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Article

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iEDDA Reaction of Molecular Iodine-Catalyzed Synthesis of 1,3,5-triazines *via* functionalization of sp^3 C-H bond of Acetophenones with Amidines: An Experimental Investigation and DFT Study

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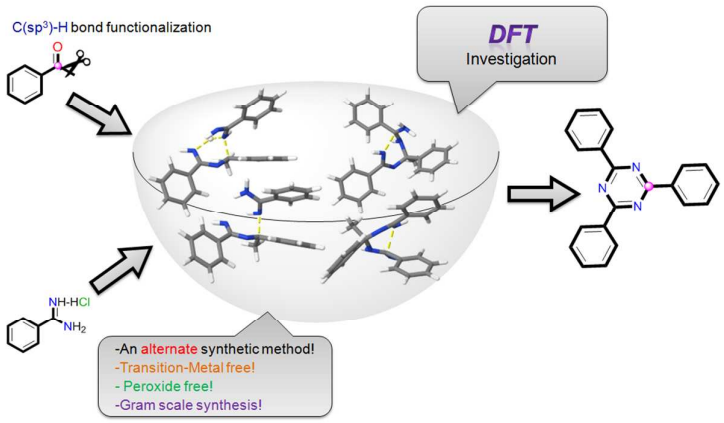
Keywords: Diels-Alder, Iodine, 1,3,5-triazines, DMSO, DFT-investigation.

TOC



ABSTRACT:

The present work reports an inverse electron demand Diels Alder (iEDDA) type reaction to synthesize 1,3,5-trizines from acetophenones and amidines. The use of molecular iodine in catalytic amount facilitates the functionalization of sp^3 C-H bond of acetophenones. This is a simple and efficient methodology for the synthesis of 1,3,5-triazines in good to excellent yields under transition metal-free and peroxide-free conditions. The reaction is believed to take place via an in situ iodination-based oxidative elimination of formaldehyde. DFT calculations at the M062X/6-31+G(d,p) level were employed to investigate the reaction mechanism. Reaction barriers for the cycloaddition as well as a formaldehyde expulsion steps were computed and a multi-step mechanism starting with the nucleophilic attack by

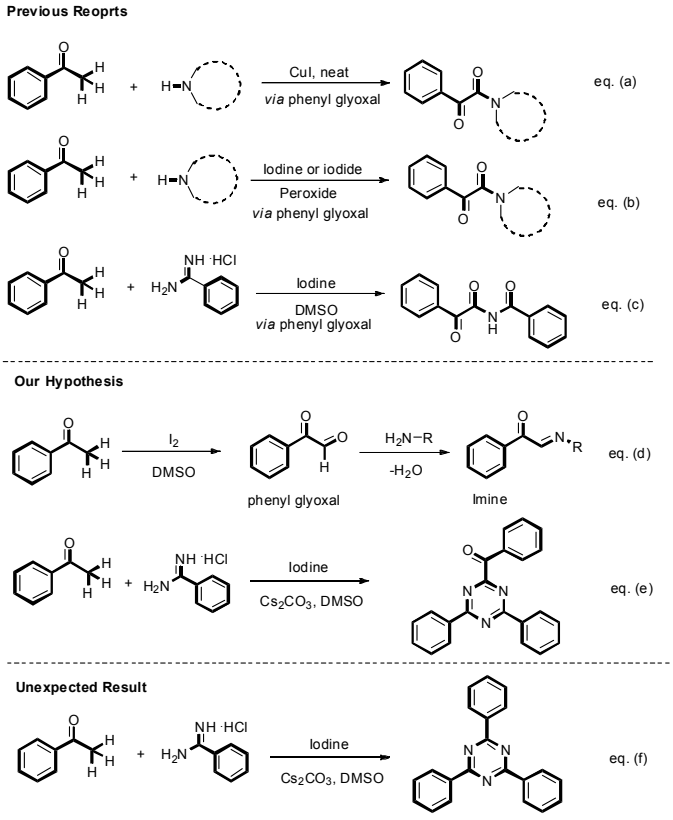
benzamidine on an *in situ* generated imine intermediate has been proposed. Both local and global reactivity descriptors were used to study the regioselectivity of the addition steps.

