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Hypervalent Iodine(III) Mediated Counter Anion Controlled Intramolecular Annulation of Exocyclic-β-Enaminone to Carbazolone and Imidazo[1,2-a]pyridine Synthesis

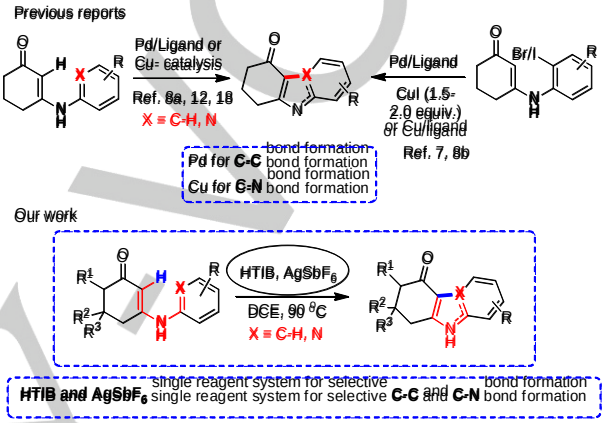
Dhananjay Bhattacherjee,[a],[b] Shankar Ram,[a],[b] Arvind Singh Chauhan,[a],[b] Yamini,[a] Sheetal,[a] and Pralay Das*[a],[b]

Dedication ((optional))

Abstract: A highly efficient and flexible protocol for intramolecular annulation of exocyclic-β-enaminones has been disclosed for the synthesis of carbazolones and imidazo[1,2-a]pyridines via counter anion controlled free radical mechanism promoted by hypervalent iodine(III). The co-operative behavior of HTIB and $AgSbF_6$ plays a linchpin role in the intramolecular annulation process through C-C and C-N bond formation to give the desired products. The mechanistic insights suggest that the two competitive reactions involved in the system guided by the nature of counter anion which decides the formation of final products. A wide variety of carbazolones and imidazo[1,2-a]pyridine molecules have been prepared and isolated in good to excellent yields.

Introduction

The transition metal free intramolecular arylation reactions have received enormous attention for the synthesis of natural products, medicinal agents and organic materials.[1] These arylation reactions can be achieved either by C-C or C-N bond formation strategy which remains a great challenge in organic chemistry especially under iodine(III) conditions and currently represents a powerful tool for the synthesis of complex building blocks.[2] In recent years, the C-C and C-N bond formation reactions has been achieved by the use of transition metal catalyst using C-H functionalization strategy.[3] However, iodine(III) oxidative C-C and C-N bond formation approach remains a promising and up surging field in synthetic chemistry. Owing to the intriguing structural features and widespread occurrence in natural products and drug intermediates such as murrayaquinone,[4a] ondansetron[4b] and alosetron[4c] etc., carbazolones gained considerable interest in the synthetic community. Moreover, these tricyclic neuroprotective compounds have been known for the treatment of chronic and acute diseases such as Parkinson, Alzheimer disease and prostaglandin mediated diseases.[5] Over the last few decades, the plethora of transition metal catalyzed methodologies for



Scheme 1. Different strategies of carbazolones and imidazo[1,2-a]pyridines synthesis

carbazolone synthesis via C-H bond activation strategies have been well documented in the previous reports.[6],[8a] Among the cyclization reactions, the CuI promoted intramolecular cyclization of N-(2-haloaryl)-substituted enaminones are the long-established methodology for the carbazolones synthesis.[7] However, Pd-catalyzed C-H arylation of β-enaminones via intramolecular Heck coupling strategy has also been reported by various groups.[8] The researchers at Merck laboratories have developed homogeneous palladium-catalyzed coupling of vinylogous amides with aryl bromides and chlorides via tandem Hartwig-Buchwald-Heck cyclisation strategy.[8a] Soderberg and co-workers demonstrated palladium catalyzed intermolecular Stille cross-coupling followed by a reductive *N*-heteroannulation for the synthesis of carbazolones.[9] However, a vast majority of reactions involve the palladium catalyzed intramolecular direct C-H bond activation of enaminones.[10] Åkermark *et al*., in 1999 disclosed a palladium-catalyzed cyclizations of arylaminoquinones to biologically important carbazoloquinones with limited substrate scope.[11] In 2011, Glorius and co-workers manifested a Pd-catalyzed oxidative coupling of two C-H-bonds within N-arylenamines that allows the efficient formation of differently substituted indoles.[6a, 12] In a recent report, He *et al*., demonstrated a formal [3+2]-cycloaddition reaction for the synthesis of carbazolequinones via the annulation of aminoquinones with *in situ* generated aryne intermediates.[13] Moreover, the hypervalent iodine(III) has also been employed to achieve carbazolones via direct intramolecular *N*-arylation reaction.[14] However, the same strategy has been failed for the annulation of exocyclic- β-enaminones.

