



## C-H Functionalization and C-N Bond Formation Approaches under Catalytic Conditions for the Synthesis of $\alpha$ -Ketoamides and 2,4-Disubstituted-1,3,5-triazines

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This work describes an easy way to perform approach for the transformation of arylmethyl ketones to  $\alpha$ -ketoamides using secondary amines as starting materials in the presence of iodine as a catalyst in water under peroxide free reaction conditions. The established amidation reaction proceeds via  $\alpha$ -C(sp<sup>3</sup>)-H functionalization and C-N bond formation approaches in water at ambient temperature. On the other hand, a novel and straightforward synthesis of 2,4-disubstituted-1,3,5-triazines via nickel-catalyzed cyclization of amidines with DMSO as one-carbon synthon has been developed. The developed strategy proceeds via C-N bond formation.

**Keywords:** C-N bond formation, Amidation, Iodine-catalyzed, C1-synthon, 1,3,5-Triazines.

### INTRODUCTION

The  $\alpha$ -ketoamides serve as an integral component of magnificent series of naturally occurring, drugs and biologically valued molecules, which exhibit enormous avenues for conversion of functional moieties into useful pharmacophores [1-11]. These structural motifs are enormously witnessed in a sequence of potent medicinal valued compound such as calpain inhibitor, FK 506, eurystatin, potent thrombin inhibitor and cyclotheonamide (Fig. 1) [12-17]. Due to the significant legacies related to these scaffolds in interdisciplinary research fields, the discovery of facile routes for their preparation remain as one of the active field of interest in synthetic organic chemistry. A great deal of synthetic molecules such as 1-arylethanol [18, 19], alkene derivatives [20,21], 2-oxo alcohols [22,23], acetophenone derivatives [24,25], ethylbenzene derivatives [26-28], 2-oxo aldehydes [29,30], alkyne compounds [31-33], aryl acetaldehydes [34] and 2-aryl ethanol [35], are employed rigorously toward findings of surrogate chemical transformations to avail the  $\alpha$ -ketoamides.

Literature survey displayed that in most of the demonstrated protocols, the preparation of  $\alpha$ -ketoamides has been achieved using metal [36-39] and non-metal [40-45] catalysts

and oxidants (**Scheme-I**). The metal-catalyzed transformations are normally executed under non-convenient reaction conditions; whereas, the metal-free reactions are conducted using overload of oxidizing agents. Hence, these major limitations related to the reported protocols restrict their wide spread opportunities in organic synthesis. Herein, we wish to report the effective preparation of  $\alpha$ -ketoamides in water as green solvent at ambient temperature using aryl-methyl-ketones as easy available substrates and the reactions proceed via I<sub>2</sub>-catalyzed C-N bond construction using C-H functionalization approach.

On the other hand, aryl-substituted 1,3,5-triazines are a prominent class of nitrogen-containing heterocycles with a wide range of biological applications [46-48]. These compounds could also be used as chelating ligands in the development of liquid crystals [49,50], organometallic materials [51,52] and transition metal catalysts [53,54]. In particular, broad-spectrum biological activities are found in heterocycles with three nitrogen atoms, such as 1,3,5-triazines [55] and 1,2,4-triazoles [56-58]. Fluconazole and voriconazole, for example, are two triazole antifungals that are commonly used in clinical settings [56]. The biological, physico-chemical and pharmacokinetic features of triazine have also been revealed to be promising (Fig. 2) [55]. Despite their diverse roles, only a few strategies