INTRODUCTION

Over the years, the inverse electron demand Diels-Alder reaction (iEDDA) has widely been explored as a new strategy to synthesize heterocyclic ring systems which are difficult to access by conventional means.[1-4] Ever since the first report on the iEDDA reaction by Bachmann and Deno in 1949, extensive studies have been done both experimentally and theoretically on such type of reactions.[2] The 1,2,-diazine,[3] 1,2,3- triazine,[4] 1,2,4-triazine,[5] and 1,2,4,5-tetrazine[6] based cycloaddtion reactions are known to be explored as a potential iEDDA reaction. Moreover, the 2,4,6-tris-(ethoxycarbonyl)-1,3,5-triazine with [4+2] cycloaddition of amidines to provide substituted 4-aminopyrimidines as an example of iEDDA reaction has also been explored.[7]

Recently, transition-metal free methodology for the functionalization of C-C bond has come into sight as a challenging and attractive area to researchers as this provides a new mode of synthetic methodology in organic chemistry.[8] Conventionally, the C-C bond cleavage has been reported by oxidative cyclometalation or in the presence of a metal complex to functionalize a specific C-C bond.[9] The direct transformation of acetophenones into valuable chemical commodity via cleavage of C(CO)-C bond has not been explored much, especially, the direct oxidative functionalization of C(CO)-C(sp^3) bond toward the formation of C−N bonds.[10] The strategy for C(sp^3)-H bond oxidative amidation through C−H/N−H oxidative coupling has always been a fascinating topic as nitrogen containing heterocycles are potentially valuable synthetic building blocks for the preparation of various heterocyclic ring systems of biological interest.[11] The C(sp^3)−H bond oxidative amidation via oxidative coupling of acetophenones with amines have been explored (Scheme 1, eq. (a) and eq. (b)).[12a-d] In addition to these, Wu and co-workers documented I_2/DMSO-catalyzed condensation of benzamidine hydrochlorides with acetophenones to construct α-ketoimides (Scheme 1, eq. (c)).[12e] All these reactions are believed to takes place via in situ oxidation of C(sp^3)-H to give phenylglyoxal containing aldehyde group. These results led us to hypothesize that the imine formation could be achieved by reacting acetophenones and primary amine through an in situ generated aldehyde group of phenylglyoxal. (Scheme 1, eq. (d)). The previous report on the I_2/DMSO-catalyzed condensation of benzamidine with acetophenone was performed in the absence of base to give α-ketoimides. With the background knowledge that the synthesis of 1,3,5- triazines are believed to progress through

Scheme 1. Functionalization of C(sp3)-H bond of Acetophenones



imine formation, we further hypothesize that carbonyl group containing substituted 1,3,5-triazines could be synthesized under the I_2/DMSO condition in the presence of base (Scheme 2, eq. (e)). We attempted to make carbonyl group containing substituted 1,3,5-triazines from acetophenone and amidines (1:2 equiv.) in the presence of base. Unexpectedly, a simple 1,3,5-triazine was formed (Scheme 2, eq. (f)). Encouraged by this unexpected result, we present herein an efficient, experimentally simple, and readily applicable method for the synthesis of 1,3,5-triazines from the reaction of acetophenones with amidines. Moreover, to elucidate the reaction mechanism, detailed DFT calculations were carried out.

