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Cerium chloride catalyzed-IBX mediated oxidative dehydrogenation of multiple heterocycles at room temperature

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Abstract. Catalytic cerium chloride activates 2-Iodoxy benzoic acid (IBX) for the oxidative dehydrogenation of tetrahydroisoquinolines, tetrahydro-β-carbolines and thiazolidines to their dehydrogenated and aromatic forms at room temperature, in moderate to excellent yields. The robustness of the protocol was further demonstrated by scaling up the reactions in multigram quantity.

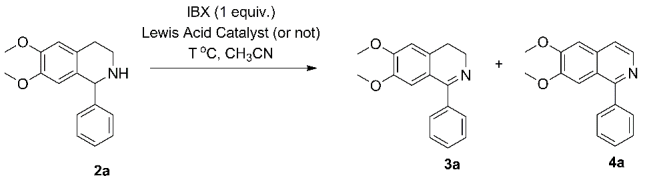
Keywords: Tetrahydroisoquinolines; Tetrahydro-β-carbolines; Thiazolidines; Oxidative dehydrogenation

Oxidative dehydrogenation is an attractive strategy to access variety of nitrogen containing heteroaromatic compounds from their heterocyclic precursors.[1] Diverse oxidants are used in catalytic as well as stoichiometric quantities to achieve this.[2] 2-Iodoxybenzoic acid, also known as IBX, had been demonstrated to serve similar purpose.[3]

IBX is a versatile reagent to conduct oxidation of organic compounds.[4] It is economical, readily available and environmental benign. Due to its fantastic reactivity it is used in different organic transformations.[5] However its major drawback is incompatibility with major organic solvents (barring dimethyl sulfoxide) and also that it requires higher temperature for most of its reactions. Majority of IBX reactions are conducted at ~45 °C or higher.[6] Hence to widen further the scope of IBX, search for a catalyst/agent that will enable to harness the oxidizing ability of IBX at room temperature is desirable. In our continuous effort towards discovering mild protocols for oxidative dehydrogenation of heterocycles, herein we report that catalytic cerium chloride ($CeCl_3$) activates IBX towards oxidative dehydrogenation of various heterocycles such as tetrahydroisoquinolines, tetrahydro-β-carbolines and thiazolidines at room temperature in moderate to excellent yield.[7-9]

To begin with, the oxidative hydrogenation of 6, 7-dimethoxy-1-phenyl-1, 2, 3, 4-tetrahydroisoquinoline, **2a**, was explored at room temperature with 1 equiv. of IBX, in a range of solvents that include dimethyl sulfoxide, acetonitrile, 1, 4-dioxane and dimethyl formamide (Table 1, entry 1-4). During the optimization stage all the reactions were conducted 50 mg scale of **2a**. The reaction in acetonitrile look propitious with about 24% conversion (as detected LCMS) to the corresponding dihydroquinazol analog **3a**. In general the reactions at r.t. w sluggish and were not complete even after 48h. Ne we tried to improve the yield by elevating reaction temperature gradually. Accordingly reaction was conducted in acetonitrile with 1 equ of IBX at 40, 50, 60 and 70 °C (Table 1, entry 5- Higher temperature did improve the conversion, w the best being 69% at 70 °C (Table 1, entry However we intend to develop a protocol oxidative dehydrogenation of heterocycles wh would be amenable to scale up and focused developing a room temperature strate Consequently in the following experiments screened various Lewis acid catalysts along with II at room temperature to improve or at the minim reproduce the yield reported in entry 8. According **2a** was reacted with 1 equiv. of IBX in acetonitr with variety of Lewis acids (0.25 equiv.) such aluminium chloride ($AlCl_3$), ferric chloride (FeC cerium chloride heptahydrate ($CeCl_3.7H_2$ anhydrous cerium chloride ($CeCl_3$), titanium chlor ($TiCl_4$) and $BF_3.OEt_2$ (Table 1, entry 9-14). O reactions with $CeCl_3$ and $FeCl_3$ exhibited 81 and 4 of conversion to **3a** respectively, with mi formation of the over oxidized product **4a** (10-15 (Table 1, entry 12 and 10). The average reaction ti ranged from 4-6 h. To our utmost gratification reduced quantity of $CeCl_3$ catalyst (0.1 equiv.) a displayed similar conversion as with 0.25 eq (Table 1, entry 15). Hence the optimized protocol for the room temperature oxidative dehydrogenation of **2a**, included 1 equiv. of IBX and 0.1 equiv. of $CeCl_3$ in acetonitrile.

