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Metal-Free in Situ sp^3, sp^2, and sp C-H Functionalization and Oxidative Cross Coupling with Benzamidines Hydrochloride: A Promising Approach for the Synthesis of α-Ketoimides

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Abstract: A new metal-free tandem protocol for the synthesis of α-ketoimides *via* sp^3, sp^2, and sp C-H functionalization followed by oxidative cross coupling with benzamidines hydrochloride by using catalytic iodine with TBHP in DMSO has been developed. Wide range of functional group tolerance, inexpensive catalyst, operational simplicity and good to excellent yields of the products are the striking features of this method.

Keywords: C-H Functionalization, Metal-free synthesis, Iodine, *tert*-Butyl hydroperoxide (TBHP), Kornblum oxidation, α-Ketoimides.

Introduction

Amides, imides, α-ketoamides and α-ketoimides are versatile synthetic building blocks owing to easy further functional group manipulation resulting in ready access to diverse biologically active heterocyclic ring systems.[1] Additionally they are crucial segments in numerous natural products, drugs and proteins.[2]

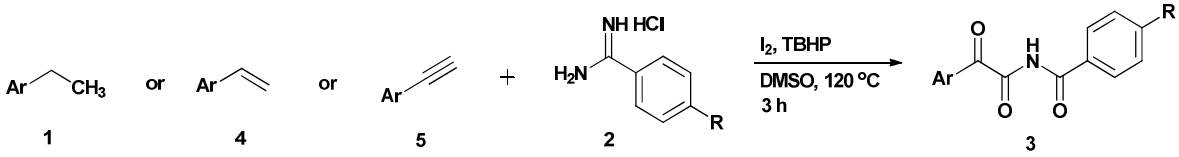
Imides are key constituents of variotin, aniracetam, and many heterocycles.[2] Similarly, a suitably substituted α-ketoamide is a precursor of bioactive FK506, rapamycin, $FKBP_{12}$, Na-channel blocker GW 356194, 5-HT6 binding ligands, α-diones and β-lactams *etc*.[3] Hence, several methodologies have been developed for synthesizing this group of building blocks.

Conventionally, a carboxylic acid or its derivative is coupled with an amine to give an amide[4] while acyl halides are used in the preparation of imides.[5] α-Ketoamides are synthesized by amidation of α-ketoacids[6], α-ketoaryl halides[7], cyanoketones[8], oxidation or photochemical reaction of amides[9], double carboxylative amidation of aryl halides[10], oxidation of acyl cyanophosphoranes followed by the amidation of α,β-diketone nitrile[11] and reaction of isocyanides with aromatic acyl chlorides.[12] Yoo and Li[13] used copper while Liu *et al.*[14] used *n*-Bu_4NI, together with TBHP for the synthesis of amides from aldehydes. Recent years have seen efforts devoted towards the synthesis of α-ketoamides and α-ketoimides via C-H activation. This strategy has emerged as an impressive novel tool for its diverse applications.

The Cu-catalyzed synthesis of α-ketoamides through oxidative coupling of phenyl acetylenes, aryl acetaldehydes, α-carbonyl aldehydes and aryl methyl ketones with anilines is well documented.[15] However, the use of toxic metal oxidants limits the utility of these methods especially in case of synthesis of drug intermediates owing to possible contamination of these with trace amount of heavy metals. Iodine or iodine-peroxide has emerged as effective reagent

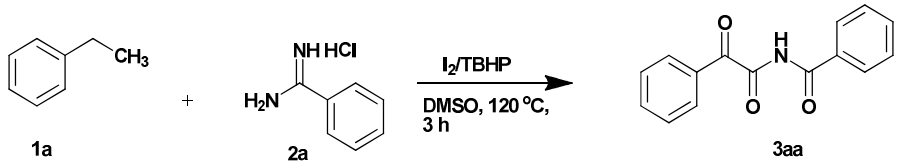
for sp^3 C-H bond oxidative amidation of methyl ketones.[16] Zhang and co-workers had employed anodic oxidation of aryl methyl ketones.[17] Mupparapu *et al*. have used dimethyl sulfoxide for the oxidative amidation of 2-oxoaldehydes.[18] The synthesis of polysubstituted oxazoles was reported through domino oxidative cyclization by using I_2/TBHP.[19a] Wang *et*. *al* synthesized 2,5-disubstituted oxazoles by using 2-amino-1-phenylethanone and aromatic aldehydes,[19b] 2-phenylquinazolines from 2-amino benzophenones and benzylic amines,[19c] quinazolines from α-amino acids and 2-aminobenzoketones,[19d] ketones from benzylic methylenes and nitriles from primary amines by using I_2/TBHP.[19e] Jurczak and co-workers[20] reported the diastereoselective addition of Grignard reagents to chiral α-ketoimides derived from Oppolzer's sultam.

Considering the advantages of domino reaction and limitations of aforementioned methods, herein we present a novel metal-free synthetic protocol for the synthesis of α-ketoimide from diverse substrates. We have centered our attention on multiple C-H bond functionalization of ethyl arenes (**1**), ethylene arenes (**4**), and ethyne arenes (**5**) followed by oxidative coupling with benzamidines hydrochloride (**2**) to give α-ketoimides (**3**) (Scheme 1).



Scheme 1. The tandem oxidative cross coupling of ethyl arenes, ethylene arenes, and ethyne arenes with benzamidines hydrochloride.

Table 1. Optimization studies for the oxidative imidation of ethylbenzene



Entry	Catalyst (eq.)	Oxidant (eq.)	Solvent	Temp. (^oC)	Yield (%)[d]
1[a]	I_2 (1.0)	TBHP (2.0)	DMSO	80	26
2[a]	I_2 (1.0)	TBHP (3.0)	DMSO	80	33
3[a]	I_2 (1.0)	TBHP (3.0)	DMSO	100	58
4[a]	I_2 (1.0)	TBHP (3.0)	DMSO	120	64
5[a]	I_2 (1.0)	TBHP (3.0)	DMSO	130	56
6[a]	I_2 (1.0)	TBHP (3.0)	DMSO	140	43
7[a]	I_2 (0.5)	TBHP (3.0)	DMSO	120	72
8[a]	I_2 (0.3)	TBHP (3.0)	DMSO	120	84

9[a]	I_2 (0.2)	TBHP (3.0)	DMSO	120	87
10[a]	I_2 (0.1)	TBHP (3.0)	DMSO	120	81
11[b]	I_2 (0.2)	TBHP (3.0)	DMSO	120	Trace
12[a]	I_2 (0.2)	DTBP (3.0)	DMSO	120	0
13[a]	I_2 (0.2)	IBX (3.0)	DMSO	120	35
14[a]	I_2 (0.2)	DMP (3.0)	DMSO	120	Trace
15[a]	I_2 (0.2)	DIB (3.0)	DMSO	120	Trace
16[a]	I_2 (0.2)	HTIB (3.0)	DMSO	120	Trace
17[a]	I_2 (0.2)	DDQ (3.0)	DMSO	120	Trace
18[a]	I_2 (0.2)	$K_2S_2O_8$ (3.0)	DMSO	120	Trace
19[a]	I_2 (0.2)	O_2 (1.0 atm)	DMSO	120	0
20[c]	-	TBHP (3.0)	DMSO	120	-
21[a]	NIS (0.2)	TBHP (3.0)	DMSO	120	22
22[a]	KI (0.2)	TBHP (3.0)	DMSO	120	14
23[a]	CuI (0.2)	TBHP (3.0)	DMSO	120	18
24[a]	TBAI (0.2)	TBHP (3.0)	DMSO	120	28
25[a]	I_2 (0.2)	TBHP (3.0)	DMF	120	-
26[a]	I_2 (0.2)	TBHP (3.0)	1,4-dioxane	120	-
27[a]	I_2 (0.2)	TBHP (3.0)	THF	120	-
28[a]	I_2 (0.2)	TBHP (3.0)	Toluene	120	-