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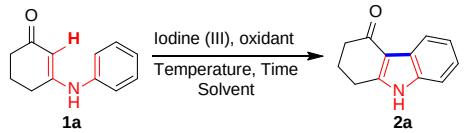
Table 1. Optimization of reaction conditions for oxidative annulation of exocyclic-*β*-enaminone[a]

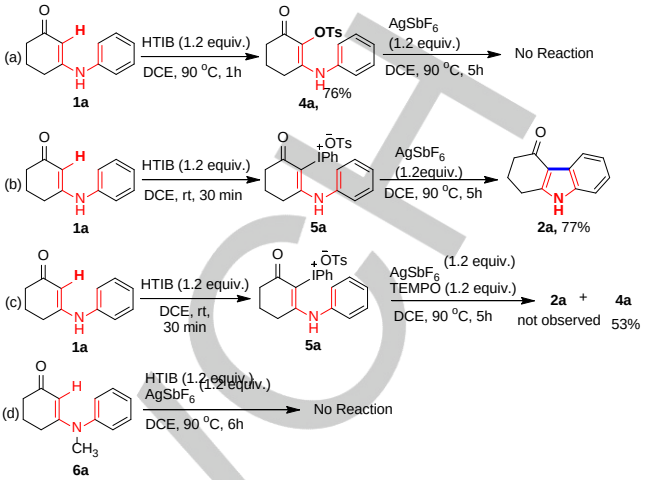


entry	Iodine (III)	counter-anion species	solvent	temperature (^{o}C)	time (h)	yield (%)[b]
1	PIFA	m-CPBA	DCE	60	10	nr
2	PIFA	$AgBF_4$	DCE	60	10	-
3	PIFA	AgO	DCE	60	10	nr
4	PIFA	O_2	DCE	60	10	traces
5	PIFA	$AgSbF_6$	DCE	60	10	51
6	PIFA	$Cu(OAc)_2$	DCE	60	10	traces
7	DIB	$AgSbF_6$	DCE	60	10	37
8	HTIB	$AgSbF_6$	DCE	60	10	61
9	HTIB	$AgSbF_6$	ACN	60	10	nd
10	HTIB	$AgSbF_6$	DMF	60	10	nd
11	HTIB	$AgSbF_6$	Toluene	60	10	nr
12	**HTIB**	**$AgSbF_6$**	**DCE**	**90**	**10**	**80**
13	HTIB	$AgSbF_6$	DCE	100	12	80
14[c]	HTIB	$AgSbF_6$	DCE	100	12	79
15	PIFA	$AgSbF_6$	DCE	90	10	63
16	HTIB	$AgSbF_6$	DCE	90	5	49
17	-	$AgSbF_6$	DCE	90	10	nd
18	HTIB	-	DCE	90	10	nd

[a]Reaction conditions: 3-(phenylamino)cyclohex-2-enone (**1a**) (0.2655 mmol), HTIB (0.3191 mmol), $AgSbF_6$ (0.3191 mmol) in DCE (2 mL) at 90 ^{o}C (oil bath temperature) for 12 hours; [b] yields referred to isolated yields; [c] 1.5 equivalent of HTIB was used.