Table 1. Optimization of oxidative dehydrogenation of 6, 7-dimethoxy-1-phenyl-1, 2, 3, 4-tetrahydroisoquinoline, **2a**.

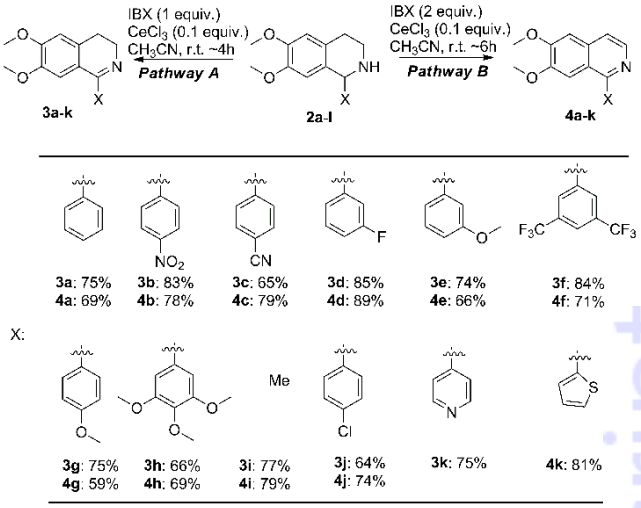


#	Solvent[c]	Catalyst (0.25 equiv.)	T (°C)	Time (h)	Conversion (%)[a]	
					3a	**4a**
1	DMSO	-	r.t.	48	21	-
2	ACN	-	"	"	24	-
3	1, 4-Dioxane	-	"	"	16	-
4	DMF	-	"	"	12	-
5	ACN	-	40	6	40	02
6	"	-	50	"	45	06
7	"	-	60	"	52	06
8	"	-	70	"	69	10
9	"	$AlCl_3$	r.t.	24	02	-
10	"	$FeCl_3$	"	6	45	08
11	"	$CeCl_3.7H_2O$	"	24	10	-
12	"	$CeCl_3$ (anh.)	"	4	81	12
13	"	$TiCl_4$	"	24	-	-
14	"	$BF_3.OEt_2$	"	24	8	-
15	"	$CeCl_3$ (anh.)[b]	"	4	75	10

[a)] Conversion monitored by LCMS.[b)] Reaction with 0.1 equiv. of $CeCl_3$ (anh.).[c)] DMSO: Dimethyl Sulfoxide; ACN: Acetonitrile; DMF: Dimethyl Formamide

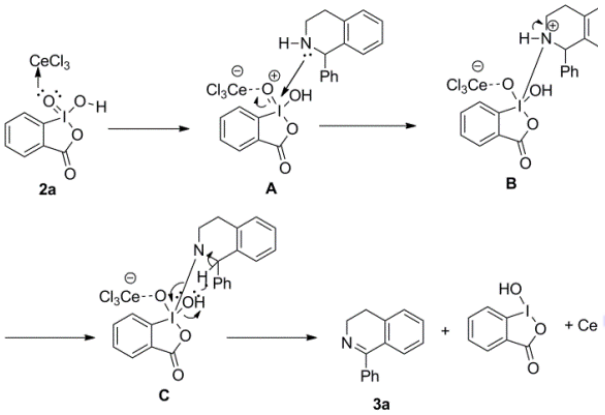
With the condition optimized, variety of 1-substituted tetrahydroisoquinolines (1-THIQs), **2a-l** underwent oxidative dehydrogenation to afford the corresponding 3, 4-dihydroisoquinoline analogs **3a-k** in good to excellent yields. Interestingly the condition was amenable to aromatic, heteroaromatic and aliphatic substitutions. For aromatic moieties both the electron donating and electron withdrawing substituents were fluently accessed (Scheme 1, pathway A). The final products **3a-k** were obtained after column purification of the reaction mixture.