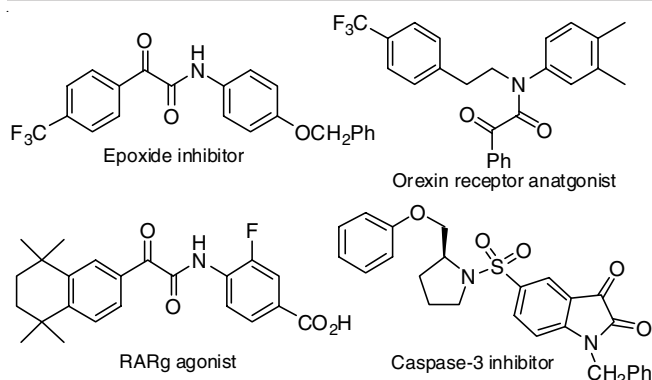
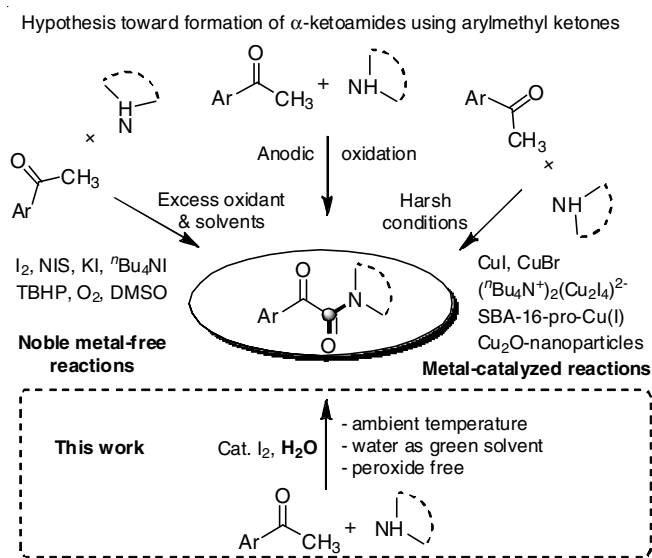
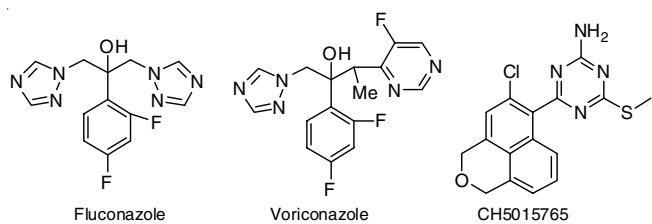
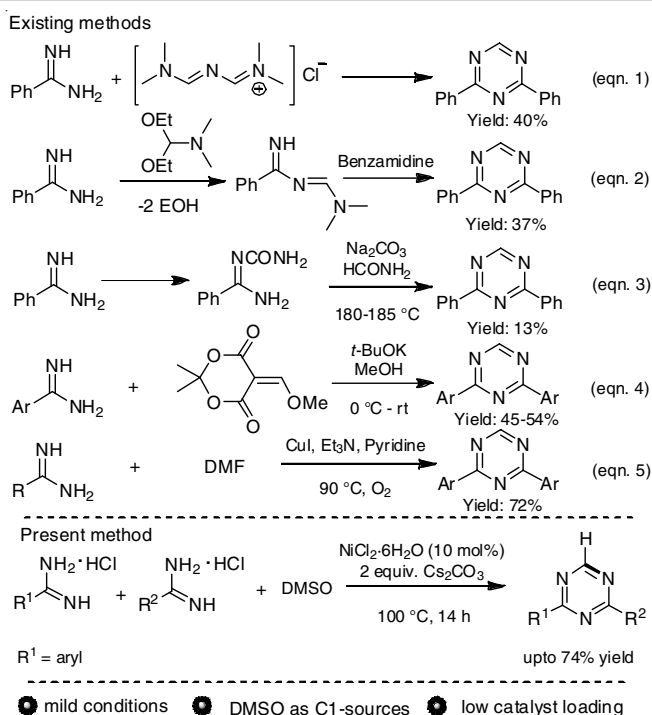
Fig. 1. Important bioactive scaffolds embedded with  $\alpha$ -ketoamide moietiesScheme-I: Hypothesis for the formation of  $\alpha$ -ketoamide moieties

Fig. 2. Important drug molecules embedded with nitrogen-containing heterocycle frameworks

for generating this class of molecule have been reported. Alternative approaches to obtain symmetrical 2,4,6-triaryl-1,3,5-triazines have received a lot of attention in past decades [59-63]. Nonetheless, the synthesis of 2,4-disubstituted-1,3,5-triazines remains to be a challenging goal. Classically, cyclization reactions of aryl amidines with special prefunctionalized formylating reagents such as diimino salt [64], *N*-[(dimethylamino)methylene]benzamidinium [65], *N*-carbamoyl benzamidinium [66] and  $\alpha$ -methoxymethylene Meldrum's acid [67], pyridine [68] have been used to achieve this goal (Scheme-II, eqns. 1-5). However, these methods suffer from either harsh reaction conditions, such as high temperatures (180-185 °C), hazardous reagents or relatively low yields. Furthermore, the pre-functionalization steps may increase the difficulty of the



Scheme-II: Hypothesis for methods accessing 2,4-disubstituted-1,3,5-triazines

workup method over time, resulting in a negative impact on the environment. As a consequence, it's essential in developing efficient approaches to making 2,4-disubstituted-1,3,5-triazines directly from readily available feedstock. Herein, a novel nickel catalyzed cyclization of amidines with DMSO, a one-carbon source, for the facile synthesis of 2,4-disubstituted-1,3,5-triazines (Scheme-II, eqn. 5) is presented. This methodology is an effective addition to the preceding synthesis, which delivers highly efficient access to a wide range of three nitrogen containing heterocycles.