In 2014, Zhao and co-workers reported that hypervalent iodine (III) conditions were not suitable for the carbazolone synthesis starting from enaminones and α-iodo-N-arylated product was the end result of the reaction.[1c] Moreover, in our previous report we have observed the formation of α-tosylated product when β-enaminones subjected to react under hydroxy(tosyloxy)iodobenzene conditions.[15] Inspiring from observation by Crivello *et al*., we postulated the introduction of $AgSbF_6$ in the reaction system for the desired annulation reaction.[22] To our delight, the combine synergistic role of hydroxyl(tosyloxy)iodobenzene (HTIB) and silver hexafluoroantimonate ($AgSbF_6$) plays uniquely to bring about the desired transformation to solve the lingering problem of iodine(III) mediated annulation of exocyclic-*β*-enaminones.

On the other hand, imidazo[1,2-a]pyridine moiety with fused imidazole and pyridine ring represents an important scaffold with diverse range of biological activities.[16] The most highlighted synthetic protocols involve oxidative coupling, multicomponent reactions and hydroamination reactions.[17] In 2016, Liu *et al.*, developed a practical method for the synthesis of imidazo[1,2-a]pyridine derivatives using molecular iodine as a sole oxidant in the presence of CuI.[18] However, iodine(III) mediated oxidative annulation of enaminones for the synthesis of carbazolones and



Scheme 2. Control experiments.

imidazo[1,2-a]pyridines still unknown in literature.

In past few years, our research group dedicatedly involved in the development of new and known class of cyclohexane-1,3-diones and their applications in commercially valuable molecules synthesis.[19] In continuation to our research on exploiting the intrinsic reactivity of hypervalent iodine(III) reagents in organic transformation, herein, we reported iodine(III) mediated intramolecular annulation of exocyclic-β-enaminones triggered by counter anion.

Results and Discussion

We have started our initial assessment by choosing 3-(phenylamino)cyclohex-2-enone (**1a**) as bench stable moiety for the intramolecular annulation reaction under hypervalent iodine(III) conditions. To establish the best reaction conditions various parameters such as iodine(III) reagent, counter-anion species, solvent, temperature and time were critically investigated (Table 1, entry 1-11). The best yield of the corresponding carbazolone were observed when 1 equiv. of 3-(phenylamino)cyclohex-2-enone, 1.2 equiv. of HTIB and 1.2 equiv. of $AgSbF_6$ subjected to react in dichloroethane solvent at 90 ^{o}C temperature for 10 hours (Table 1, entry 12). However, increase in the time, temperature as well as hypervalent iodine equivalency did not increase the yield of the final product (Table 1, entry 13-14). However, replacing HTIB with PIFA under same reaction conditions gave 63% yield of the desired product (Table 1, entry 15). Furthermore, the synergistic effect of the reagents was further observed where the absence of one reagent did not lead to the product formation even in trace quantity (Table 1, entry 17-18).

In order to get insight into the reaction mechanism, several control experiments were performed as shown in scheme 2. At the commencement of reaction, we have observed the formationof tosylation product **4a** under HTIB condition.

However, the tosylation product **4a** on separate treatment with $AgSbF_6$ did not

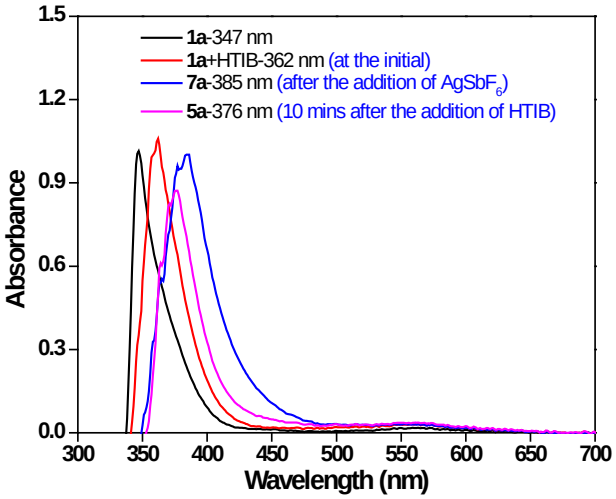
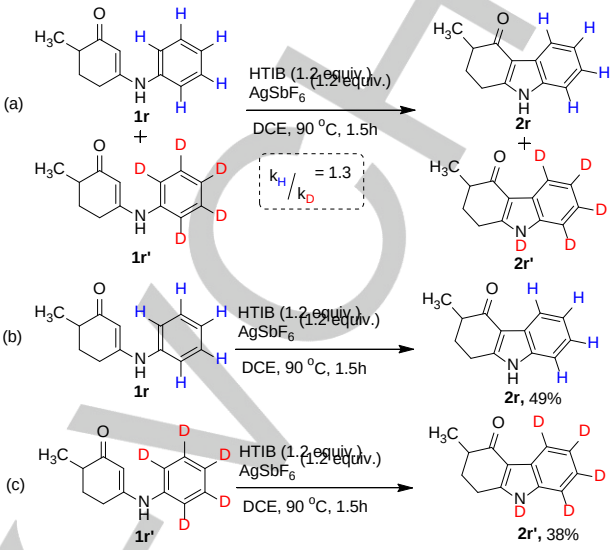