Taking a cue from the formation of over oxidized aromatic isoquinolines as side products (during the optimization studies [Table 1, entry 12]), the 1-THIQs were readily converted to their aromatic analogs **4a-k** with two equivalents of IBX (Scheme 1, pathway B) and the desired compounds were isolated after column purification. A variety of substituents were again tolerated. 1-substituted dihydro and aromatic isoquinoline products obtained from these reactions are observed frequently as motifs in natural products and drug candidates.[10] Hence, this mild synthetic strategy adds immense value to access these classes of heterocycles.



Scheme 1. Oxidative dehydrogenation of 1-THIQs.

A tentative mechanism for this transformation depicted below with **2a** as the model substrate. T reaction might have been initiated with a fac coordination of $CeCl_3$ (anh.) with IBX, there increasing its oxidative capability and leading to formation of intermediate A. Next, we envisior sequence based on pertinent iodine oxidati chemistry where iodine reduction occurs in concerted pathway to afford B, which undergo elimination to generate **3a**.[11] Complete aromatizati to **4a** with 2 equiv. of IBX could also be an II dependent pathway where a continuous oxidation the dehydrogenated product **2a**, with the equivalent of IBX led to the formation of the desi aromatic product.



Scheme 2. Putative mechanism of oxidative dehydrogenation of 1-THIQs

To rule out the possibility for anhydrous cerium chloride to work as a drying agent, we performed the reaction of **2a** in acetonitrile in presence of activated 4 Å molecular sieves and one equivalent of IBX and

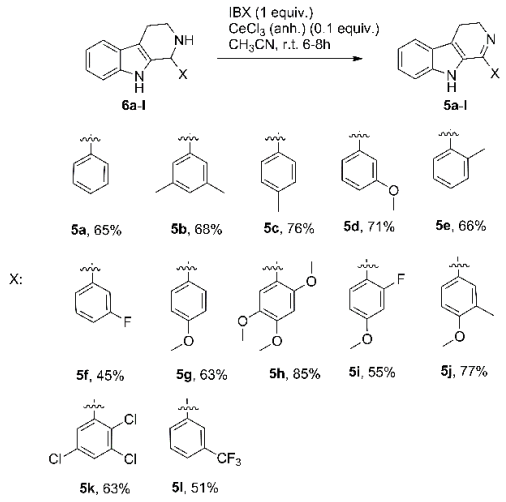
without anhydrous $CeCl_3$. We obtained compound **3a** in 41% yields after 8 hr of the reaction along with 5% of **4a**. Since, the yield of **3a** reduced drastically, in this reaction in comparison to the one with anhydrous $CeCl_3$, we believe that it is not acting as a drying agent.

In a bid to observe the coordination of anhydrous $CeCl_3$ with IBX or with the amines we monitored the reaction via ^{1}H-NMR in DMSO-D_6 solvent. In the first case we took IBX in DMSO-D_6 and recorded the NMR. After which we have added $CeCl_3$ in the NMR tube and recorded the NMR in an interval of half an hour for four hours. Unfortunately we did not observe any visible change in the chemical shift values.

In another effort we took compound **2a** and $CeCl_3$ and performed similar experiment. Here too we did not observe any change in the chemical shift of the peaks in the NMR.

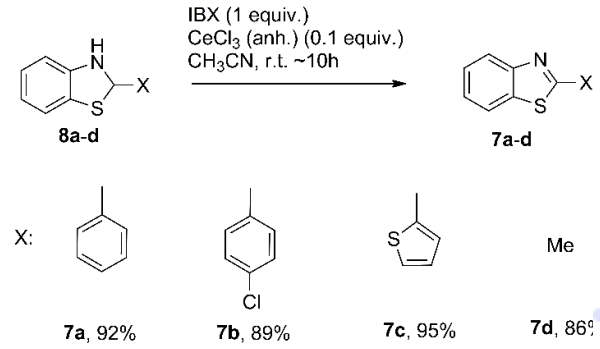
We believe that may be our proposed pathway is the one opted by this transformation, however we were unable to prove the same through NMR. To decipher this further investigation is being conducted right now.