[a]Reaction conditions: **1a** (1.0 mmol), catalyst, and oxidant was heated in sealed tube for 1.0 h, **2a** (1.0 mmol) in solvent (3.0 mL) was then added and heating continued for 2 h. [b]Reaction condition: **1a** (1.0 mmol), I_2 (0.2 mmol), TBHP (3.0 mmol) and **2a** (1.0 mmol) in DMSO was heated in sealed tube at 120 ^oC for 3 h. [c]Reaction condition: **1a** (1.0 mmol), TBHP (3.0 mmol) was heated in sealed tube at 120 ^oC for 1.0 h, **2a** (1.0 mmol) in DMSO was then added and heating continued for 2 h. [d]Isolated yield.
TBHP = *tert*-butyl hydroperoxide, DTBP = di-*tert*-butyl peroxide, IBX = *o*-iodoxy-benzoic acid, DMP = 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)one, DIB = (diacetoxyiodo)benzene, HTIB = [hydro(tosyloxy)iodo]benzene, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, $K_2S_2O_8$ = potassium persulfate.

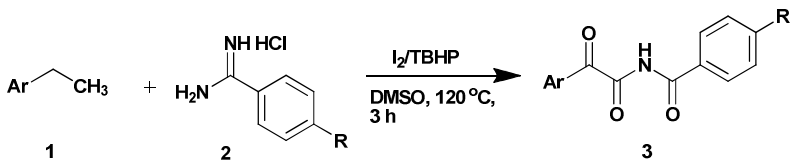
The model reaction between ethylbenzene (**1a**) and benzamidine hydrochloride (**2a**) in presence of I_2/TBHP in DMSO was run to test our speculations thus for the same we optimized the reaction conditions. Optimization of reaction conditions was carried out through reacting ethylbenzene (**1a**) in presence of 1.0 eq. of I_2 and 2.0 eq. TBHP as an oxidant at 80 ^oC for 1 h. Benzamidine hydrochloride (**2a**) in DMSO was added to this reaction mixture and heating continued for 2 h to obtain α-ketoimide (**3aa**) in 26% yield. A slight increase in yield (33%, Table 1, entry 2) was obtained when the same reaction was run by using 3.0 eq. of TBHP. Next, the reactions at varying temperatures (Table 1, entries 3−6) were carried out to improve the yield, and 120 °C was found to be the optimum condition for the oxidative coupling reaction.

Then, the amount of I_2 was varied from 0.5 to 0.1 eq. at 120 ^oC by using 3.0 eq. TBHP in DMSO (Table 1, entries 7-10). Use of 0.2 eq. of I_2 in presence of 3.0 eq. of TBHP in DMSO as solvent gave the best yield (87%). We carried out the neat reaction by adding all components at the same time but could isolate only a trace amount of the product (Table 1, entry 11). This

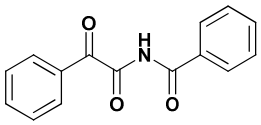
clearly indicates the importance of stepwise addition. We screened different oxidants namely DTBP, IBX, DMP, DIB, HTIB, DDQ, $K_2S_2O_8$, and molecular oxygen with 0.2 eq. of molecular I_2. A 35% yield was observed in the case of IBX whereas with other oxidants either no reaction occurred or formation of product in trace amounts was observed (Table 1, entries 12-19). The reaction did not proceed in absence of iodine thereby highlighting its importance as a catalyst for this reaction (Table 1, entry 20). Then to further investigate the scope of catalyst, we used different catalysts for this reaction such as NIS, KI, CuI, and TBAI. Low yields (14-28%) were obtained (Table-1, entries 21-24) by using above mentioned catalysts.

No product was formed when DMF, 1,4-dioxane, THF, and toluene were used as a solvents thereby indicating the dual role of DMSO as a solvent as well as co-oxidant in this reaction (Table-1, entries 25-28). Similar results were obtained when ethylbenzene (**1a**) was replaced by styrene (**4a**) and phenylacetylene (**5a**).

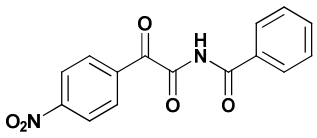
Table 2. I_2/TBHP catalyzed synthesis of α-ketoimides from ethyl arenes and benzamidines hydrochloride[a, b]



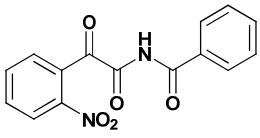
1 2 3



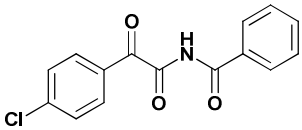
3aa (87%)



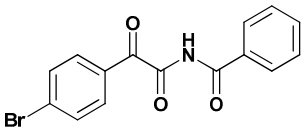
3ba (87%)



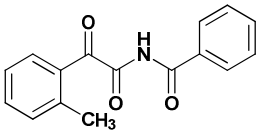
3ca (81%)



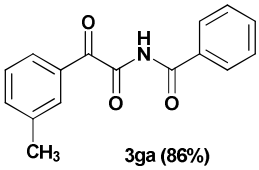
3da (85%)



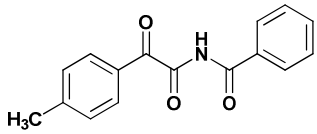
3ea (86%)



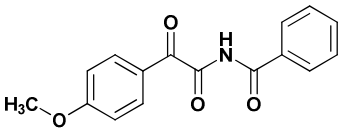
3fa (84%)



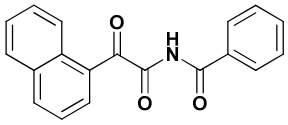
3ga (86%)



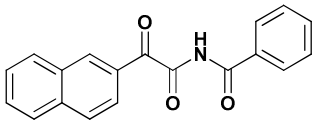
3ha (88%)



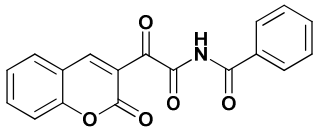
3ia (82%)



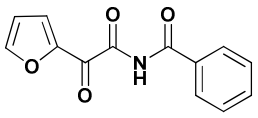
3ja (88%)



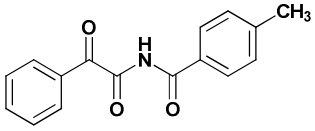
3ka (86%)



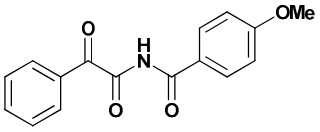
3la (88%)



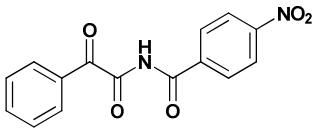
3ma (84%)



3ab (84%)



3ac (83%)



3ad (85%)

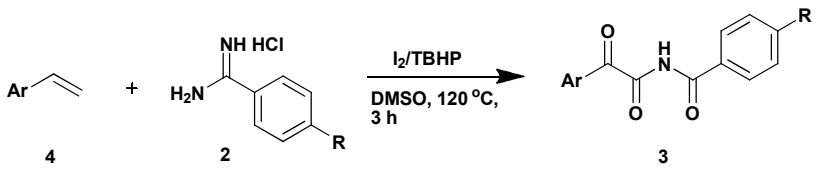
[a]Reaction conditions: **1** (1.0 mmol), I_2 (0.2 mmol), and TBHP (3.0 mmol) was heated in sealed tube at 120 ^{o}C for 1.0 h, **2** (1.0 mmol) in DMSO (3.0 mL) was added and heating continued for 2 h. [b]Isolated yield.