## EXPERIMENTAL

All the reagents and starting materials were availed from the commercial suppliers (Alfa-Aesar, Sigma-Aldrich, Merck, S.D. Fine chemicals, HI Media) and employed without prior purification unless otherwise mentioned. Experiments were executed in 10 mL round bottom flask equipped with magnetic stirrer. Solvents utilized for extraction and purification purposes were thoroughly distilled prior to use. Thin-layer chromatography (TLC) was conducted on TLC plates purchased from Merck. Products were identified by soaking in  $\text{KMnO}_4$  staining solution followed by heating or with UV light ( $\lambda = 254 \text{ nm}$ ). The purified products were obtained by CombiFlash MPLC. All HRMS spectra were obtained using 6545 QTOF LC/MS, Agilent instrument equipped with an auto sampler in EI-QTOF method in acetonitrile solvent.  $^1\text{H}$  ( $^{13}\text{C}$ ) NMR spectra were obtained at 400 (100) MHz on a Bruker spectrometer employing  $\text{CDCl}_3$  as solvent. The  $^1\text{H}$  &  $^{13}\text{C}$  chemical shifts were referenced to residual solvent signals at  $\delta_{\text{H/C}} 7.26/77.28$  ( $\text{CDCl}_3$ ) relative to TMS as internal standards. Coupling constants  $J$  [Hz] were directly taken from the spectra and are not averaged.

**General experimental procedure for the synthesis of  $\alpha$ -ketoamide derivatives (3a-e):** A 10 mL reaction flask was

charged with the mixture of arylmethyl ketones **1a-e** (1.0 mmol), amines **2** (1.1 mmol),  $I_2$  (0.3 mmol) in  $H_2O$  (2 mL) and then the reaction mixture was stirred at 25 °C for 16 h under aerial conditions. After completion of the reaction (progress was monitored by TLC;  $SiO_2$ , hexane/EtOAc = 4:1), the reaction mixture was quenched with saturated sodium thiosulphate solution, diluted with water (20 mL) and extracted with ethyl acetate (3  $\times$  15 mL). The combined organic layer was dried over anhydrous  $Na_2SO_4$ . Solvent was removed under reduced pressure and the remaining residue was purified over silicagel column chromatography using hexane/EtOAc = 4:1 as an eluent to obtain the desired products **3a-e** in high yields.

**N,N-Diethyl-2-oxo-2-phenylacetamide (3a)** [36]: Yellow oil;  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  7.97-7.91 (m, 1H), 7.63 (t,  $J$  = 3.4 Hz, 1H), 7.55-7.42 (m, 2H), 3.57 (q,  $J$  = 7.2 Hz, 1H), 3.25 (q,  $J$  = 7.1 Hz, 1H), 1.34-1.24 (m, 2H), 1.21-1.11 (m, 1H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  190.9, 167.2, 133.7, 132.9, 128.8, 129.3, 41.7, 39.3, 13.8, 13.1; MS ( $m/z$ ): calculated 205.1  $[M]^+$ , found 206.1  $[M + 1]^+$ .

**1-Pyrrole-2-(4-methylphenyl)-1,2-dione (3b)**: White solid, m.p: 81-82 °C (Lit. [69]: 77-79 °C);  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  = 7.90 – 7.86 (m, 1H), 7.29 (d,  $J$  = 8.0 Hz, 1H), 3.65 (t, 1H), 3.41 (t,  $J$  = 6.5 Hz, 1H), 2.42 (s, 2H), 1.99 – 1.90 (m, 2H); MS ( $m/z$ ): calculated 217.1  $[M]^+$ , found 218.1  $[M + 1]^+$ .

**1-Pyrrole-2-(4-bromophenyl)-1,2-dione (3c)**: White solid, 68-70 °C (Lit. [69]: 67-69 °C);  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  7.89-7.86 (m, 1H), 7.66-7.63 (m, 1H), 3.64 (t, 1H), 3.43 (t, 1H), 1.98-1.93 (m, 2H); MS ( $m/z$ ): calculated 281.0  $[M]^+$ , found 282.0  $[M + 1]^+$ .

