EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201800879

Link to VoR: http://dx.doi.org/10.1002/ejoc.201800879

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An iodine catalyzed metal free oxidative ring opening of 1-aryltetrahydro-β-carbolines: Facile synthesis of C_2 aroyl and aryl methanimino indole derivatives

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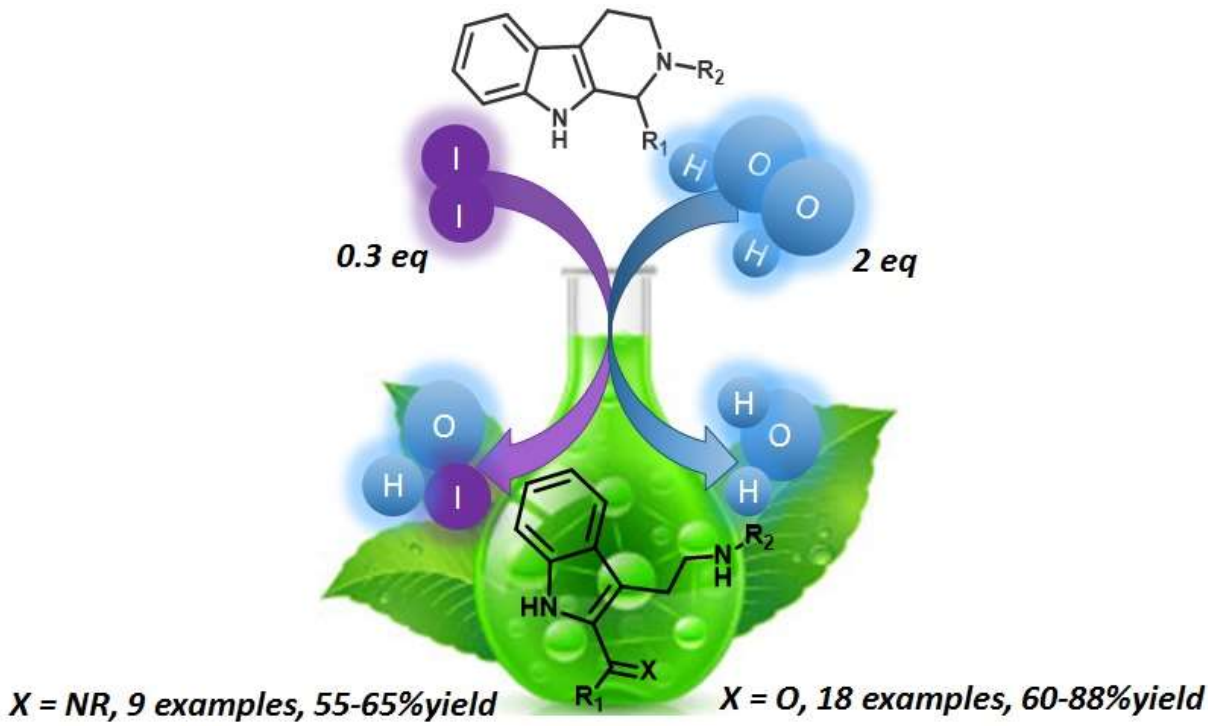


Abstract

C_2 substituted indole compounds have garnered a lot of attention due to their diverse biological activities. Various methods have been reported to access these compounds. Inspired from hydrolysis of imines, an oxidative ring opening reaction of 1-aryltetrahydro-β-carboline with catalytic iodine in aqueous hydrogen peroxide and also in presence of appropriate amines has been reported for the generation of 2-aroyl and arylmethanimine indole derivatives under mild reaction condition with ethanol as the solvent and under solvent free conditions respectively. This metal free strategy facilitates the formation of the desired substituted C_2 indoles in moderate to excellent yield. The utility of this reaction is demonstrated by a facile multigram scale synthesis of Luzindole, a selective melatonin receptor antagonist and an investigational drug against depression and circadian rhythm.

Introduction

By virtue of their presence in plethora of diverse natural products and biologically active compounds, C_2 functionalized indole derivatives occupy a niche position in synthetic organic and medicinal chemistry.[1] Among them C_2 aroyl and amino methyl compounds are extremely significant. Precisely, C_2 aroyl moieties are available as calmadulin-dependent protein kinase II (CAMKII) receptors, **1**, histone deacetylase receptors **2**, antagonists for tubulin polymerization **3**/**4**, cyclooxygenase-2 (COX-2) receptors, indoleamine-2, 3-dioxygenase (IDO) receptors **5**, platelet derived growth factor (PDGF) kinase receptors and agonists for peroxisome proliferator-activated receptors (PPAR) (Figure 1).[2-7] They can also be envisioned as a suitable precursor for the synthesis of Luzindole **7**, a selective inhibitor of melatonin receptors MT1 over MT2 and is an investigational drug for anti-depression and disruption of circadian rhythm (Figure 1).[8] Additionally the C_2-arylmethanimine analogs of indoles can be conceived as precursors for C_2-aminomethyl indoles a key motif that exists in several biologically active compounds, including calindol **6**, a Ca^{2+} sensing receptor and various melatonin receptor antagonists.[9-11]