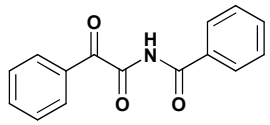
In order to study the wider applicability of this protocol, we investigated a range of substituted ethyl arenes (**1**). It was found that various functional groups were compatible with the reaction

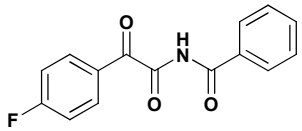
conditions furnishing the desired products **3aa-3ad** (Table 2) in good to excellent yields. Methyl, methoxy, nitro and halogen substituents remained unaffected during the course of the reaction and their position in the benzene ring did not show any significant impact on the rate of reaction as well as yield of products. 2-Methyl-, 3-methyl-, 4-methyl- and 4-methoxy-ethylbenzene reacted with benzamidine hydrochloride (**2a**) and formed the corresponding α-ketoimides **3fa**, **3ga**, **3ha** and **3ia** respectively in 82-88% yield. 4-Chloro- and 4-bromo-ethylbenzene underwent a smooth reaction to give the corresponding α-ketoimide **3da** and **3ea** in 85 and 86% respectively. 4-nitro- and 2-nitro-ethylbenzene reacted satisfactorily with benzamidine hydrochloride (**2a**) providing the corresponding products **3ba** and **3ca** in 87 and 81% respectively. Likewise, 1-ethylnaphthalene and 2-ethylnaphthalene also offered the corresponding α-ketoimides (**3ja**, **3ka**) in 88 and 86% respectively. Notably, heteroaryl ethanes such as 3-ethyl-2*H*-benzopyran-2-one and 2-ethylfuran reacted well with selectivity and furnished the corresponding α-ketoimides **3la**, and **3ma** in 88 and 84% yields respectively.

The scope of the study was further extended to substituted benzamidines hydrochloride. The electron neutral (4-CH_3), electron-deficient (4-NO_2), and electron-rich (4-OMe) groups on the phenyl rings of benzamidines hydrochloride reacted smoothly to afford the corresponding products **3ab**−**3ad** in 83−85% yields (Table 2).

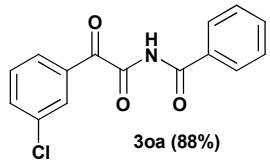
Table 3. I_2/TBHP catalyzed synthesis of α-ketoimides from ethylene arenes and benzamidines hydrochloride[a,b]



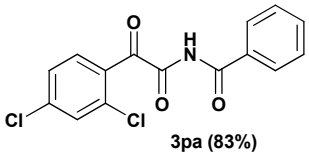

3aa (90%)



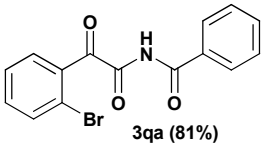
3na (86%)



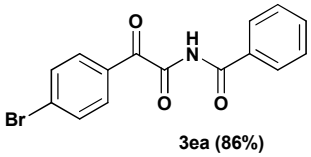
3oa (88%)



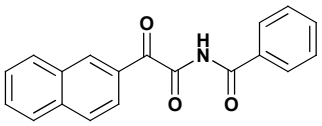
3pa (83%)

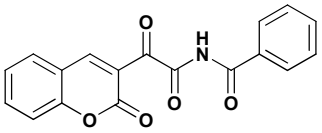


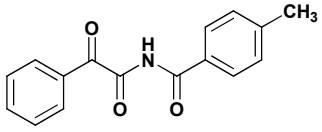
3qa (81%)



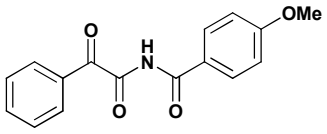
3ea (86%)


3ka (89%)

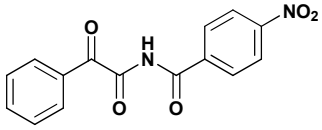

3la (87%)



3ab (84%)



3ac (85%)



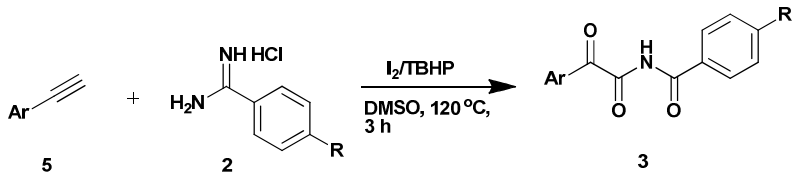
3ad (82%)

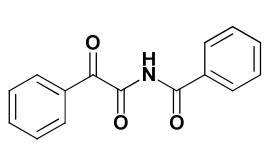
[a]Reaction conditions: **1** (1.0 mmol), I_2 (0.2 mmol), and TBHP (3.0 mmol) was heated in sealed tube at 120 ^oC for 1.0 h, **2** (1.0 mmol) in DMSO (3.0 mL) was added and heating continued for 2 h. [b]Isolated yield.

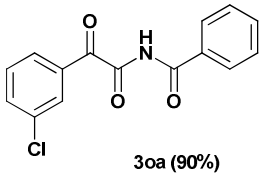
Delighted with these inspiring results we next focused our attention on C-H functionalization of ethylene arenes (**4**) and their subsequent oxidative coupling with benzamidines hydrochloride (**2**). With the optimal conditions in hand, the scope of the imidation was investigated. The reaction of styrene (**4a**) with benzamidine hydrochloride (**2a**), catalyzed with I_2/TBHP gave the corresponding α-ketoimide (**3aa**, 90%) in excellent yield. To our pleasure, various substituents on the aryl ring such as (4-F, 3-Cl, 2,4-Cl, 2-Br, 4-Br) were compatible with reaction conditions and desired products (Table 3, **3na**, **3oa**, **3pa**, **3qa**, and **3ea**) were acquired in good to excellent yields (81-88%). Further 2-ethylenenaphthalene and 3-ethylene-2*H*-benzopyran-2-one also offered the desired products (**3ka**, **3la,** Table 3) in 89 and 87% yield respectively. Then the range of various substituted benzamidines hydrochloride was screened. It was found that the 4-CH_3, 4-NO_2 and 4-OMe substituted benzamidines hydrochloride reacted smoothly to form the

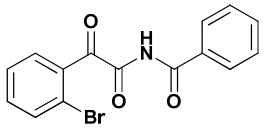
corresponding oxidative coupling products (**3ab**-**3ad,** Table-3) in good yields (82-85%). The above results indicate that the steric and electronic nature of the ethylene arenes have little influence on the reaction efficiency.