**1-Pyrrole-2-(4-chlorophenyl)-1,2-dione (3d)**: Yellow oily liquid,  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  7.99-7.93 (m, 1H), 7.51-7.43 (m, 1H), 3.64 (t, 1H), 3.44 (t, 1H), 1.99-1.92 (m, 2H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  189.6, 163.1, 140.7, 130.2, 130.5, 128.3, 45.5, 44.7, 24.8, 22.7; MS ( $m/z$ ): calculated 237.0  $[M]^+$ , found 238.0  $[M + 1]^+$ .

**1-Morpholino-2-(4-(trifluoromethyl)phenyl)ethane-1,2-dione (3e)**: Violet solid, m.p: 128-129 °C (Lit. [39] 127.3-127.5 °C);  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  8.09 (d,  $J$  = 8.1 Hz, 1H), 7.79 (d,  $J$  = 8.2 Hz, 1H), 3.84-3.78 (m, 2H), 3.70-3.66 (m, 1H), 3.43-3.38 (m, 1H); MS ( $m/z$ ): calculated 287.0  $[M]^+$ , found 288.0  $[M + 1]^+$ .

**General experimental procedure for the synthesis of 2,4-disubstituted-1,3,5-triazines (5)**: A 10 mL round bottom flask was charged with a mixture of amidine hydrochloride derivatives **4a-f** (1.0 mmol), nickel(II) chloride hexahydrate (0.1 mmol, 15.17 mg), cesium carbonate (2 mmol, 416 mg) and DMSO (1 mL). The round bottom flask was then heated at 100 °C for 14 h. After completion of the reaction (progress was monitored by TLC;  $SiO_2$ , hexane/EtOAc = 40:1), the mixture was diluted with ethyl acetate (15 mL) and water (20 mL) and extracted with ethyl acetate (3  $\times$  10 mL). The combined organic layers were washed with brine (3  $\times$  10 mL) and dried over anhydrous  $Na_2SO_4$ . The solvent were removed under reduced pressure and the crude products were purified by column chromatography using silica gel (100-200 mesh) with hexane/EtOAc (40:1) as the eluent to obtain the desired 2,4-disubstituted-1,3,5-triazines (**5**).

**2,4-Diphenyl-1,3,5-triazine (5a)** [70]: Yellow solid, yield: 80 mg (74%);  $R_f$  = 0.65 ( $SiO_2$ , hexane/EtOAc = 9:1); Purification system: column chromatography ( $SiO_2$ , 100-200) (hexane/EtOAc = 97:3);  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  9.27 (s, 1H; 6H), 8.65 (d,  $^3J$  = 8.0 Hz, 4H; 8H), 7.61 (tt,  $^3J$  = 7.9 Hz, 2H; 10-H), 7.55 (t,  $^3J$  = 7.9 Hz, 4H; 9H) ppm;  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  171.3 (C-2 and C-4), 166.7 (C-6), 133.5 (C-7), 132.8 (C-10), 128.9 (C-9), 128.7 (C-8) ppm; HRMS (EI-QTOF,  $[M + H]^+$ ): calculated for  $C_{15}H_{12}N_3$ : 234.1031; found: 234.1027.

**3,3'-(1,3,5-Triazine-2,4-diyl)dianiline (5b)**: Yellow solid, Yield: 71 mg (66%);  $R_f$  = 0.55 ( $SiO_2$ , hexane/EtOAc = 9:1); Purification system: Column chromatography ( $SiO_2$ , 100-200) (hexane/EtOAc = 95:5);  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  9.48 (t,  $^4J$  = 3.2 Hz 2H; 8H), 9.41 (s, 1H; 6H), 9.01 (d,  $^3J$  = 8.0 Hz, 2H; 12H), 7.8 (t,  $^3J$  = 8.0 Hz, 2H; 11H), 6.6 (d,  $^3J$  = 7.9 Hz, 2H; 10H) ppm; HRMS (EI-QTOF,  $[M + H]^+$ ): calculated for  $C_{15}H_{14}N_5$ : 264.1249; found: 264.1245.