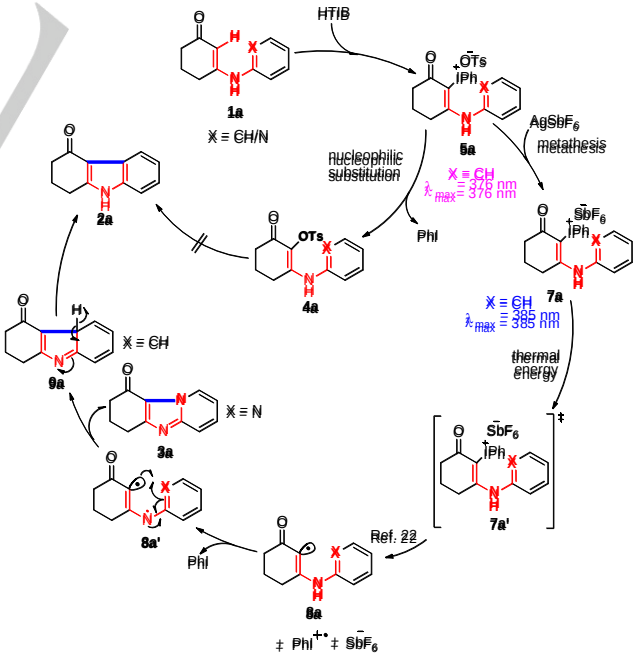
Figure 1: UV-Vis studies of reaction intermediates

lead to the formation of desired **2a**. This experiment clearly ruled out the intermediacy of **4a** (Scheme 2-a). The compound **1a** on treatment with HTIB gives intermediate **5a** which is quite stable at room temperature and procures the desired product **2a** in 77% yield on treatment with $AgSbF_6$ (Scheme 2-b). To check the involvement of free radicals, the intermediate **5a** subjected to react in presence of TEMPO under same reaction conditions; no product (**2a**) formation was observed. However, in such case formation of **4a** was observed as an exclusive product. This experiment clearly indicates the existence of two competitive reactions *i.e.*, free radical annulation and nucleophilic substitution which are responsible for the formation of **2a** and **4a** respectively. At standard conditions, the free radical annulation pathway is faster than the nucleophilic substitution by tosylate ion. However, in the presence of TEMPO which inhibits the formation of free radicals makes the nucleophilic substitution reaction to proceed much faster for **4a** synthesis**.** The tertiary enaminones **6a** did not lead to any product formation indicates the involvement of N-H bond in the annulation process. This fact further proved by the deuterium labeling experiment (Scheme 3) where deuterium incorporation was observed over N-center (Scheme 3b). The isotopic scrambling was observed in the product and in accordance with NMR spectra 60% H/D exchanged product was noticed (Scheme 3a).[21] Moreover, the deuterium labeling experiment revealed the observed k_H/k_D = 1.3, indicating that the aromatic C-H bond cleavage may not be the rate determining step of the reaction (Scheme 3). UV studies were performed which is in support of the proposed metathesis step involved in the mechanism (Figure 1). When HTIB added to the reaction mixture a red shift at 362 nm was observed indicates the interaction between **1a** and HTIB. Moreover, the red shift at 385 nm from 376 nm strongly supports the metathesis step involved in the mechanism (Scheme 4). On the basis of control experiments and precedent literature,[20],[15] most plausible mechanism has been sketched in Scheme 4. In the first step, HTIB undergoes ligand exchange reaction with the reactant **1a**