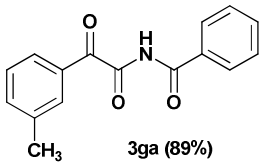
Table 4. I_2/TBHP catalyzed synthesis of α-ketoimides from ethyne arenes and benzamidines hydrochloride[a,b]

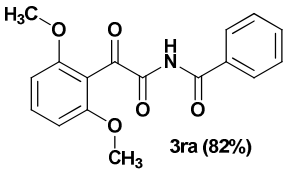


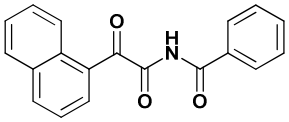

3aa (92%)

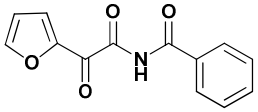

3oa (90%)

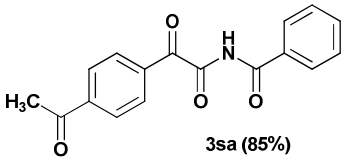

3qa (84%)

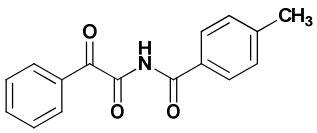

3ga (89%)

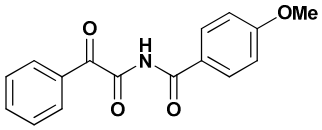

3ra (82%)

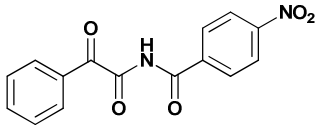

3ja (90%)


3ma (86%)


3sa (85%)


3ab (87%)

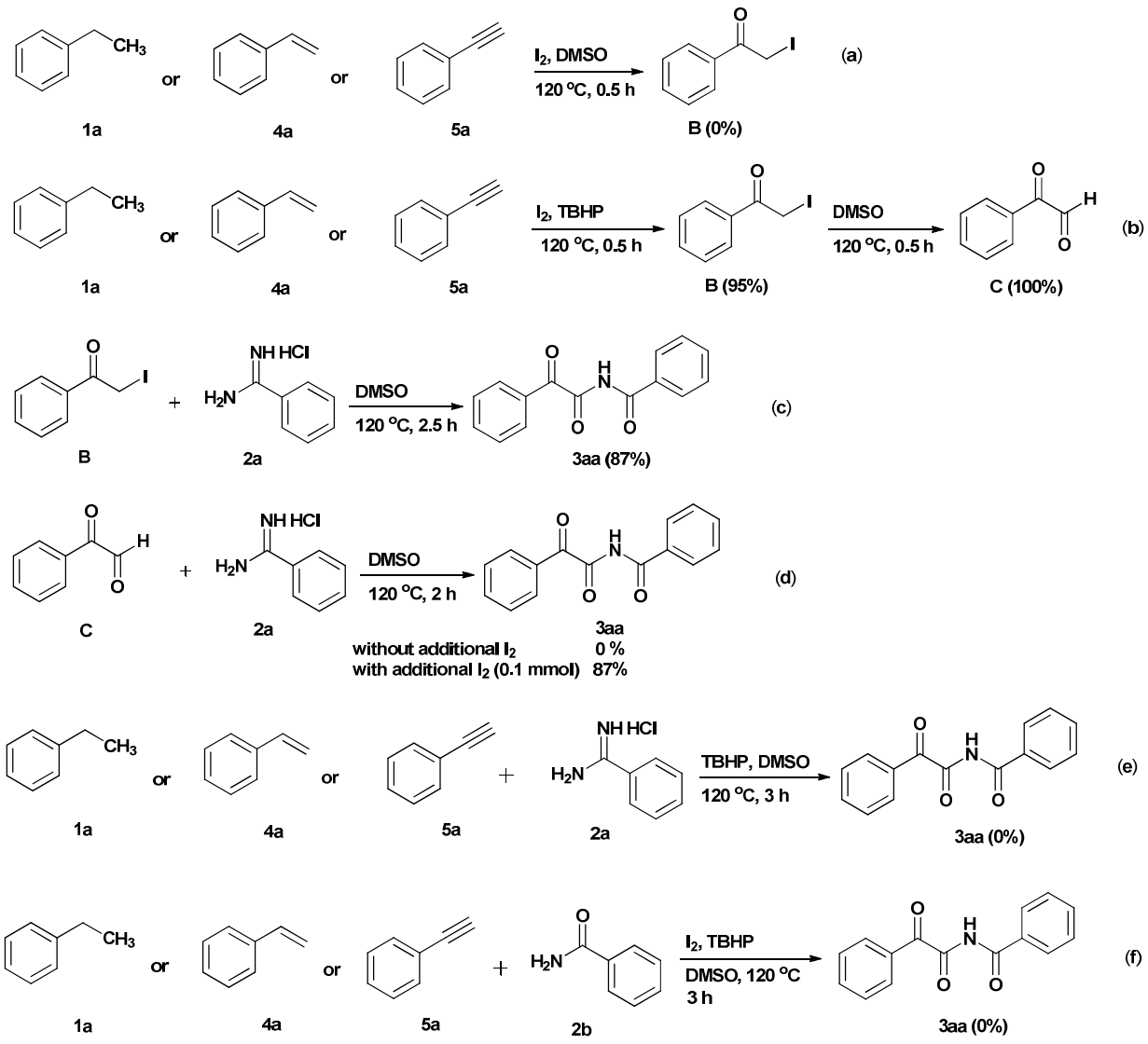

3ac (85%)


3ad (83%)

[a]Reaction conditions: **1** (1.0 mmol), I_2 (0.2 mmol), and TBHP (3.0 mmol) was heated in sealed tube at 120 °C for 1.0 h, **2** (1.0 mmol) in DMSO (3.0 mL) was added and heating continued for 2 h. [b]Isolated yield.

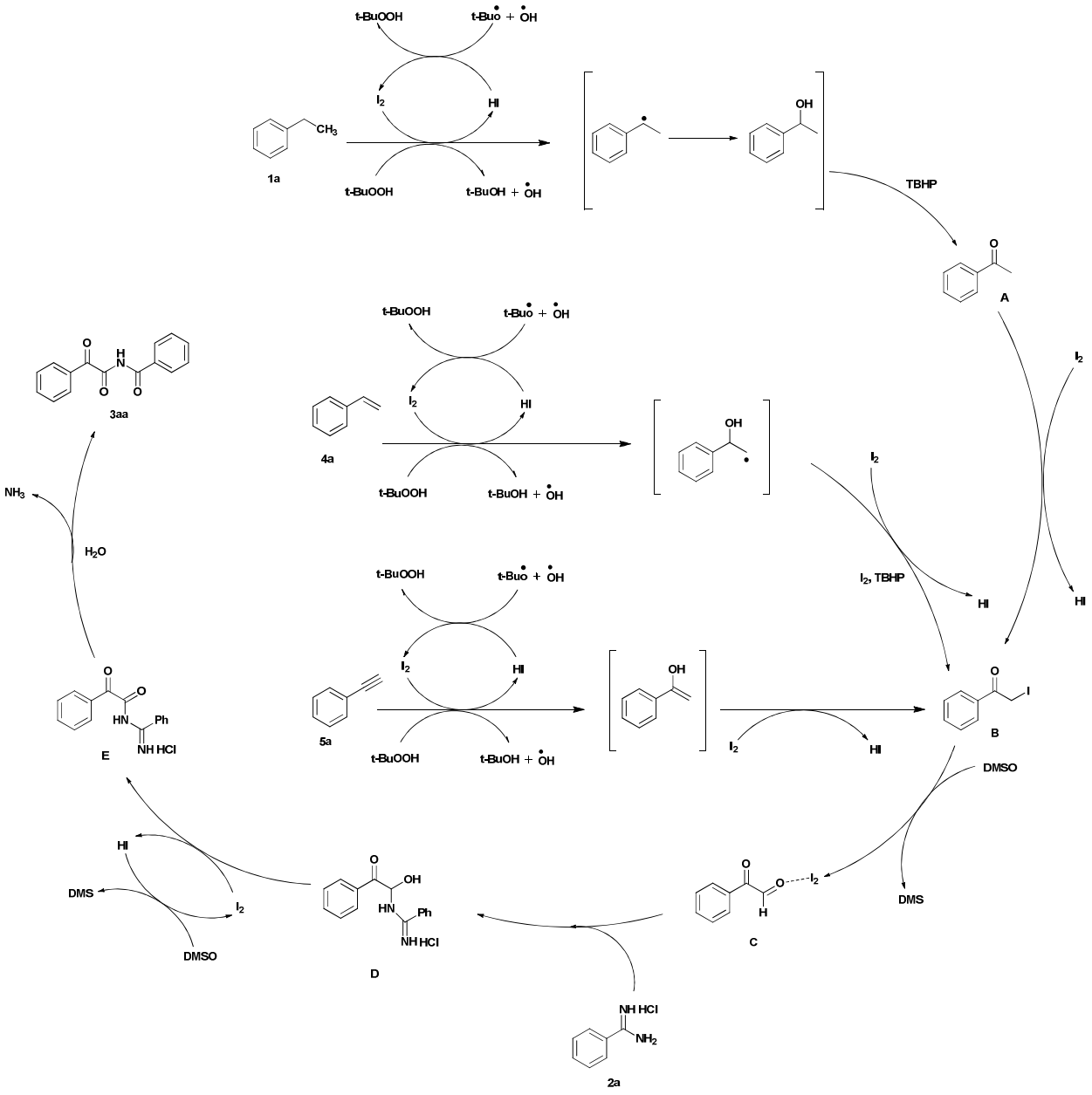
With all these results of ethyl arenes (**1**) and ethylene arenes (**4**) in hand, we intended to observe the outcome of the reaction of ethynyl arenes (**5**) with benzamidines hydrochloride (**2**). Thus, phenylacetylene (**5a**) was first treated with benzamidine hydrochloride (**2a**) to give the N-(2-oxo-2-phenylacetyl)benzamide **3aa** in excellent yield (Table 4, 92%). We then studied the effect of various functional groups onto the oxidative imidation reaction. We found that methyl, methoxy, and halogen groups were compatible with the reaction conditions and afforded the corresponding imides (Table 4, **3ga**, **3ra**, **3oa**, and **3qa**) in good to excellent yields (82-90%). The reaction of 1-ethynylnaphthalene with benzamidine hydrochloride (**2a**) gave the corresponding product in excellent yield (**3ja**, Table-4, 90%). Intriguingly, 4-ethynyl furan reacted smoothly to give N-(2-(furan-2-yl)-2-oxoacetyl)benzamide (**3ma**, Table 4) in 86% yield. Interestingly, the reaction of 4-ethylphenylacetylene selectively gave the N-(2-(4-acetylphenyl)-2-oxoacetyl)benzamide (**3sa**, Table-4, 85%) under optimal condition as the reactivity of acetylene is higher than that of ethyl. Benzamidines hydrochloride bearing 4-CH_3, 4-NO_2 and 4-OMe groups reacted smoothly to form the corresponding products (**3ab-3ad**, Table 4) in 83-87% yield.