1,3,5-triazines are important class of heterocycles found in many natural products and have promising biological activities.[13] They are known to be used as a ligand in catalysis and possess photophysical properties.[14] In spite of having numerous application of 1,3,5-triazine scaffolds, only in the recent years researchers have focused on the synthetic pathway for the preparation of triazines. Typically, the substituted 1,3,5-triazines are synthesized by palladium (Pd) catalysed coupling of halogenated 1,3,5-triazines with phenyl boronic acids[15]and from nitriles *via* cyclotrimerization in the presence of amines.[16] Various transition metal catalyzed approaches include the reaction of amidines with (i) DMF in the presence of

CuI/pyridine/triethyl-amine base,[17] (ii) benzylalcohols either in the presence of Ru-phosphine complex or $Cu(OAc)_2$ as a catalyst.[18] Subsequently, the transition-metal free approaches includes the reaction of amidines with (i) prepared 4H-pyrido[1,3]oxazin-4-ones (ii) benzylamines (iii) benzylalcohols (iv) methylarenes, and (v) styrenes.[19]

RESULTS AND DISCUSSION

Table 1. Optimization of reaction conditions[a]

Entry	I_2 (mol%)	Temp (^oC)	Time (h)	Yield (%)[b]
1	20	130	24	96
2	20	130	20	96
3	20	130	16	95
4	20	130	12,14	81,90
5	20	120	16	95
6	20	110	16	95
7	20	100	16	87
8	15	110	16	94
9	10	110	16	83
10	5	110	16	62

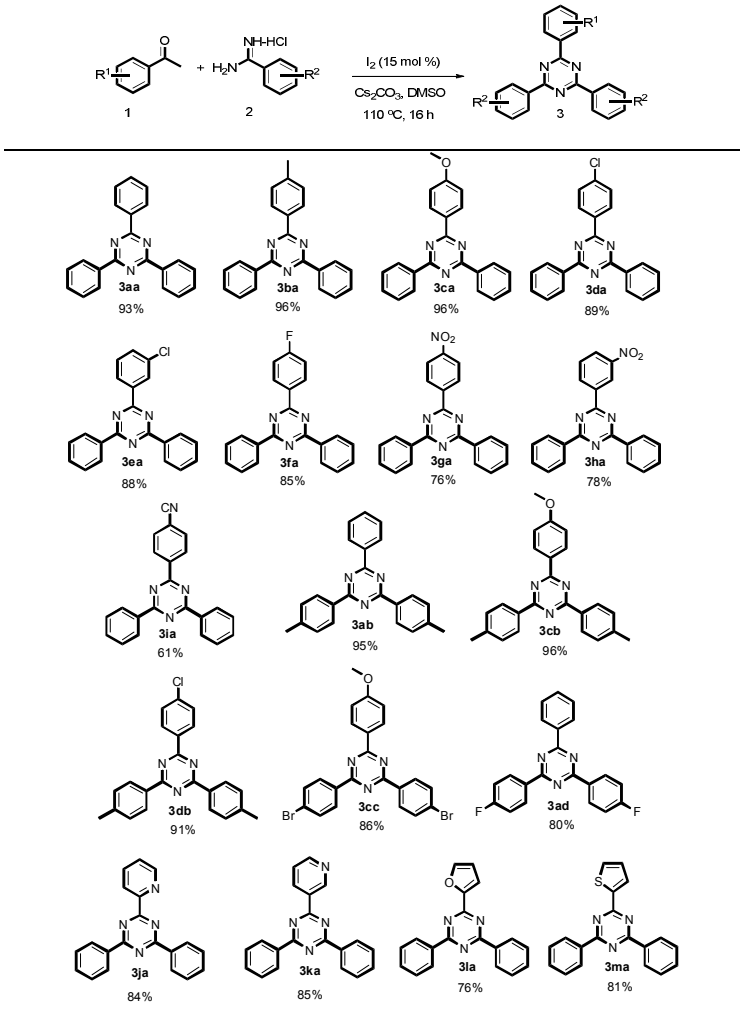
[a] Reaction conditions: acetophenone (**1a**, 0.75 mmol), benzamidine hydrochloride (**2a**, 1.0 mmol), Cs_2CO_3 (1.1 mmol) in 2.0 mL DMSO. [b] GC Yield.