Scheme 3. Isotopic scrambling experiment

and gave intermediate **5a**. As stated previously intermediate **5a** could undergo nucleophilic substitution or metathesis to produce **4a** or **7a** respectively. Since metathesis step is faster under the reaction conditions, intermediate **7a** forms immediately over intermediate **5a**.



Scheme 4. Plausible mechanism of annulation of exocyclic-β-enaminones

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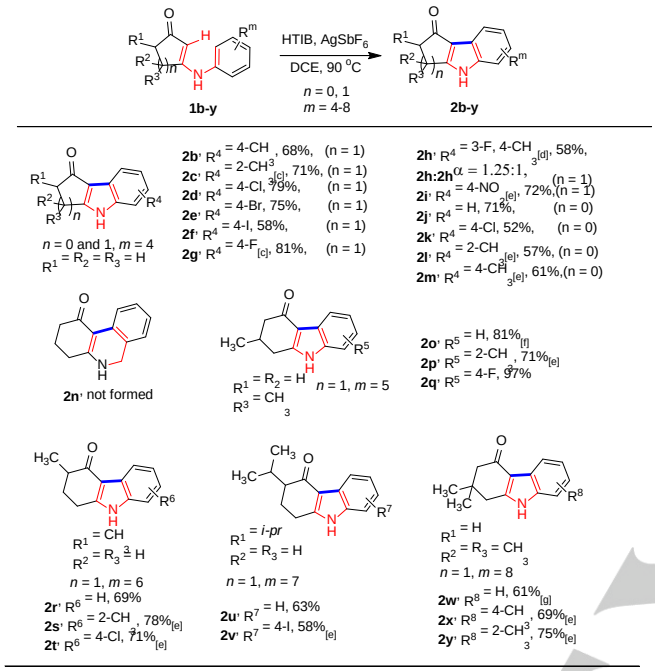
The seminal work by Crivello and co-workers showed that iodonium salts having hexafluoroantimonate as a counter ion can act as a photo initiators and initiate free radical reaction via radical-cation pathway.[22] Due to the low bond energy of the C-I bond (26-27 kcal/mol), the intermediate can efficiently produce

Table 2. Effect of alkyl and aryl substitution and ring size of the oxidative annulation reaction [a][b]

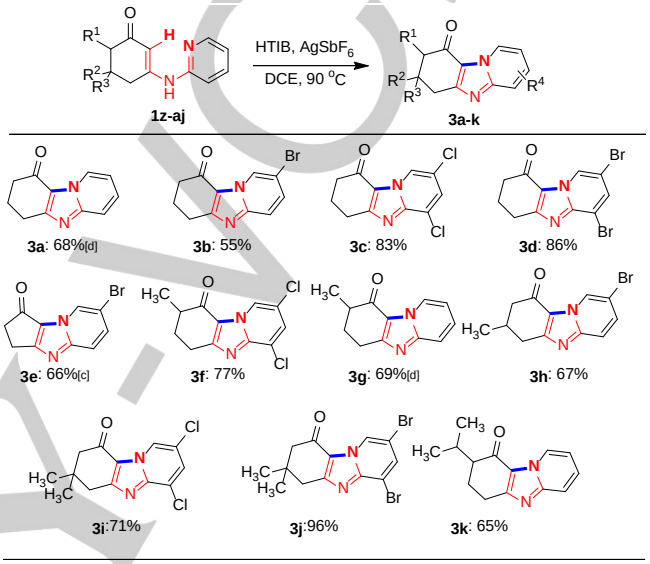


[a] Reaction conditions: **1b-y** (1 equiv.), HTIB (1.2 equiv.), $AgSbF_6$ (1.2 equiv.) in DCE (2 mL) at 90 °C (oil bath temperature) for 12 hours; [b] yields referred to isolated yields; [c]reaction time 8h; [d]yield referred to recovred starting material; [e]2 equiv. HTIB was used; [f]1.5 equiv. HTIB was used; [g]reaction time 10h.

active radical species under the thermal condition. Hence the hemolytic cleavage of intermediate **7a** produces free radical intermediate **8a** via **7a´**. Once the intermediate **8a** is formed it starts free radical cyclisation led to **3a** via intermediate **8a´**. The re-aromatisation of **9a** finally affords desired carbazolone**2a**. This step further supported by the deuterium labeling experiment (scheme 3).