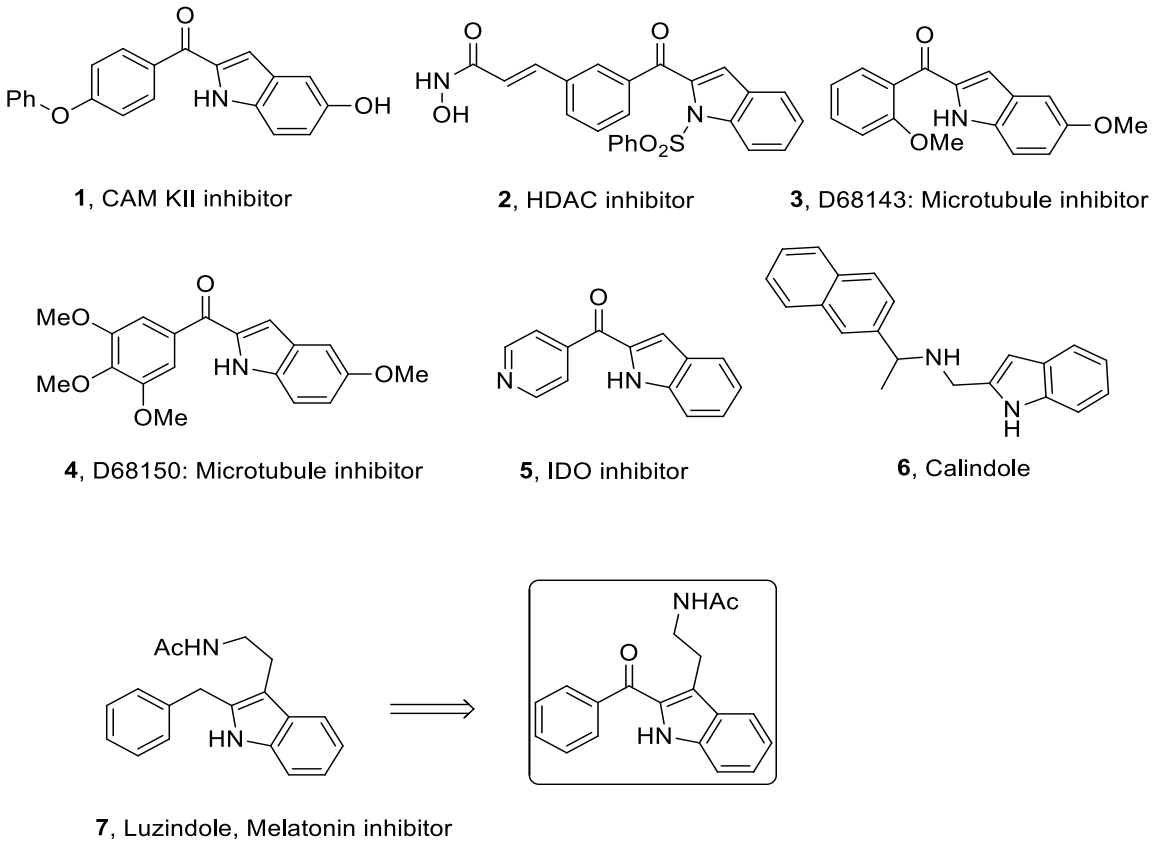


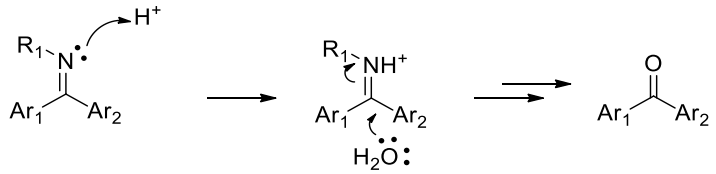
Figure 1. Representative biologically active 2-aroyl or benzyl derivatives

Despite being an important building block, there are fewer available strategies to access 2-aroyl and 2-arylmethanimine indoles. The available methods include a combination of visible light (photoredox) and palladium (II) catalyzed dehydrogenative C_2 aroylation of indoles at room temperature, *n*-butyl lithium mediated C_2-aroylation of N-phenylsulfonyl indole with aroyl chlorides and N-bromosuccinimide (NBS) promoted oxidative ring opening of 1-aryltetrahydro-β-carbolines in presence of water and acetic acid in tetrahydrofuran (THF).[5], [12-13] It is noteworthy that these process involve toxic metal catalysts, environmentally harmful solvents and harsh conditions (such as strong bases) which evidently, provides opportunity for the development of a practical and mild approach for 2-aroylation and arylmethanimination of indole derivatives. And if such indole derivatives are based on tryptamines then it further augments the utility of the protocol, as natural products and drug candidates gleaned from tryptamines are important for their biological efficacy and activity.[14-17]