To demonstrate the versatility of this methodology, dihydro-β-carbolines **5a-l** were synthesized in good yields from their corresponding tetrahydro-β-carboline precursor **6a-l**. Unlike the substituted dihydro and aromatic isoquinolines, herein the dihydro-β-carbolines with electron donating substituted aromatic group at 1-position such as 4-methyl,2-methyl, 3 and 4-methoxy (**5c**, **d**, **e** and **g**) were synthesized in much higher yields compared to their electron withdrawing analogs *viz*. 3-trifluoromethyl and 3-fluoro, **5f** and **l** (Scheme 3). A variety of β-dihydrocarbolines with di and trisubstituted aromatic moiety such as **5b**, **h**, **i**, **j** and **k** could also be synthesized (Scheme 3). Average reaction time ranged from 6 to 8 h. There were nearly 5-10% formation of the over oxidized aromatic β-carbolines. Hence pure **5a-l** were obtained after column purification of the reaction mixture.



Scheme 3. Oxidative dehydrogenation of tetrahydro-β-carbolines

Similar procedure was harnessed to aromatize 2-arylbenzothiazolidines **8a-d** to their corresponding benzothiazoles. A focused library of four benzothiazoles **7a-d**, containing aromatic, heteroaromatic and aliphatic substitution at 2-position were synthesized in excellent yield (Scheme 4).



Scheme 4. Oxidative dehydrogenation of thiazolidines

Finally to demonstrate the robustness of this proto the syntheses of compounds **3a**, **4g** and **5k** w scaled up to ~3 g quantity to afford them in 65-7 yield (Figure 1). Interestingly during the scale- mild exotherm was observed during the addition IBX, hence the reaction mixture was cooled to ~4 during the addition and the reagents were ad slowly. This resulted in the increment of reacti time to about 8 to 15 h for all the heterocycles.

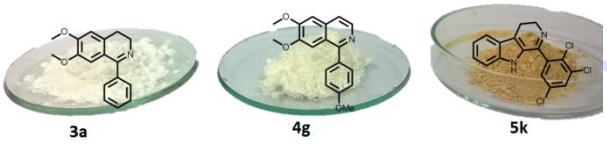


Figure 1. Scale-up synthesis of **3a**, **4g** and **5k** in 3g scale

To summarize, we have identified catalytic ceri chloride (anh.) that activates IBX at ro temperature towards oxidative hydrogenation substituted-THIQs, tetrahydro-β-carbolines a thiazolidines. This methodology augments effectiveness of IBX as an oxidant and widens application. Since the methodology was tolerated diverse substitution on the N-heterocycles (analogues over three different heterocycles) it can applied in generating library of molecules for structure activity relationship studies in drug discovery research. Finally it was demonstrated to be robust even at higher scale.

Experimental Section

General Procedure

All reactions were carried out in flame-dried round bottom flasks with magnetic stirring. Unless otherwise noted, all

experiments were performed under argon atmosphere. All reagents and most of the saturated building blocks were purchased from Sigma Aldrich, Acros, Alfa Aesar, Ark Pharm, AK Scientific, Acros Organics, Aurora Building Blocks, Aurora Screening Library, Chemlievliva Pharmaceutical Product List (China) and Chembridge Screening Library. Solvents were treated with 4 Å molecular sieves and distilled prior to use. Purifications of reaction products were carried out by column chromatography using Chem Lab silica gel (100-200 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded with tetramethylsilane (TMS) as internal standard at ambient temperature unless otherwise indicated at Bruker 400 and 500 MHz at 400 and 500 MHz for ^{1}H NMR and 100 and 125 MHz for ^{13}C NMR. Chemical shifts are reported in parts per million (ppm) and coupling constants are reported as Hertz (Hz). Splitting patterns are designated as singlet (s), broad singlet (bs), doublet (d), triplet (t). Splitting patterns that could not be interpreted or easily visualized are designated as multiple (m). The Mass Spectrometry analysis was done on the 6540 UHD Accurate-Mass QTOF LC/MS system (Agilent Technologies) equipped with Agilent 1290 LC system obtained by the Dept. of Chemistry, School of Natural Sciences, Shiv Nadar University, Uttar Pradesh 201314, India.