A few control experiments (Scheme 2) were performed in order to affirm our proposed mechanism. To prove the involvement of TBHP in the formation of phenacyl iodide (**B**), a key intermediate, we treated ethylbenzene (**1a**), or styrene (**4a**), or phenylacetylene (**5a**) with I_2 and DMSO. The reaction failed to produce phenacyl iodide (**B**) thereby implying the crucial role played by TBHP in its formation, through radical intermediates (Scheme 2a). When substrates (**1a**, **4a**, and **5a**) was treated with I_2/TBHP successive formation of acetophenone, Phenacyl iodide (**B**) was observed and then treatment with DMSO gives phenyl glyoxal (**C**). Thus proving the requirement of TBHP as an oxidant, and DMSO as an co-oxidant (Scheme 2b). Phenacyl iodide (**B**) reacted with benzamidine hydrochloride (**2a**) in DMSO forming α-ketoimide (**3aa**) exclusively (Scheme 2c). In the presence of additional iodine, phenylglyoxal (**C**) was reacted with **2a** and afford the oxidative coupling product **3aa** in 87% yield (Scheme 2d). These results clearly confirmed that the phenacyl iodine (**B**) and phenylglyoxal (**C**) was the intermediate in this transformation. However, this reaction cannot be performed smoothly in the absence of I_2 (Scheme 2d and 2e). This clearly highlights the significant role of I_2 in C-H functionalization. α-Ketoimide (**3aa**) was not formed when the substrates (**1a**, **4a**, and **5a**) were reacted with benzamide (**2b**) under optimum condition (Scheme 2f). The results showed that benzamidine hydrochloride (**2a**) may be reacted with phenyl glyoxal (**B**) generated in situ from the diverse substrates (**1a**, **4a**, and **5a**) first and then underwent hydrolysis to obtain the target product.



Scheme 2. Control experiment

In context of control experiment the plausible mechanism for multiple C-H activation followed by oxidative cross-coupling is depicted in Scheme 3. In the beginning reaction presumably proceeded via formation of benzylic radical of ethylbenzene and then 1-phenyl ethanol using I_2/TBHP, which eventually were oxidized to acetophenone (**A**). This was confirmed by using TLC, GC-MS and ^{1}H-NMR. Acetophenone (**A**) on iodination offered α-iodo acetophenone (**B**), a key intermediate, which was also obtained from styrene (**4a**) and phenylacetylene (**5a**) using I_2/TBHP. This α-iodo acetophenone (**B**) was further transformed to aryl glyoxal (**C**) through Kornblum oxidation which on reaction with benzamidine hydrochloride (**2a**) followed by sequential oxidation and hydrolysis furnished the α-ketoimide (**3aa**).



Scheme 3. Plausible reaction mechanism

General methods

Chemical reagents were obtained from commercial suppliers and used without further purification. All reactions were performed in sealed tube and monitored by TLC performed on aluminum plates (0.25 mm, E. Merck) precoated with silica gel Merck 60 F-254. Reactions were conducted under atmospheric condition in anhydrous solvents such as DMSO, DMF, 1,4-

dioxane, THF and toluene. Developed TLC plates were visualized under a short-wavelength UV lamp. Yields refer to spectroscopically (^{1}H, ^{13}C NMR) homogeneous material obtained after column chromatography. Column chromatography was performed on silica gel (100:200 mesh size) supplied by S. D. Fine Chemicals Limited, India. IR spectra were recorded on a JASCO–FT/IR-4100 LE with attenuated total reflection (ATR) method. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solution with a Brüker 300, 400 and Agilent/Brüker 500 MHz spectrometers. Chemical shifts (δ) are reported relative to $SiMe_4$ (δ = 0.0) as an internal standard. The number of protons (n) for a given resonance is indicated by nH. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet; ddd, doublet of doublet of doublet; tt, triplet of triplet; br, broad; *J*, coupling constant in Hz. ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solution with a Brüker 75, 100 and Agilent/Brüker 125 MHz spectrometers and resonances are given in ppm. High-resolution mass spectra were obtained by using positive electronspray ionization (ESI) by Time of Flight (TOF) method.

General experimental procedure for the synthesis of α-ketoimides:

A sealed tube equipped with a magnetic stirrer bar was charged with ethyl arenes (**1**) or ethylene arenes (**4**) or ethyne arenes (**5**) (1.0 mmol), I_2 (0.20 mmol), *tert*-butyl hydroperoxide (TBHP, 3.0 mmol, 70% aq. solution). The reaction vessel was carried out at 120 ^{o}C for 1 h. After disappearance of the reactant monitored by TLC, benzamidines hydrochloride (**2**) in DMSO (3 mL) was added to the above reaction mixture at R. T. and heated for 2 h. After completion, the reaction mass was quenched with 10% aq. $Na_2S_2O_3$ solution (20 mL) and extracted with EtOAc (3 x 30 mL). The above organic layer was washed with brine solution (1 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane:ethyl acetate (75:25) as eluent to afford desired products **3**.