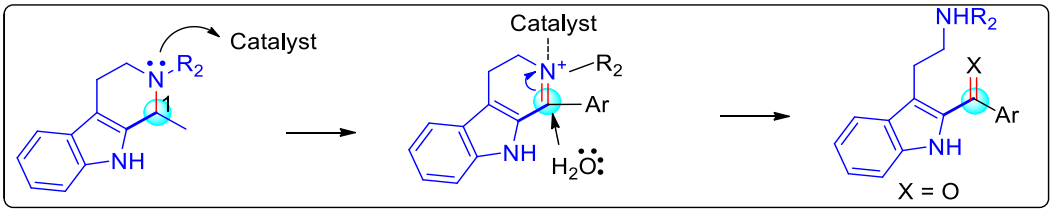
Results and discussion

To generate an efficient strategy for the C_2 aroylation and arylmethanamination of indoles we envisioned a catalytic oxidative ring opening of C_1-substituted tetrahydro-β-carbolines to functionalize the C_2-H of the indole. We took a cue from the acid catalyzed hydrolysis of diaryl imines (Scheme 1) and realized that a transient imine formation at C_1-N bond of the 1-aryltetrahydro-β-carbolines could facilitate a ring opening of the substrate in presence of an appropriate aqueous source (Scheme 1a). Realizing iodine's rich heritage as a green catalyst and an alternative to transition metals in organic synthesis we envisaged that catalytic molecular iodine in the presence of an appropriate terminal oxidant and water/amine could facilitate a ring cleavage on 1-aryltetrahydro-β-carbolines which could afford our desired products (Scheme 1b).[18]

a) Hydrolysis of diaryl imine:



b) This work (new mode of C_2 functionalization):

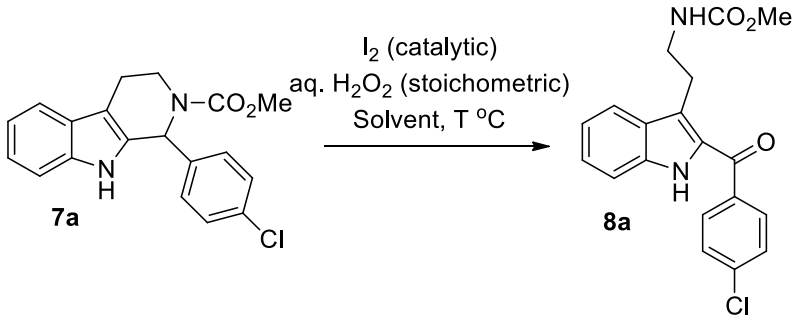


Scheme 1. The concept of our C_2 aroylation or aminomethylation of indole derivatives

For the optimization of C_2 aroylation reaction we began with molecular iodine as catalyst and aqueous hydrogen peroxide as the oxidant. The table below (Table 1), depicts the reaction condition for oxidative ring opening of the 1-(4-chlorophenyl)-N-carbomethoxytetrahydro-β-carboline, **7a** as the model substrate (synthesized from **6a**) in dimethyl sulfoxide (DMSO) as the solvent. The desired aroyl indole **8a** was obtained in poor yield of 12% with 0.1 equiv of molecular iodine and two equiv of aq. hydrogen peroxide (aq. H_2O_2) as the oxidant at 40 °C (entry 1). Changing the solvent to methanol, dimethyl formamide or isopropanol, could not improve the yield (entry 2-4). However, by increasing the amount of the molecular iodine to 0.3 equiv in DMSO improved the yield of **8a** to 25% (entry 5). Interestingly, changing the solvent to

acetonitrile and then to tetrahydrofuran improved the yields further to 40 and 65% respectively (entry 6 and 7). Conducting the reaction at higher temperature viz. 70 and 90 °C proved detrimental as it increased the formation of byproducts. Finally, we were extremely gratified to obtain **8a** in ~82% yield when the reaction was conducted with 0.3 equiv of molecular iodine, 2 equiv of aq. H_2O_2 in ethanol as the solvent at 40 °C (entry 10) for 6h.