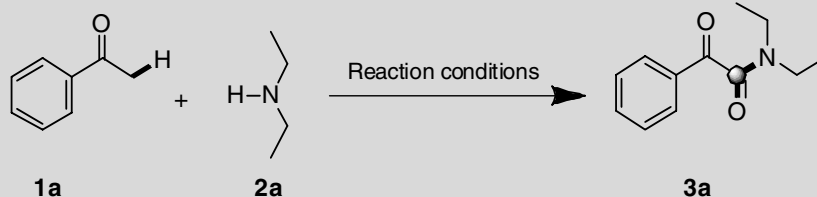
**2,4-bis(3-Fluoro-4-methylphenyl)-1,3,5-triazine (5c)**: Pale yellow solid, yield: 60 mg (54%);  $R_f$  = 0.65 ( $SiO_2$ , hexane/EtOAc = 9:1); Purification system: Column chromatography ( $SiO_2$ , 100-200) (hexane/EtOAc = 97:3);  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  9.21 (s, 1H; 6H), 8.31 (dd,  $^3J$  = 8.0 Hz, 2H; 12H), 8.25 (dd,  $^3J$  = 7.9 Hz, 2H; 11H), 7.34 (t,  $^3J$  = 7.9, 3.4 Hz, 2H; 8H), 2.39 (s, 6H; 13H) ppm; HRMS (EI-QTOF,  $[M + H]^+$ ): calculated for  $C_{17}H_{14}F_2N_3$ : 298.1155; found: 298.1151.

**2,4-bis(3-Nitrophenyl)-1,3,5-triazine (5d)**: Yellow solid, Yield: 70 mg (70%);  $R_f$  = 0.65 ( $SiO_2$ , hexane/EtOAc = 9:1); Purification system: Column chromatography ( $SiO_2$ , 100-200) (hexane/EtOAc = 97:3);  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  9.48 (t,  $^4J$  = 3.2 Hz, 2H; 8H), 9.41 (s, 1H; 6H), 9.01 (tt,  $^3J$  = 8.0 Hz, 2H; 12H), 8.5 (dt,  $^3J$  = 7.9 Hz, 2H; 10H), 7.8 (t,  $^3J$  = 7.9 Hz, 2H; 11H) ppm;  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  168.9 (C-2 and C-4), 166.3 (C-6), 147.9 (C-9), 135.9 (C-7), 133.5 (C-12), 129.0 (C-11), 126.4 (C-10), 122.9 (C-8) ppm; HRMS (EI-QTOF,  $[M + H]^+$ ): calculated for  $C_{15}H_{10}N_5O_4$ : 324.0732; found: 324.0728.

## RESULTS AND DISCUSSION

Previous reports and conditions employed for the synthesis of  $\alpha$ -ketoamides [1-45], we aspired to devise the novel conditions toward constructing  $\alpha$ -ketoamides. To serve this commitment, we have chosen easy available acetophenone (**1a**) and diethylamine (**2a**) as initial substances. To understand the reactivity, **1a** was reacted with **2a** in the presence of catalytic amounts of TBAI (30 mol%) and TBHP (2 equiv.) in DMSO at 70 °C for 12 h (Table-1, entry 1). Satisfyingly, it was viewed that the expected product **3a** has been generated in 34% yield as the outcome of this reaction. We wondered to realize that the transformation seized the product **3a** formation when TBAI is replaced with KI as catalyst (Table-1, entry 2). Next, we have introduced  $I_2$  as catalyst in the presence of TBHP as oxidant in DMSO at 70 °C for 16 h (Table-1, entry 3), which conveys the outcome with 45% yield of the product **3a**; whereas, the outcome remain unsatisfactory with 27% yield of the product **3a** (Table-1, entry 4). Next, we have conducted a transformation using **1a** and **2a** in the presence of 30 mol%  $I_2$  as catalyst in the presence of TBHP as oxidant in toluene as solvent at 70 °C for 16 h (Table-1,