Characterization data of compounds 3aa-3sa and 3ab-3ad

N-(2-oxo-2-phenylacetyl)benzamide (**3aa**): light yellow solid; mp 138–140 ℃; **IR (ATR)** ṽ (cm^{-1}): 3445, 3288, 1723, 1684, 1596, 1346, 1210, 761, 714; **^{1}H NMR** ($CDCl_3$, 400 MHz, ppm): δ = 9.86 (bs, 1H), 8.13 (d, *J* = 7.2 Hz, 2H), 7.92 (d, *J* = 7.6 Hz, 2H), 7.62–7.69 (q, *J* = 7.6 Hz, 2H), 7.50-7.55 (m, 4H); **^{13}C NMR** ($CDCl_3$, 75 MHz, ppm): δ = 186.62, 165.31, 134.71, 134.00, 132.40, 131.06, 130.17, 129.14, 128.95, 128.13; **HRMS** (ESI): calc. for [($C_{15}H_{11}NO_3$)H] [M+H]$^+$ 254.0817, found 254.0822.

N-(2-(4-nitrophenyl)-2-oxoacetyl)benzamide (**3ba**): Yellow solid; mp 80–82 ^{o}C; **IR (ATR)** ṽ (cm^{-1}): : 3256, 1718, 1693, 1675, 1530, 1342, 1205, 765, 718; **^{1}H NMR** (DMSO-d_6, 300 MHz, ppm): δ = 12.10 (bs, 1H), 8.40 (d, *J* = 8.7 Hz, 2H), 8.20 (d, *J* = 8.7 Hz, 2H), 7.86 (t, *J* = 6.9, 1.5 Hz, 2H), 7.43-7.55 (m, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz, ppm): δ = 185.21, 170.09, 168.21, 150.56, 136.04, 133.51, 131.42, 130.08, 128.40, 127.16, 123.15; **HRMS** (ESI): calc. for [($C_{15}H_{10}N_2O_5$)H] [M+H]$^+$ 299.0668, found 299.0673.

N-(2-(2-nitrophenyl)-2-oxoacetyl)benzamide (**3ca**): Yellow solid; mp 76–78 ^{o}C; **IR (ATR)** ṽ (cm^{-1}): 3251, 1719, 1692, 1671, 1526, 1349, 1208, 746; **^{1}H NMR** (DMSO-d_6, 300 MHz, ppm): δ = 12.17 (bs, 1H), 8.38-8.41 (dd, *J* = 8.1, 1.0 Hz, 1H), 8.10-8.17 (ddd, *J* = 8.1, 7.8, 1.5, 1.0 Hz, 2H), 7.96-8.00 (m, 2H), 7.85-7.90 (m, 2H), 7.48-7.54 (distorted dd, *J* = 7.8, 6.9 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz, ppm): δ = 184.43, 170.52, 165.57, 148.61, 136.21, 134.66, 132.82, 131.67, 131.26, 128.79, 128.59, 124.89, 123.61; **HRMS** (ESI): calc. for [($C_{15}H_{10}N_2O_5$)H] $[M+H]^+$ 299.0668, found 299.0673.

N-(2-(4-chlorophenyl)-2-oxoacetyl)benzamide (**3da**): Yellow solid; mp 72–74 ℃; **IR (ATR)** ṽ (cm^{-1}): 3447, 1695, 1590, 1421, 1214, 1091, 693; **^{1}H NMR** ($CDCl_3$, 300 MHz, ppm): δ = 10.03 (bs, 1H), 8.07 (d, *J* = 8.1 Hz, 2H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.46-7.66 (m, 5H); **^{13}C NMR** ($CDCl_3$, 75 MHz, ppm): δ = 185.39, 169.31, 165.41, 141.47, 134.12, 131.50, 131.01, 130.90, 129.39, 129.17, 128.19; **HRMS** (ESI): calc. for [($C_{15}H_{10}ClNO_3$)H] $[M+H]^+$ 288.0427, found 288.0422.

N-(2-(4-bromophenyl)-2-oxoacetyl)benzamide (**3ea**): Yellow solid; mp 74–76 ^{o}C; **IR (ATR)** ṽ (cm^{-1}): 3444, 1695, 1585, 1219, 1071, 978, 695; **^{1}H NMR** ($CDCl_3$, 500 MHz, ppm): δ = 9.67 (bs, 1H), 8.03 (d, *J* = 7.0 Hz, 2H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.65-7.69 (distorted dd, *J* = 8.0, 5.5 Hz, 3H), 7.53 (t, *J* = 5.5 Hz, 2H); **^{13}C NMR** (DMSO-d_6, 75 MHz, ppm): δ = 186.55, 170.64, 167.39, 134.03, 132.34, 131.66, 131.44, 131.25, 130.70, 130.21, 128.78; **HRMS** (ESI): calc. for [($C_{15}H_{10}BrNO_3$)H] $[M+H]^+$ 331.9922, found 331.9926.

N-(2-oxo-2-(o-tolyl)acetyl)benzamide (**3fa**): White solid; mp 152–154 ^{o}C; **IR (ATR)** ṽ (cm^{-1}): 3445, 3290, 1712, 1692, 1675, 1602, 1341, 1242, 1218, 742; **^{1}H NMR** ($CDCl_3$, 500 MHz, ppm): δ = 9.74 (bs, 1H), 7.81 (d, *J* = 6.0 Hz, 4H), 7.54 (distorted t, *J* = 7.0, 6.0 Hz, 1H), 7.46 (distorted t, *J* = 7.0, 6.0 Hz, 4H), 2.42 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz, ppm): δ = 186.82, 168.89, 165.91, 141.61, 134.66, 134.60, 134.01, 132.76, 130.79, 129.05, 128.18, 127.69, 123.21, 21.41; **HRMS** (ESI): calc. for [($C_{16}H_{13}NO_3$)H] $[M+H]^+$ 268.0973, found 268.0976.

N-(2-oxo-2-(m-tolyl)acetyl)benzamide (**3ga**): White solid; mp 164–166 ^{o}C; **IR (ATR)** ṽ (cm^{-1}): 3447, 3287, 1715, 1697, 1680, 1608, 1344, 1247, 1222, 751; **^{1}H NMR** ($CDCl_3$, 500 MHz, ppm): δ = 9.57(bs, 1H), 8.09 (s, 1H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 7.0 Hz, 2H), 7.61-7.66 (distorted dd, *J* = 8.0 Hz, 2H), 7.52 (distorted t, *J* = 7.0 Hz, 2H), 7.46 (distorted t, *J* = 7.5, 7.0 Hz, 1H), 2.33 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz, ppm): δ = 186.03, 170.92, 166.31, 148.89, 135.80, 134.13, 132.65, 131.31, 129.30, 128.94, 128.36, 128.28, 127.74, 21.44; **HRMS** (ESI): calc. for [($C_{16}H_{13}NO_3$)H] $[M+H]^+$ 268.0973, found 268.0978.

N-(2-oxo-2-(p-tolyl)acetyl)benzamide (**3ha**): White solid; mp 156–158 ^{o}C; **IR (ATR)** ṽ (cm^{-1}): 3450, 3292, 1720, 1685, 1675, 1612, 1352, 1254, 1226, 749; **^{1}H NMR** ($CDCl_3$, 500 MHz, ppm): δ = 9.70 (bs, 1H), 8.09 (d, *J* = 8.0 Hz, 2H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.64 (t, *J* = 7.5, 7.0 Hz, 1H), 7.52 (t, *J* = 8.0, 7.5 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3H); **^{13}C NMR** (DMSO-d_6, 75

MHz, ppm): δ = 187.25, 171.07, 167.09, 145.00, 133.90, 130.44, 129.97, 129.68, 128.97, 128.75, 21.29; **HRMS** (ESI): calc. for $[(C_{16}H_{13}NO_3)H]$ $[M+H]^+$ 268.0973, found 268.0969.