Table 1. Optimization of reaction condition

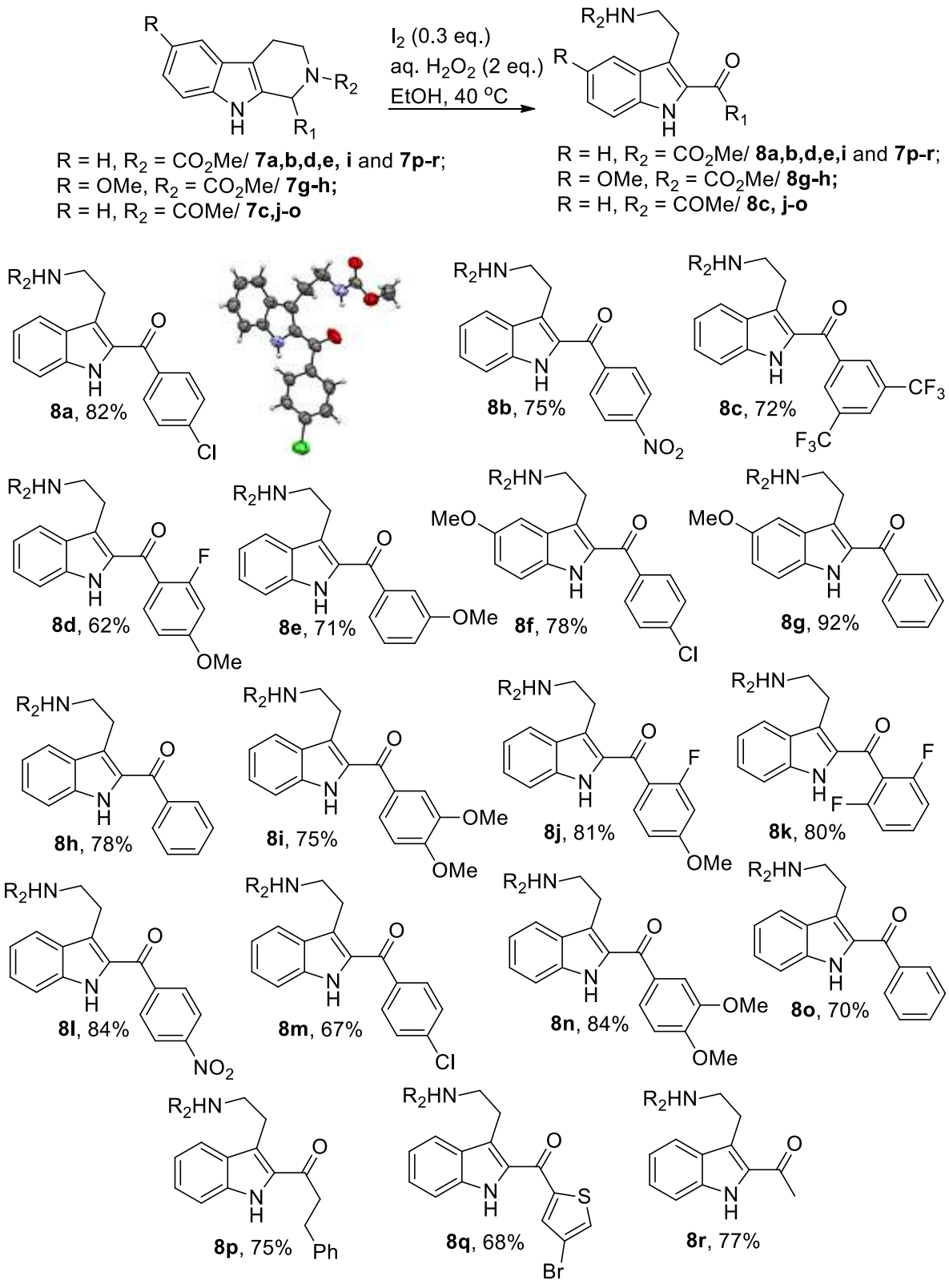


Entry	Temperature (T °C)	Catalyst equivalent	Solvent[b]	Time (h)	Yield (%)[a]
1	40	0.1	DMSO	16	12
2	"	"	MeOH	"	8
3	"	"	DMF	"	10
4	"	"	IPA	"	4
5	"	0.3	DMSO	10	25
6	"	"	ACN	7	42
7	"	"	THF	"	65
8	70	"	"	16	37
9	90	"	"	"	21
10	40	"	EtOH	6	82

[a] Isolated yield (reaction scale 50mg); [b] DMSO: Dimethyl sulfoxide; MeOH: Methanol; DMF: Dimethyl formamide; IPA: Isopropanol; ACN: Acetonitrile; THF: Tetrahydrofuran; EtOH: Ethanol.