TABLE-1  
OPTIMIZATION OF CONDITIONS FOR THE REACTION BETWEEN **1a** AND **2a**<sup>a</sup>



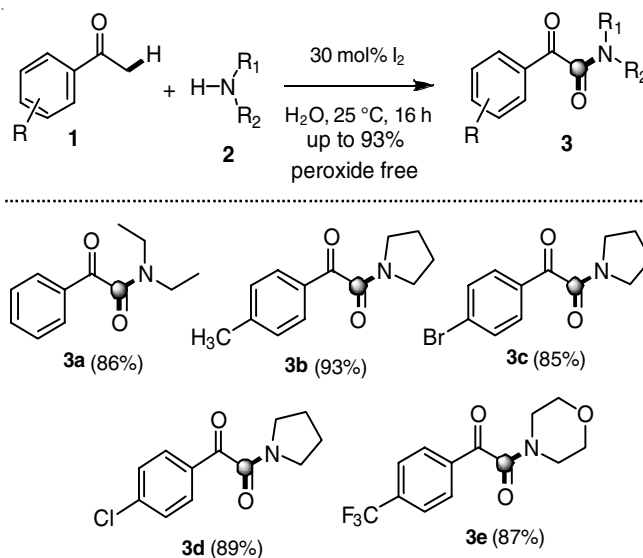
Entry	Catalyst (mol %)	Additive (equiv.)	Solvent	Temp. (°C)	Time (h)	<b>3a</b> <sup>b</sup> ; Yield (%)
1	TBAI (30)	TBHP (2)	DMSO	70	12	34
2	KI (30)	TBHP (2)	DMSO	70	16	–
3	I <sub>2</sub> (30)	TBHP (2)	DMSO	70	16	45
4	NIS (30)	TBHP (2)	DMSO	70	16	27
5	I <sub>2</sub> (30)	TBHP (2)	Toluene	70	16	26
6	I <sub>2</sub> (30)	TBHP (2)	THF	70	16	–
7	I <sub>2</sub> (30)	TBHP (2)	DCM	RT	16	31
8	I <sub>2</sub> (30)	TBHP (2)	EtOH	60	16	38
9	I <sub>2</sub> (30)	TBHP (2)	H <sub>2</sub> O	70	16	78
10	I <sub>2</sub> (30)	TBHP (2)	H <sub>2</sub> O	RT	16	84
11	I <sub>2</sub> (30)	–	H <sub>2</sub> O	RT	16	89
12	–	–	H <sub>2</sub> O	RT	16	–

<sup>a</sup>The reactions were executed using **1a** (1.0 mmol) and **2a** (1.1 mmol) in solvent (2 mL). <sup>b</sup>Isolated yields of the product **3a**.

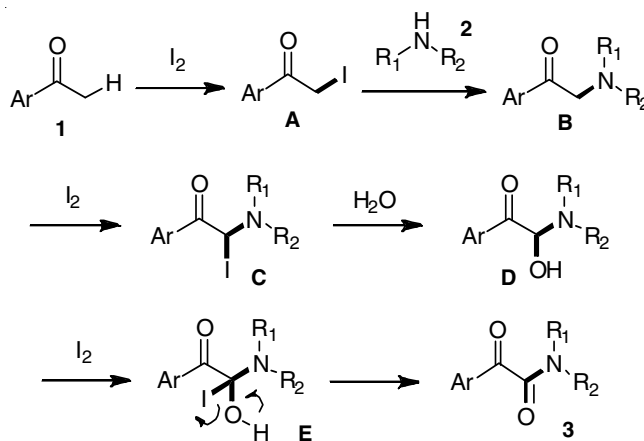
entry 5). It is recognized that the conditions were unable to synthesize the product **3a** in improved yields. Then, the outcome of this transformation was verified with different solvents such as tetrahydrofuran, dichloromethane, ethylalcohol and water (Table-1, entries 6-9). It was understood that among the solvents employed water has revealed the best outcome of this transformation. Then, the involvement and influences of peroxide such as TBHP and temperature of required for this transformation is examined (Table-1, entries 10-11). Fortunately, it has been found that the best yield of the product **3a** has been realized when the reaction was carried out in presence of 30 mol% I<sub>2</sub> as catalyst in water as solvent at 25 °C for 16 h (Table-1, entry 11), which issued 89% yield of the product **3a**. It has been also realized that in absence of I<sub>2</sub> as catalyst the reaction did not proceed toward obtaining of desired product **3a** (Table-1, entry 12). Therefore executing the detailed screening experiments, it is found that the conditions developed in Table-1, entry 11 displayed maximum efficiency for this reaction and chosen as standard conditions.

The obtained optimized conditions were then applied in an array of substrates in order to examine the utility of the best observed reaction conditions. In this directions, various substrates having electron donating group like methyl (-Me) and electron withdrawing functional groups like bromo (-Br), chloro (-Cl) and trifluoromethyl (-CF<sub>3</sub>) were exposed under the identified best conditions. The experimental results exhibited that irrespective of the substituents and electronic nature of the starting material ketones **1**, all the reactions proceeded easily with different amine components **2** to produce the products **3b-e** with high yields (**Scheme-III**).