N-(2-(4-methoxyphenyl)-2-oxoacetyl)benzamide (**3ia**): Off white solid, mp 158–160 °C; **IR (ATR)** ṽ (cm^{-1}): 3448, 3295, 1718, 1691, 1675, 1604, 1269, 1152, 738; **^{1}H NMR** ($CDCl_3$, 400 MHz, ppm): δ = 10.13 (bs, 1H), 8.23 (d, *J* = 4.4 Hz, 2H), 8.07 (d, *J* = 5.6 Hz, 1H), 7.93 (s, 2H), 7.64 (s, 1H), 7.52 (s, 1H), 6.99 (distorted t, *J* = 7.6, 6.4 Hz, 2H), 3.90 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz, ppm): δ = 184.58, 165.11, 164.04, 133.79, 133.22, 132.35, 129.10, 128.07, 125.34, 114.36, 113.77, 55.66; **HRMS** (ESI): calc. for $[(C_{16}H_{13}NO_4)H]$ $[M+H]^+$ 284.0923, found 284.0919.

N-(2-(naphthalen-1-yl)-2-oxoacetyl)benzamide (**3ja**): Light yellow solid; mp 74-76 °C; **IR (ATR)** ṽ (cm^{-1}): 3442, 3281, 1715,1681, 1645, 1397, 1318, 1219, 768, 695; **^{1}H NMR** ($CDCl_3$, 400 MHz, ppm): δ = 9.79(s, 1H), 9.12 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 2H), 7.93 (distorted t, *J* = 7.2 Hz, 3H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.48-7.65(m, 5H); **^{13}C NMR** ($CDCl_3$, 100 MHz, ppm): δ = 188.69, 172.43, 165.23, 135.54, 134.11, 133.96, 133.60, 131.29, 131.08, 129.18, 129.14, 128.72, 128.10, 127.98, 126.99, 125.86, 124.31; **HRMS** (ESI): calc. for $[(C_{19}H_{13}NO_3)H]$ $[M+H]^+$ 304.0973, found 304.0967.

N-(2-(naphthalen-2-yl)-2-oxoacetyl)benzamide (**3ka**): Light yellow solid; mp 184-186 °C; **IR (ATR)** ṽ (cm^{-1}): 3448, 1715, 1684, 1627, 1465, 1251, 710; **^{1}H NMR** ($CDCl_3$, 400 MHz, ppm): δ = 9.84(s, 1H), 8.82 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.89-8.00 (m, 5H), 7.51-7.65 (m, 5H); **^{13}C NMR** ($CDCl_3$, 100 MHz, ppm): δ = 186.46, 165.25, 136.53, 134.09, 134.03, 132.59, 131.50, 130.31, 129.82, 129.69, 129.31, 129.15, 128.20, 128.06, 127.26, 124.50; **HRMS** (ESI): calc. for $[(C_{19}H_{13}NO_3)H]$ $[M+H]^+$ 304.0973, found 304.0969.

N-(2-oxo-2-(2-oxo-2*H*-chromen-3-yl)acetyl)benzamide (3la): Yellow solid; mp 216-218 °C; **IR (ATR)** ṽ (cm^{-1}): 3262, 1725, 1708, 1671, 1602, 1563, 1252, 956, 760; **^{1}H NMR** (DMSO-d_6, 400 MHz, ppm): δ = 12.39 (s, 1H), 9.07 (s, 1H), 8.03–8.10 (dd, *J* = 8.0, 7.6 Hz, 3H), 7.84 (t, *J* = 7.6 Hz, 1H), 7.72 (t, *J* = 7.6, 7.2 Hz, 1H) 7.49-7.59 (m, 4H); **^{13}C NMR** (DMSO-d_6, 100 MHz, ppm): δ = 182.73, 170.16, 167.93, 158.83, 154.80, 148.65, 135.56, 134.00, 131.46, 130.10, 128.84, 128.64, 125.44, 119.93, 118.11, 116.54; **HRMS** (ESI): calc. for $[(C_{18}H_{11}NO_5)Na]$ $[M+Na]^+$ 344.0534 found 344.0537.

N-(2-(furan-2-yl)-2-oxoacetyl)benzamide (3ma): Off white solid; mp 154-156 °C; **IR (ATR)** ṽ (cm^{-1}): 3241, 1723, 1652, 1465, 1411, 1351, 1273, 773; **^{1}H NMR** ($CDCl_3$, 400 MHz, ppm): δ = 10.01 (s, 1H), 8.55 (t, *J* = 3.6, 3.2 Hz, 1H), 8.24 (d, *J* = 3.2 Hz, 1H), 8.20 (s, 1H), 7.82 (s, 1H), 7.67 (s, 1H), 7.54 (distorted t, *J* = 3.2, 2.0 Hz, 2H), 7.48 (d, *J* = 3.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz, ppm): δ = 178.30, 164.39, 160.90, 157.59, 148.51, 137.24, 131.16, 128.71, 124.77, 113.27, 110.94; **HRMS** (ESI): calc. for $[(C_{13}H_9NO_4)Na]$ $[M+Na]^+$ 266.0429, found 266. 0430.

N-(2-(4-fluorophenyl)-2-oxoacetyl)benzamide (**3na**): Off white solid; mp 158-160 °C; **IR (ATR)** ṽ (cm^{-1}): 3438, 1694, 1589, 1423, 1214, 1085, 698; **^{1}H NMR** (DMSO-d_6, 300 MHz, ppm): δ = 12.48 (s, 1H), 7.98-8.05 (m, 4H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.55 (t, *J* = 7.8, 7.5 Hz, 2H), 7.44 (t, *J* = 8.7 Hz, 2H); **^{13}C NMR** (DMSO-d_6, 75 MHz, ppm): δ = 186.16, 170.84, 167.34, 165.55 (d, J_F = 252.3 Hz), 134.00, 132.00 (d, J_F = 9.75 Hz), 130.36, 129.20 (d, J_F = 2.8 Hz),

128.83, 128.80, 116.45 (d, J_F = 22.3 Hz); **HRMS** (ESI): calc. for $[(C_{15}H_{10}FNO_3)H]$ $[M+H]^+$ 272.0723, found 272.0729.

N-(2-(3-chlorophenyl)-2-oxoacetyl)benzamide (**3oa**): Light white solid, mp 74-76 ^oC; **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3445, 3275, 1713, 1694, 1678, 1513, 1238, 768; **^{1}H NMR** ($CDCl_3$, 500 MHz, ppm): δ = 9.59 (bs, 1H), 8.11 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.63-7.68 (distorted dd, *J* = 8.5 Hz, 2H), 7.54 (distorted t, *J* = 7.0, 6.5 Hz, 2H), 7.48 (distorted t, *J* = 7.5 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz, ppm): δ = 185.08, 170.85, 169.35, 134.62, 133.38, 132.80, 132.45, 130.16, 129.75, 128.75, 128.18, 127.44, 125.50; **HRMS** (ESI): calc. for $[(C_{15}H_{10}ClNO_3)H]$ $[M+H]^+$ 288.0427 found 288.0423.

N-(2-(2,4-dichlorophenyl)-2-oxoacetyl)benzamide (**3pa**): Yellow solid; mp 78-80 ^oC; **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3451, 3279, 1717, 1687, 1673, 1509, 1244, 759; **^{1}H NMR** (DMSO-d_6, 300 MHz, ppm): δ = 12.55 (s, 1H), 8.07 (t, *J* = 9.0, 8.4 Hz, 2H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.86 (s, 1H), 7.66-7.75 (distorted q, *J* = 9.6, 8.7, 6.9 Hz, 2H), 7.60 (distorted t, *J* = 6.9 Hz, 2H); **^{13}C NMR** (DMSO-d_6, 75 MHz, ppm): δ = 183.93, 170.40, 167.75, 139.68, 134.92, 134.16, 133.40, 130.82, 130.16, 129.35, 128.92, 128.80, 128.36; **HRMS** (ESI): calc. for $[(C_{15}H_9Cl_2NO_3)H]$ $[M+H]^+$ 322.0037, found 322.0035.