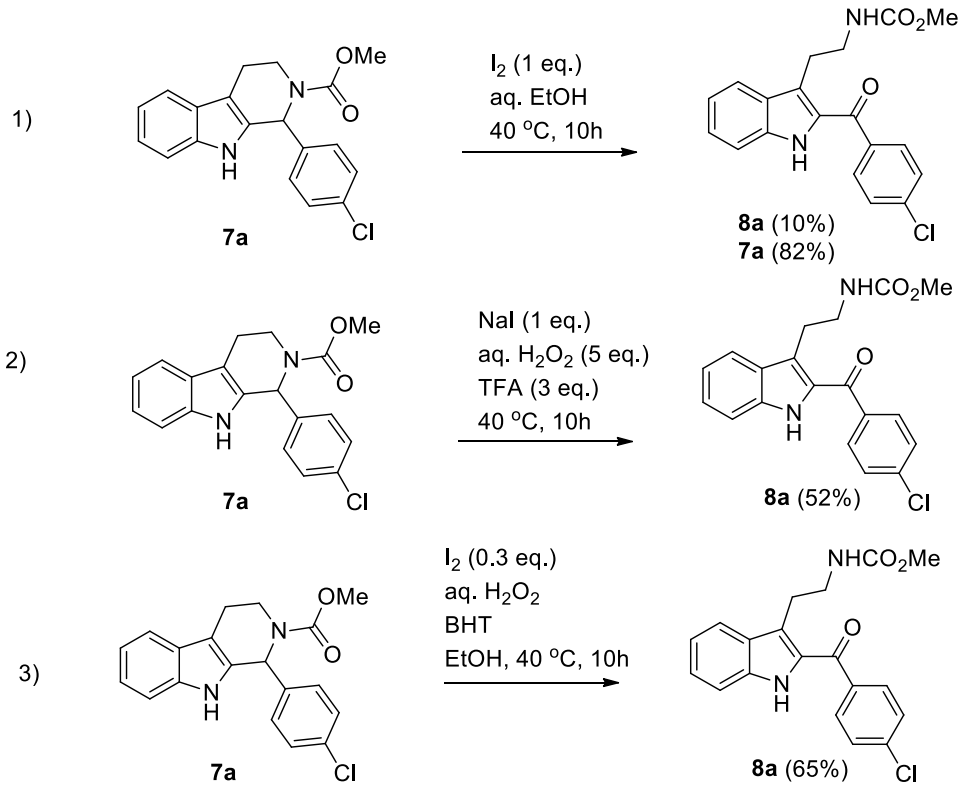
Scheme 2 depicts the scope and limitation of the oxidative ring opening reaction of 1-aryl-N-carbomethoxytetrahydro-β-carbolines **7a-l** and N-acetyl-1-aryltetrahydro-β-carbolines **7m-r** under the optimized reaction condition. The substrates **7a-l** and **m-r** where obtained by protecting

tetrahydro-β-carbolines, **6a**-**l** which in-turn were synthesized *via* Pictet-Spengler reaction of tryptamine and its derivatives with appropriate aldehydes (*Experimental*).[19-21] The substrates **7a**-**r** obtained from the reactions were clean enough to be taken forward without any purification. Molecular iodine catalyzed ring opening of **7a**-**r** in presence of hydrogen peroxide, afforded the corresponding C_2-aroyl indole products **8a**-r in moderate to excellent yields (62-88%), irrespective of the presence of electron withdrawing or electron donating groups on the C_1 aryl moiety of the tetrahydro-β-carbolines and N-acetyl or carbomethoxy functionalities on the carboline nitrogen (Scheme 2). The reaction condition was also amenable to promote C_2-aroylation with aliphatic **7p**/**r** and heteroaromatic **7q** substituted tetrahydro-β-carbolines to afford the desired compounds **8p**-**r** in excellent yield. This is perhaps one of the very few examples where C_2 position of the indoles are functionalized under metal free catalytic condition. The final compounds were purified by flash column chromatography and were characterized by nuclear magnetic resonance spectroscopy (^{1}H and ^{13}C) and high resolution mass spectroscopy. The structure of these C_2-arolylated indole derivatives were confirmed by singly crystal X-ray of compound **8a** (Scheme 2).



