Found: 485.9404 [M^++Na].
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