The optimized reaction conditions were further applied to explore the substrate versatility of exocyclic-β-enaminones for the anticipated annulation reaction (Table 2). Various electronically rich enaminones substituted with methyl group **1b-c** delivered the corresponding annulation product **2b-c** in 68-71% yields. The haloarylamino substituted β-enaminones **1d-g** gave the anticipated carbazolones **2d-g** in 58-81% yields. Next we have chosen unsymmetrical disubstituted β-enaminone **1h** which afforded two different regio-isomers (2h and 2hα) in 58% yield in 1.25:1 ratio. In our reaction conditions the strongly electron withdrawing group such as $–NO_2$ substituted enaminone **1i** was also targeted for the synthesis of carbazolones. Intriguingly the formation of α-tosylation product **2i** was observed in 73% yield. This result forced us to thinkabout the mechanism of the reaction. There may be two competitive reactions *viz*. annulation and α-tosylation depending on the behavior and the availability of electron density at the nitrogen of exocyclic-β-enaminones. In our study various EDG and EWG substituted cyclopentane-1,3-dione derived enaminones were also targeted to see the effect of ring size to the product yield. However, no such significant difference was observed and the corresponding products **2j-m** were obtained in 52-71% yields. Moreover, the N-benzyl substituted exocyclic-β-

Table 3. Synthesis of imidazo[1,2-a]pyridine derivatives[a][b]



[a] Reaction conditions: **1z-aj** (1 equiv.), HTIB (1.2 equiv.), $AgSbF_6$ (1.2 equiv.) in DCE (2 mL) at 90 °C (oil bath temperature) for 12 hours; [b] yields referred to isolated yields; [c] $AgSbF_6$ was added after 30 mins, [d]reaction carried out for 8h.

enaminones**1n** gave only tosylated product instead of desired cyclisation product. This fact clearly indicates the direct involvement of nitrogen lone pair of electron in conjugation with aryl ring is necessary in the annulation process.

Next, we have focused on the effect of alkyl substitution on the enaminone ring to the desired product formation process (Table 2). Electronically rich monoalkyl substituted exocyclic-β-enaminones **1o-p** gave the carbazolones **2o-p** in 71-81% yields. Previously, we have observed that the fluoro substituted exocyclic-β-enaminones afforded the anticipated carbazolones with excellent yield. Here, in case of 5-methyl substituted exocyclic-β-enaminone **1q,** no significant steric effect was observed and **2q** obtained in 97% yield. In the case of 4-methyl substituted exocyclic-β-enaminones **1r-t,** the profound electronic effect was observed over steric effect which gave the good yields of corresponding carbazolones **2r-t**. On introducing bulkier isopropyl group at the 4-position of exocyclic-β-enaminones **1u-v**, lower yield of the desired products **2u-v** were observed and the fact indicating the slower down of reaction rate by the vicinal bulky group at rate determining C-H bond activation process. Moreover, 5,5-dialkylsubstitued electron rich exocyclic-β-enaminones **1w-y** excellently gave the desired corresponding products **2w-y** in 61-75% yields. Inspired from these results, we have attempted acyclic exocyclic-β-enaminones under the standard reaction conditions for the

synthesis of substituted indole derivatives. However, the reactant remains unconsumed and the formation of the desired product was not observed.[21]

In our ongoing work, we focused on the C-C bond formation reactions for the synthesis of carbazolone analogues. However, the striking outcome of this research was found when 2-aminopyridine derived exocyclic-β-enaminones were efficiently converted into imidazo[1,2-a]pyridine derivatives under the same reaction protocol. When 2-aminopyridine derived exocyclic-β-enaminones were subjected to react under the same reaction conditions, the highly selective C-N bond formation reaction was observed rather than C-C bond formation (Table 3). Imposing the inherent biological importance of imidazo[1,2-a]pyridine derivatives this method could be an useful protocol for synthetic community.