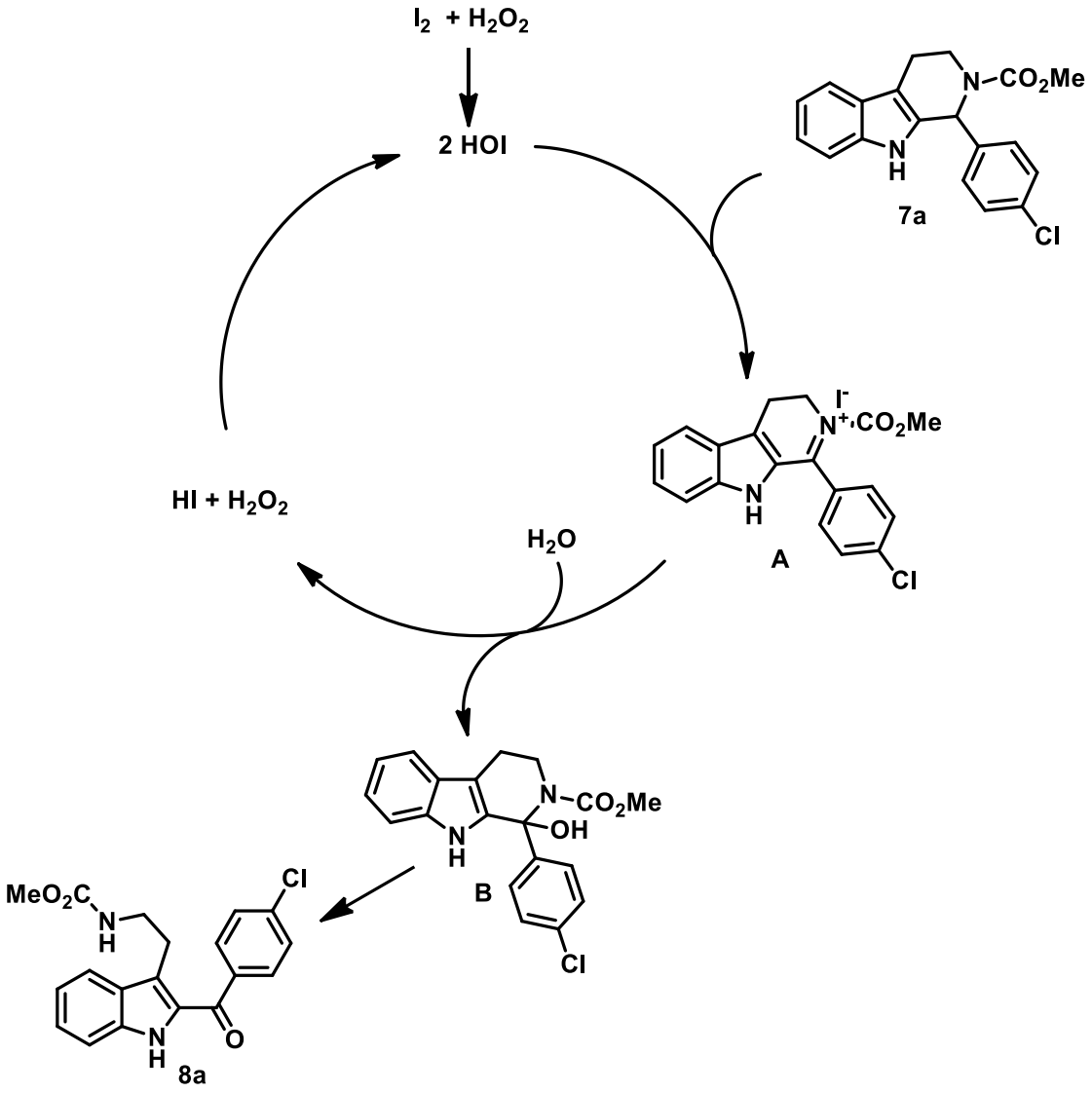
Scheme 2. Demonstration of the generic nature of molecular iodine catalyzed, aq. H_2O_2 mediated oxidative ring opening of 1-aryltetrahydro-β-carbolines

Several control experiments were conducted to propose a putative reaction mechanism for this transformation. It is reported that 1-aryltetrahydro-β-carbolines underwent oxidative ring opening to provide C_2 aroylated indole derivatives with stoichiometric quantity of NBS, in water, acetic acid and tetrahydrofuran.[13] Taking a cue from this, performing the reaction with 1 equiv of molecular iodine in the absence of aq. H_2O_2 in ethanol yielded compound **8a** in ~ 10% yield and 80% unreacted **7a** (Scheme 3, eq. 1). This indicated the possibility that the oxidative ring opening of the tetrahydro-β-carbolines required both iodine and hydrogen peroxide. It is also well documented in the literature that iodine catalyzed oxidations are facilitated by aq. H_2O_2, where few of the examples suggested that hypoiodous acid (HOI) can be considered as an active species.[22] Interestingly, treatment of **7a** with one equiv of sodium iodide, aq. H_2O_2 in trifluoroacetic acid medium (which is known to generate either HOI or its protonated version) [23] facilitated the oxidative ring opening to afford the desired product **8a** in 52% yield (Scheme 3, eq. 2). Additionally, in a bid to assess any involvement of radical in the reaction, it was conducted in the presence of the radical inhibitor BHT (3, 5-di-tert-4-butylhydroxytoluene), which barely had any effect on the rate of the reaction (Scheme 3, eq. 3).



Scheme 3. Control experiments to decipher the reaction mechanism

Based on the observation from the control experiments and literature, Scheme 4 depicts the putative reaction mechanism for the oxidative ring opening of 1-aryltetrahydro-β-carbolines, We believe the secondary amine of the 1-aryltetrahydro-β-carboline **7a** is oxidized to the corresponding iminium ion **A** by HOI (generated by the reaction of molecular iodine and aq. hydrogen peroxide). A nucleophilic attack **A** at C_1 with water (as nucleophile) generated **B**. Ring cleavage of **B**, facilitated by keto formation at C_1 leads to the formation of **8a**. The hydrogen iodide generated by the addition of water at **A** is reoxidized to HOI by hydrogen peroxide (Scheme 4).



Scheme 4. Putative reaction mechanism

To support the putative mechanism of oxidative ring opening, we performed density functional theory calculations to rationalize the conversion of intermediate **B** into **8a**. All calculations were executed in gas phase calculations based on their *ab initio* and crystal (Fig. 2) geometries, respectively, using Gaussian 09, revision D.01. [24-26] Both molecules were optimized (Fig 2) using density functional theory method and with B3LYP exchange correlation functional.[29] The basis set used was 6-311G (d, p). The corresponding change in molecular energies between the intermediate **B** and the product **8a** was estimated to be of -13.54 kcal/mol, with product **8a** at lower energy (Figure 2). This suggested that **8a** is energetically more stable than **B**, thereby facilitating the oxidative ring opening reaction.