The plausible reaction mechanism has also been formulated in **Scheme-IV** for the generation of  $\alpha$ -ketoamides under the influence of molecular iodine as catalyst in water at room temperature. It may be expected that in the first step the formation of  $\alpha$ -iodocarbonyl compound **A** may occur in the presence



**Scheme-III:** Synthesis of  $\alpha$ -ketoamides using established reaction conditions



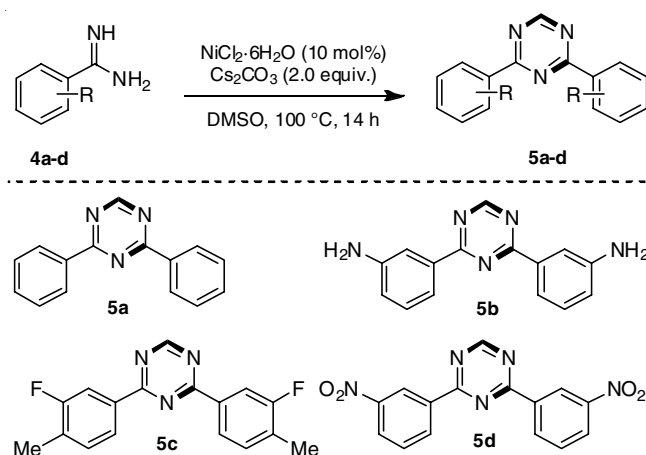
**Scheme-IV:** Plausible reaction for the formation of  $\alpha$ -ketoamides

of molecular iodine as catalyst, which after nucleophilic attack by amine derivative **2** delivers the  $\alpha$ -amino carbonyl derivative **B**. The  $\alpha$ -amino carbonyl derivative **B** in the presence of molecular iodine produces the  $\alpha$ -iodo carbonyl derivative **C**, which followed by hydrolysis, iodination at  $\alpha$ -position and cleavage of C-I bond generates the expected product  $\alpha$ -ketoamides **3**.

On the other hand, having analyzed the utility of 2,4-disubstituted-1,3,5-triazines and the reported methods for their preparation, we aimed to examine the best reaction conditions. For that purpose, benzamidine hydrochloride (**4a**) was selected as the suitable starting substrate. To start with, we have proceeded with a reaction of **4a** under the assistance of 10 mol% of  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  as catalyst in DMSO as solvent at 100 °C for 14 h (Table-2, entry 1), which showed that the starting substrates remain unreactive. Increasing the amounts of catalyst up to 20 mol% revealed same outcome (Table-2, entry 2); whereas, introducing a base such as 1 equiv. of  $\text{K}_3\text{PO}_4$  gives satisfactory results with the generation of 2,4-diphenyl-1,3,5-triazine (**5a**) in 35% yield (Table-2, entry 3). In next step, an ability of bases such as  $\text{K}_2\text{CO}_3$ , DABCO,  $\text{Cs}_2\text{CO}_3$  and pyridine were also examined (Table-2, entries 4-7). It has been recognized that the bases like  $\text{K}_2\text{CO}_3$  and  $\text{Cs}_2\text{CO}_3$  were efficient for the completion of this desired transformation with satisfactory outcome. However, the utilization of 2 equiv. of  $\text{Cs}_2\text{CO}_3$  under the influence of 10 mol%  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  as catalyst produced 74% of expected product **5a** (Table-2, entry 6). An increase in the amounts of  $\text{Cs}_2\text{CO}_3$  up to 3 equiv. and changing of solvents to DMA and DMF has no incremental benefits toward the outcome of this transformation (Table-2, entries 8-10). Further, it was also described that altering the reaction temperature and time, the yield of the assumed product **5a** has been dropped (Table-2, entries 11,12). Hence, the best suitable conditions were assumed when the reaction of **4a** was conducted employing 10 mol%  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  as catalyst, 1 equiv. of  $\text{Cs}_2\text{CO}_3$  as base in DMSO at 100 °C for

14 h (Table-2, entry 6) and these conditions were concluded as standard condition for this transformation.

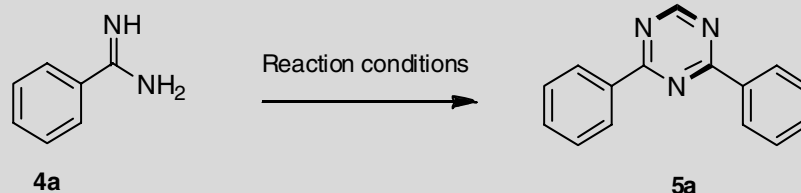
The standard conditions were then employed on various amidine derivatives **4** to realize the capacity of the developed conditions (**Scheme-V**). It has been demonstrated that the amidine derivatives embedded with amino ( $-\text{NH}_2$ ), methyl ( $-\text{Me}$ ), fluoro ( $-\text{F}$ ) and nitro ( $-\text{NO}_2$ ) groups were successfully endured under the standard conditions to obtain the desired 2,4-disubstituted-1,3,5-triazine molecules **5a-d** in good yields and functional group tolerance.