The present reaction conditions were then applied for the synthesis of various imidazo[1,2-a]pyridine from exocyclic-*β*-enaminones. The various mono and di-substituted 2-aminopyridine derived enaminones showed excellent selectivity towards C-N bond formation to afford imidazo[1,2-a]pyridine derivatives (Table 3, **3a-k**). In such case, we have observed that di-halosubstituted exocyclic-*β*-enaminones **1z-ac** gave excellent yield of **3a** and **3d**. Moreover, the variation in ring size did not significantly affect the yield of the desired product **3e.** Next, mono-methyl, dimethyl and isopropyl substituted enaminones **1ae-aj** were targeted for the anticipated imidazo[1,2-a]pyridine synthesis. To our delight, the corresponding imidazo[1,2-a]pyridines **3f-3k** were obtained in good to excellent yields.

Conclusions

In conclusion, operationally simple and efficient reagent system has been developed for the synthesis of diverse array of carbazolones and imidazo[1,2-a]pyridine molecules under iodine(III) conditions. Moreover, the expanded scope of this single reagent system is highly useful for the C-C as well as C-N bond formation reaction with wide functional group accessibility and could be a complementary to Pd and Cu catalysis. An interesting mechanistic pathway was found to be responsible for the transformation has been investigated with spectral evidences. Furthermore, this transformation would inspire synthetic chemists for drug development research under milder condition.

Experimental Section

Typical procedure for the synthesis of 2,3-dihydro-1H-carbazol-4(9H)-one (2a): An oven dried screw cap reaction vial was charged with 3-(phenylamino)cyclohex-2-enone (50 mg, 0.267 mmol) in dichloroethane (2 mL) as a solvent and then [hydroxy(tosyloxy)iodo]benzene (HTIB) (125.71 mg, 0.3207 mmol) and silver hexafluoroantimonate (110.19 mg, 0.3207 mmol) was added to the reacting solution. The mixture was allowed to stir for 12 hours at 90 °C and the progress of the reaction was monitored by TLC until completion. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by silica gel (mesh 60-120) chromatography (50% ethyl acetate in n-hexane) to afford the desired carbazolones **2a** as white solid in 80% (39.5 mg) yield. Melting point: 216-217 °C. The molecule was characterised by ^{1}H, ^{13}C NMR spectra and HRMS and IR analysis.^{1}H NMR (300 MHz; DMSO-*d6*) *δ (ppm)* 2.09-2.13 (m, 2H), 2.42 (t, *J* = 12.26 Hz, 2H), 2.95 (t, *J* = 11.88 Hz, 2H), 7.11-7.19 (m, 2H), 7.39 (d, *J* = 6.63 Hz, 1H), 7.94 (d, *J* = 6.21 Hz 1H), 11.86 (brs, NH); ^{13}C NMR (75 MHz; DMSO-*d6*) *δ (ppm)* 22.70, 23.40, 37.78, 111.49, 111.73, 120.15, 121.46, 122.38, 124.50, 135.83, 152.25, 192.84; HRMS (ESI) $(M+Na)^+$ calcd. for $C_{12}H_{11}NNaO^+$ is 208.0733 obsd. 208.0732; IR (cm^{-1}) 3358, 3055, 3032, 2953, 2945, 1601, 1454, 1249, 1176.