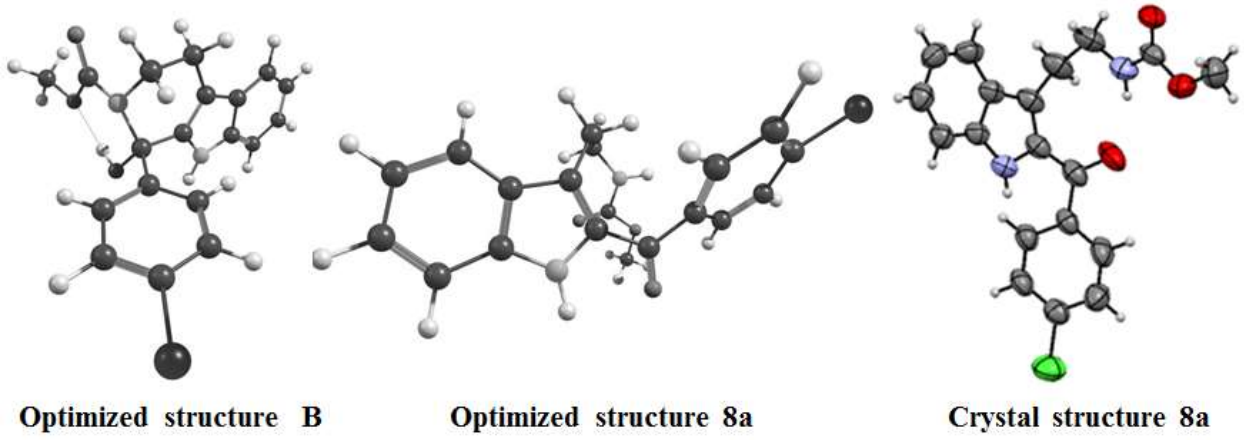
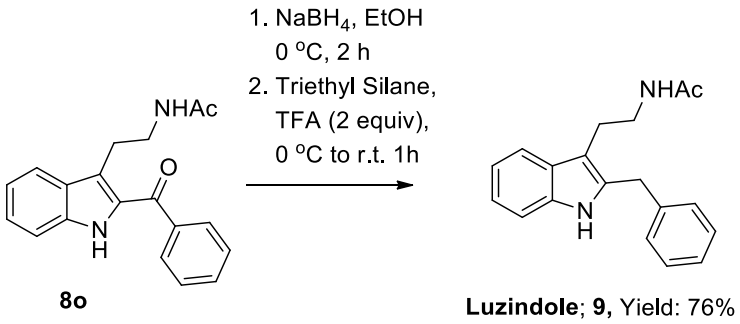


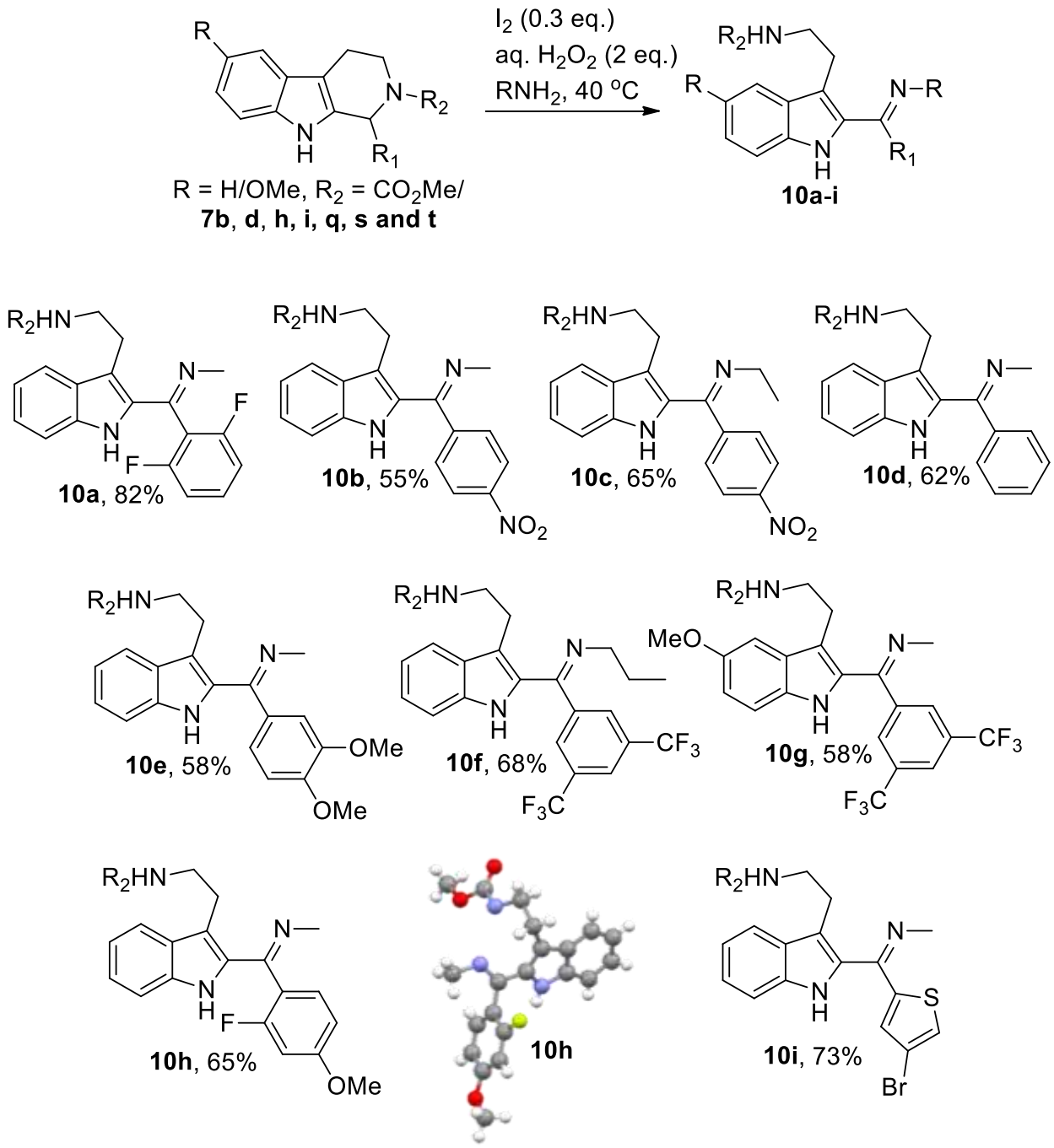
Figure 2. Optimized molecular structure of the proposed intermediates and the crystal structure of **8a**