N-(2-(2-bromophenyl)-2-oxoacetyl)benzamide (**3qa**): Yellow solid; mp 70-72 ^oC; **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3456, 3274, 1719, 1688, 1587, 1211, 747; **^{1}H NMR** ($CDCl_3$, 400 MHz, ppm): δ = 10.13 (s, 1H), 7.91-8.02 (distorted ddd, *J* = 7.6, 6.8 Hz, 2H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.58-7.64 (distorted q, *J* = 7.2 Hz, 1H), 7.43-7.52 (m, 5H); **^{13}C NMR** ($CDCl_3$, 100 MHz, ppm): δ = 186.50, 168.73, 165.71, 137.10 134.56, 134.32, 134.05, 132.82, 130.87, 129.10, 128.25, 127.62, 123.12; **HRMS** (ESI): calc. for $[(C_{15}H_{10}BrNO_3)H]$ $[M+H]^+$ 331.9922 found 331.9929.

N-(2-(2,6-dimethoxyphenyl)-2-oxoacetyl)benzamide (3ra): Light yellow solid, mp 124–126 ^oC; **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3448, 3287, 1708, 1677, 1655, 1602, 1252, 1160, 742; **^{1}H NMR** ($CDCl_3$, 400 MHz, ppm): δ = 10.05 (s, 1H), 7.96 (d, *J* = 6.8 Hz, 2H), 7.59 (t, *J* = 8.4, 6.8 Hz, 2H), 7.46 (d, *J* = 6.8 Hz, 2H), 7.17 (d, *J* = 7.2 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz, ppm): δ = 185.14, 170.92, 165.96, 154.92, 154.33, 133.84, 130.58, 129.04, 128.21, 124.11, 122.65, 114.40, 112.22, 56.75, 55.89; **HRMS** (ESI): calc. for $[(C_{17}H_{15}NO_5)H]$ $[M+H]^+$ 314.1028, found 314.1031.

N-(2-(4-acetylphenyl)-2-oxoacetyl)benzamide (3sa): Off white solid, mp 191-192 ^oC; **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3452, 3275, 1718, 1680, 1668, 1560, 1248, 1162, 784; **^{1}H NMR** ($CDCl_3$, 500 MHz, ppm): δ = 9.80 (bs, 1H), 8.16 (d, *J* = 7.5 Hz, 2H), 8.02 (d, *J* = 7.5 Hz, 2H), 7.78-7.82 (distorted dd, *J* = 7.0, 5.0 Hz, 3H), 7.66 (distorted t, *J* = 5.0 Hz, 1H), 2.67 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz, ppm): δ = 197.24, 186.91, 167.10, 165.33, 145.33, 134.85, 132.61, 130.30, 130.03, 129.12, 128.36, 27.28; **HRMS** (ESI): calc. for $[(C_{17}H_{13}NO_4)H]$ $[M+H]^+$ 296.0923, found 296.0927.

4-methyl-N-(2-oxo-2-phenylacetyl)benzamide (**3ab**): White solid; mp 148–150 ^{o}C; **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3352, 3288, 1719, 1681, 1674, 1518, 1256, 1228, 751; **^{1}H NMR** ($CDCl_3$, 500 MHz, ppm): δ = 9.76 (bs, 1H), 8.12 (d, *J* = 7.5 Hz, 2H), 7.80-7.81 (distorted dd, *J* = 8.0, 1.5 Hz, 2H), 7.66 (distorted tt, *J* = 7.5, 1.5 Hz, 1H), 7.53 (distorted tt, *J* = 7.5, 1.5 Hz, 2H), 7.30 (d, *J* = 7.5 Hz, 2H), 2.43 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz, ppm): δ = 186.85, 165.27, 145.27, 134.79, 132.55, 130.24, 129.97, 129.06, 128.30, 21.85; **HRMS** (ESI): calc. for $[(C_{16}H_{13}NO_3)H]$ $[M+H]^+$ 268.0973, found 268.0970.

4-methoxy-N-(2-oxo-2-phenylacetyl)benzamide (**3ac**): White solid; mp 162–164 ^{o}C; **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3260, 1721, 1685, 1675, 1585, 1254, 1226, 749; **^{1}H NMR** ($CDCl_3$, 500 MHz, ppm): δ = 9.83 (bs, 1H), 8.09 (d, *J* = 7.5 Hz, 2H), 7.89 (d, *J* = 9.0 Hz, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz, ppm): δ = 186.99, 164.80, 164.42, 134.70, 132.63, 130.58, 130.11, 129.06, 123.05, 114.55, 55.76; **HRMS** (ESI): calc. for $[(C_{16}H_{13}NO_4)H]$ $[M+H]^+$ 284.0923, found 284.0925.

4-nitro-N-(2-oxo-2-phenylacetyl)benzamide (**3ad**): Light yellow solid; mp 188–190 ^{o}C; **IR (ATR)** $\tilde{\nu}$ (cm^{-1}): 3336, 3250, 1736, 1680, 1515, 1356, 1208, 1168, 768, 720; **^{1}H NMR** ($CDCl_3$, 500 MHz, ppm): δ = 9.54 (bs, 1H), 8.38 (d, *J* = 9.0 Hz, 2H), 8.28 (d, *J* = 8.5 Hz, 2H), 7.89 (d, *J* = 7.0 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 8.0, 7.5 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz, ppm): δ = 186.27, 170.20, 165.57, 151.62, 137.10, 136.20, 134.57, 131.14, 129.46, 128.22, 124.21; **HRMS** (ESI): calc. for $[(C_{15}H_{10}N_2O_5)H]$ $[M+H]^+$ 299.0668, found 299.0671.

Conclusion:

In summary, an iodine catalyzed operationally simple synthetic protocol for formation of α-ketoimide from diverse substrates in presence of TBHP has been developed. We strongly believe that this functional group tolerant metal-free tandem synthetic approach would be useful for the synthesis of complex molecules in the field of pharmaceuticals and materials.

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Author Contributions:

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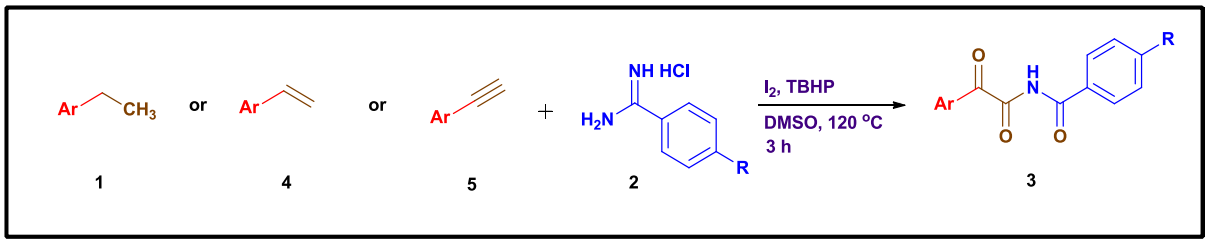
Graphical abstract

Metal-Free in Situ sp^3, sp^2, and sp C-H Functionalization and Oxidative Cross Coupling with Benzamidines Hydrochloride: A Promising Approach for the Synthesis of α-Ketoimides



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