Typical procedure for the synthesis of 7,8-dihydrobenzo[4,5]imidazo[1,2-a]pyridin-9(6H)-one (3a): An oven dried screw cap reaction vial was charged with 3-(pyridin-2-ylamino)cyclohex-2-enone (50 mg, 0.265 mmol) in dichloroethane (2 mL) as a solvent and then [hydroxy(tosyloxy)iodo]benzene (HTIB) (124.65 mg, 0.318 mmol) and silverhexafluoroantimonate (109.26 mg, 0.318 mmol) was added to the reacting solution. The mixture was allowed to stir for 8 hours at 90 °C and the progress of reaction was monitored by TLC until completion. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by silica gel (mesh 60-120) column chromatography to afford 7,8-dihydrobenzo[4,5]imidazo[1,2-a]pyridin-9(6H)-one **3a** in 68% yield (33.5 mg), as white semi-solid using 50% EtOAc in n-hexane as eluent. ^{1}H NMR (600 MHz; DMSO-*d6*) *δ (ppm)* 2.13-2.17 (m, 2H), 2.58 (t, *J* = 6.66 Hz, 2H), 2.96 (t, *J* = 6.24 Hz, 2H), 7.22-7.24 (m, 1H), 7.62-7.65 (m, 1H), 7.75 (d, *J* = 8.85 Hz, 1H), 9.20 (d, *J* = 6.68 Hz, 1H); ^{13}C NMR (150 MHz; DMSO-*d6*) *δ (ppm)* 23.36, 24.79, 37.82, 114.98, 116.55, 118.79, 127.65, 129.92, 147.04, 159.78, 187.53; HRMS (ESI) $(M+H)^+$ calcd. for $C_{11}H_{11}N_2O^+$ is 187.0866 obsd. 187.0865; IR (cm^{-1}) 2924, 2858, 1631, 1498, 1429, 1329, 1259, 1182.

Typical procedure for the synthesis of 6-oxo-2-(phenylamino)cyclohex-1-en-1-yl 4-methylbenzenesulfonate (4a): An oven dried screw cap reaction vial were charged with **1a** (50 mg, 0.267 mmol) in dichloroethane (2 mL) as a solvent and then [hydroxy(tosyloxy)iodo]benzene (HTIB) (1.2 equiv) was added to the reacting solution. The mixture was allowed to stir for 1h at 90 °C and the progress of reaction was monitored by TLC until completion. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by silica gel (mesh 60-120) chromatography (40% EtOAc in n-hexane) to afford the **4a** as light brown semi-solid (72.5 mg, 76%). ^{1}H NMR (600 MHz; CD_3OD) *δ (ppm)* 1.85-1.87 (m, 2H), 2.33 (t, *J* = 6.24 Hz, 2H), 2.43 (s, 3H), 2.57 (d, *J* = 6.12 Hz, 2H), 7.02 (d, *J* = 7.56 Hz, 2H), 7.26 (t, *J* = 7.28 Hz, 1H), 7.36-7.40 (m, 4H), 7.90 (d, *J* = 8.22 Hz, 2H);^{13}C NMR (150 MHz; CD_3OD) *δ (ppm)* 20.27, 20.36, 26.86, 35.85, 123.65, 125.15, 126.27, 128.63, 128.83, 129.25, 132.92, 137.26, 145.55, 157.74, 188.87; HRMS (ESI-TOF) $(M+H)^+$ calcd. for $C_{19}H_{20}NO_4S^+$ is 358.1108 obsd. 358.1122.

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Keywords: carbazolones• imidazo[1,2-a]pyridine• hypervalent iodine• annulation• metathesis

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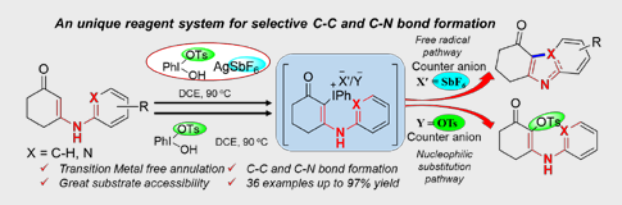

An unique reagent system: A co-operative behaviour of two reagent systems has been described in the intramolecular annulation process of exocyclic-β-enaminones. These single reagent system is highly efficient for the C-C as well as C-N bond formation process. Moreover, the specific behaviour of different counter anions for the final product formation has been evaluated with spectral evidences.

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Hypervalent Iodine(III) Mediated Counter Anion Controlled Intramolecular Annulation of Exocyclic-β-Enaminone to Carbazolone and Imidazo[1,2-a]pyridine Synthesis