In a bid to demonstrate the synthetic utility of our protocol we synthesized Luzindole, a drug used in investigating the function of melatonin in the body. It has nearly 15 fold more binding affinity for MT2 receptor over MT1 and in *in vivo* study it has demonstrated that it interferes the circadian rhythm and also exhibit anti-depressant effect.[27] Accordingly, 2 gm of **8o** was reduced at 0 ºC in ethanol and the crude intermediate was then treated with triethyl silane in presence of trifluoroacetic acid from 0 °C to r.t., to afford the crude Luzindole, **9** which was purified through column chromatography, to provide the desired product in 76% yield over two steps (Scheme 5).



Scheme 5. Synthesis of Luzindole **10a**

To extend the utility of our strategy next we focused on demonstrating the generation of C_2-arylmethanimine indole through our procedure, by incorporating appropriate amines in the reaction mixture. These arylmethanimine indoles can be suitable precursor for accessing aminomethyl indoles which have myriad biological activities.[28] Accordingly, carboline **7a** was treated with molecular iodine (0.3 equiv) and aqueous hydrogen peroxide in methyl amine as solvent at 40 °C. The desired 2-(4-chlorophenylmethanimine)indole **10a** was obtained in 56% yield (Scheme 6). To assess the robustness of the protocol carbolines **7b**, **g-i** and **p-s** were treated with ethyl and methyl amines under the optimized reaction conditions to afford the final compounds **10b-i** in decent yields (Scheme 6). Similar to C_2-aroyl derivatives, the protocol was equally amenable for accessing C_2-arylmethanamine indoles with aromatic moieties encrusted with electron withdrawing and electron donating functionalities **10b-h** and heteroaromatic analog **10i**. It was noteworthy that the reaction with ethyl amine was generally poor yielding compared to the methyl analog. We assume the nucleophilic nature of the amines plays an important role in the formation of the final compound as depicted in the mechanism for the formation of C_2-aroyl derivatives in Scheme 3. The structure of these compounds were confirmed by the representative single crystal X-ray of **10h** (Scheme 6).



Scheme 6. Synthesis of C_2 arylalkanimine indoles

Conclusions

In conclusion we report an efficient protocol for the synthesis of C_2-aroyl and arylmethanimine indole derivatives *via* iodine catalyzed oxidative ring opening of 1-aryltetrahydro-β-carboline. This C_2 functionalization strategy is environmentally benign as it utilizes catalytic molecular iodine with aq. H_2O_2 and methyl/ethylamine in ethanol (a class III) solvent. Diverse analogs with variety of functionalities include aromatic, heteroaromatic and aliphatic moiety at C_1 position of the tetrahydro-β-carbolines were converted to the desired products **8a**-**r** and **10a**-**h**. The synthetic applicability of the strategy was demonstrated by the multigram synthesis of Luzindole (5 mg @150 USD in Aldrich). This unique strategy inspired from imine hydrolysis provides access to diversely C_2-functionalized indoles bioactive scaffolds from 1-aryltetrahydro-β-carbolines and can be successfully applied in accessing Luzindole an investigational drug molecule which could cure millions of people globally suffering from depression and sleep disorder.

Acknowledgments

This work was supported by Shiv Nadar University

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