**Scheme-V:** Ni-catalyzed synthesis of 2,4-disubstituted-1,3,5-triazines

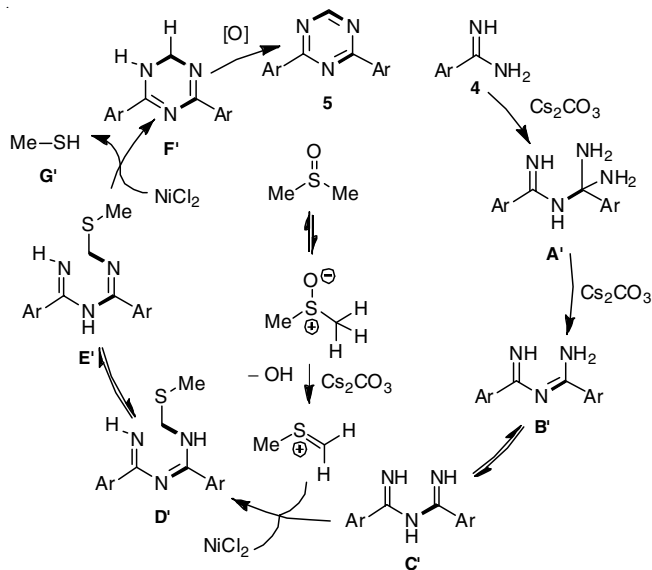
According to the proposed reaction mechanism (**Scheme-VI**), arylamidine **4** undergoes base-mediated self-condensation to form an intermediate **A'**, which upon deamination in presence of base provides a diamidine intermediate **B'**, which is in tautomerization with intermediate **C'**. The intermediate **C'** undergoes Ni-catalyzed C-N bond formation with Pummerer like intermediate ( $\text{MeSCH}_2^+$ ) which is *in situ* generated from

TABLE-2  
OPTIMIZATION OF CONDITIONS FOR THE REACTION OF **4a**<sup>a</sup>



Entry	Ni source (mol %)	Base (equiv.)	Solvent	Temp. (°C)	Time (h)	Yield <sup>b</sup> (%)
1	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ ; 20	No base	DMSO	100	14	–
2	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ ; 20	No base	DMSO	100	14	–
3	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ ; 10	$\text{K}_3\text{PO}_4$ ; 1	DMSO	100	14	35
4	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ ; 10	$\text{K}_2\text{CO}_3$ ; 2	DMSO	50	14	47
5	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ ; 10	DABCO; 2	DMSO	80	14	23
6	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ ; 10	$\text{Cs}_2\text{CO}_3$ ; 2	DMSO	100	14	74
7	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ ; 10	Pyridine; 2	DMSO	100	14	29
8	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ ; 10	$\text{Cs}_2\text{CO}_3$ ; 3	DMSO	100	14	73
9	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ ; 10	$\text{Cs}_2\text{CO}_3$ ; 3	DMA	100	14	–
10	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ ; 10	$\text{Cs}_2\text{CO}_3$ ; 3	DMF	100	14	25
11	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ ; 10	$\text{Cs}_2\text{CO}_3$ ; 3	DMSO	80	14	31
12	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ ; 10	$\text{Cs}_2\text{CO}_3$ ; 3	DMSO	100	10	55

<sup>a</sup>The reactions were executed using **4a** (1.0 mmol) in solvent (2 mL). <sup>b</sup>Isolated yields of the product **5a**.



**Scheme-VI:** Plausible reaction mechanism for 2,4-disubstituted-1,3,5-triazines

DMSO to furnish the intermediate **D'** which tautomerizes to intermediate **E'**. The intermediate **E'** sustain another Ni-catalyzed C-N bond formation to access intermediate **F'** at the expense of methanethiol (**G'**). Subsequent oxidation of intermediate **F'** by DMSO results in the formation of desired product **5**.

### Conclusion

In summary, a metal-free molecular iodine influenced  $\alpha$ -C(*sp*<sup>3</sup>)-H bond functionalization of arylmethyl ketones has been accomplished to generates the  $\alpha$ -ketoamides *via* C-N bond forming approach in water as solvent under peroxide free conditions. The devised method exhibited good scope with high yields of the products. On the other hand, a Ni(II)-catalyzed reaction pathway for the generation of 2,4-disubstituted-1,3,5-triazines has been devised. Under the reaction conditions, the DMSO acts as C1-synthon. The reaction proceeded with good functional group endurance and high yield of the desired bio-active molecules.

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### CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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