Synthesis of 3a-k

To a solution of compound **2** (200 mg, 1 equiv.) in acetonitrile, 2-Iodoxy benzoic acid (1 equiv.) was added followed by $CeCl_3$ (0.1 equiv.) and the resulting mixture was stirred at room temperature. Once TLC confirms complete consumption of the starting material the reaction mixture was quenched with sodium thiosulfate and extracted with ethyl acetate. The organic layer was evaporated and purified through column chromatography (40-60% EtOAc in hexane) to obtain the desired compounds **3a**-**k** with.

Synthesis of 4a-k

To a solution of compound **2** (200 mg, 1 equiv.) in acetonitrile, 2-Iodoxy benzoic acid (2 equiv.) was added followed by the addition of $CeCl_3$ (0.1 equiv). The reaction mixture was stirred at room temperature. Once TLC confirms complete consumption of the starting material the reaction mixture was quenched with sodium thiosulfate and extracted with ethyl acetate. The organic layer was evaporated and purified through column chromatography (30-50% EtOAc in hexane) to obtain the desired compounds **4a**-**k**.

Synthesis of 5a-l and 7a-d

To a solution of compound **6** or **8** (200 mg, 1 equiv.) in acetonitrile, 2-Iodoxy benzoic acid (1 equiv.) was added followed by $CeCl_3$ (0.1 equiv.) and the resulting mixture was stirred at room temperature. Once TLC confirms complete consumption of the starting material the reaction mixture was quenched with sodium thiosulfate and extracted with ethyl acetate. The organic layer was evaporated and purified through column chromatography (50-60% EtOAc in hexane) to obtain the desired compounds **5a-l** and **7a-d**.

Scale up synthesis 3a

To a solution of compound **2a** (4 g, 14.85 mmol) in 200 mL of acetonitrile, 2-Iodoxy benzoic acid (4.47 g, 14.85 mmol) was added at 0-4 °C, followed by $CeCl_3$ (0.1 equiv.). The reaction mixture was stirred at this temperature for one hour and slowly warmed to room temperature. Once TLC confirms complete consumption of the starting material (~8h) the reaction mixture was quenched with sodium thiosulfate and extracted with ethyl acetate. The organic layer was evaporated and purified through column chromatography (40% ethyl acetate in hexane) (R_f 0.55) to obtain the desired compound **3a** in 2.94 g (yield: 74%).

Scale up synthesis of 4g

To a solution of compound **2g** (5 g, 16.70 mmol) in 200

mL of acetonitrile, 2-Iodoxy benzoic acid (10.05 g, 33.40 mmol) was added at 0-4 °C, followed by the addition of $CeCl_3$ (0.1 equiv.). The reaction mixture was stirred at this temperature for one hour and slowly warmed to room temperature. Once TLC confirms complete consumption of the starting material (12h) the reaction mixture was quenched with sodium thiosulfate and extracted with ethyl acetate. The organic layer was evaporated and purified through column chromatography (40% ethyl acetate in hexane) (R_f 0.4)to obtain the desired compound **4g** in 3 g (yield: 65%).

Scale up synthesis of 5k

To a solution of compound **6k** (4 g, 11.37 mmol) in 2 mL of acetonitrile, 2-Iodoxy benzoic acid (3.42 g, 11 mmol) was added at 0-4 °C, followed by $CeCl_3$ (0.1 equ The reaction mixture was stirred at at this temperature one hour and slowly warmed to at room temperature. O TLC confirms complete consumption of the start material (15h) the reaction mixture was quenched w sodium thiosulfate and extracted with ethyl acetate. T organic layer was evaporated and purified through colu chromatography (50% ethyl acetate in hexane) (R_f 0.4 obtain the desired compound **5k** in 2.72 g (yield: 69%).

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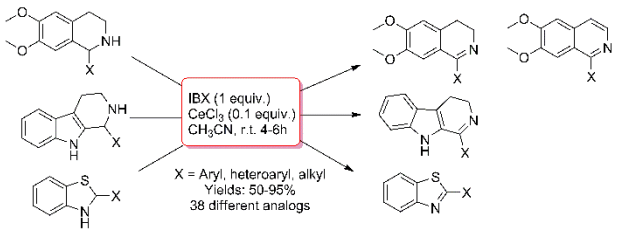

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