The reaction commenced with acetophenone (**1a**, 0.75 mmol) and benzamidine hydrochloride (**2a**, 1.0 mmol) as model substrates with Cs_2CO_3 (1.1 mmol) in the presence of 20 mol% molecular iodine in DMSO as shown in Table 1. It resulted in the formation of 96% of the desired product **3aa**, with the reaction conditions set to 130 $^\circ$C temperature for a period of 24 h (Table 1, entry 1). Firstly, a set of reactions were carried out at different time intervals and it was found that the reaction time could be reduced to 16 h providing 95% yield of the desired product **3aa** (Table 1, entries 2-4). Reducing the time interval from 16 h to 14 h significantly reduced the yield of **3aa** (Table 1, entry 4). Next, a set of experiments were performed to obtain the optimum reaction temperature (Table 1, entries 5-7). Decreasing the reaction temperature below 110°C led to a considerable lowering in the yield of **3aa** (Table 1, entry 7). This suggests that, this reaction belongs to the class of thermal Diels-Alder reactions. Further, the required concentration of iodine is also finalized through a series of experiments (Table 1, entries 8-10). Thus, 15 mol% of I_2 is found to be the optimum concentration providing a yield of 94% of **3aa** (Table 1, entry 8). Based on all these reaction

studies, the optimized reaction conditions converge to : acetophenone (**1a**, 0.75 mmol), benzamidine hydrochloride (**2a**, 1.0 mmol), Cs_2CO_3 (1.1 mmol), 15 mol% I_2 in DMSO (2.0 mL) at 110 ^oC for 16 h.

With these optimized reaction conditions in hand, the substrate generality of this reaction is then further tested using a series of substituted acetophenones and amidines. Various derivatives of 1,3,5-triazines are thus synthesized successfully as shown in scheme 2. The reaction between **1a** with **2a** yields the desired product **3aa** in 93% isolated yield. Electron neutral group (*p*-Me) and electron donating group (*p*-OMe) containing acetophenones have been found to provide the corresponding products in excellent yields. These reaction conditions turn out to be efficient for the oxidative coupling of acetophenone bearing weak

Scheme 2. Substrates study[a]

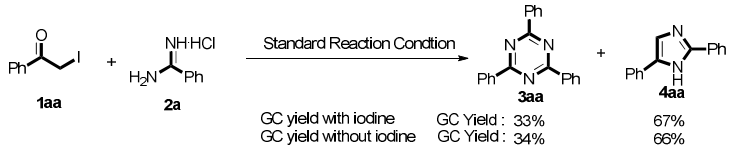


[a] Reaction conditions: acetophenones (**1**, 0.75 mmol), amidine hydrochlorides (**2**, 1.0 mmol), Cs_2CO_3 (1.1 mmol), in 2.0 mL DMSO. [b] Isolated Yield.

electron withdrawing groups (*p*-Cl, *m*-Cl and *p*-F) and strong electron withdrawing group (*p*-NO_2, *m*-NO_2 and *p*-CN) with benzamidine hydrochloride (**2a**) also. Next, different derivative of benzamidines such as *p*-methylbenzamdine hydrochloride (**2b**), *p*-bromobenzamidine hydrochloride (**2c**), *p*-chlorobenzamidine hydrochloride (**2d**) and *p*-fluorobenzamidine hydrochloride (**2e**) were explored, furnishing the respective products in very good to excellent yields. Moreover, the heteroatom containing acetophenones such as 3-pyridylmethylketone (**3ja**), 2-pyridylmethylketone (**3ka**), 2-furfuryllmethylketone (**3la**) 2-thiophenylmethylketone (**3ma**) can also be converted into their respective 1,3,5-triazine derivatives.

In order to show the synthetic applicability of this methodology, gram scale synthesis of **3aa** was attempted. To our delight, when **1a** (1.5 g, 12.50 mmol) was made to react with **2a** (2.6 g, 16.66 mmol) under the optimized reaction conditions the product **3aa** was produced with 78% (2.0 g, 6.5 mmol) yield.

Scheme 3. Control experiments

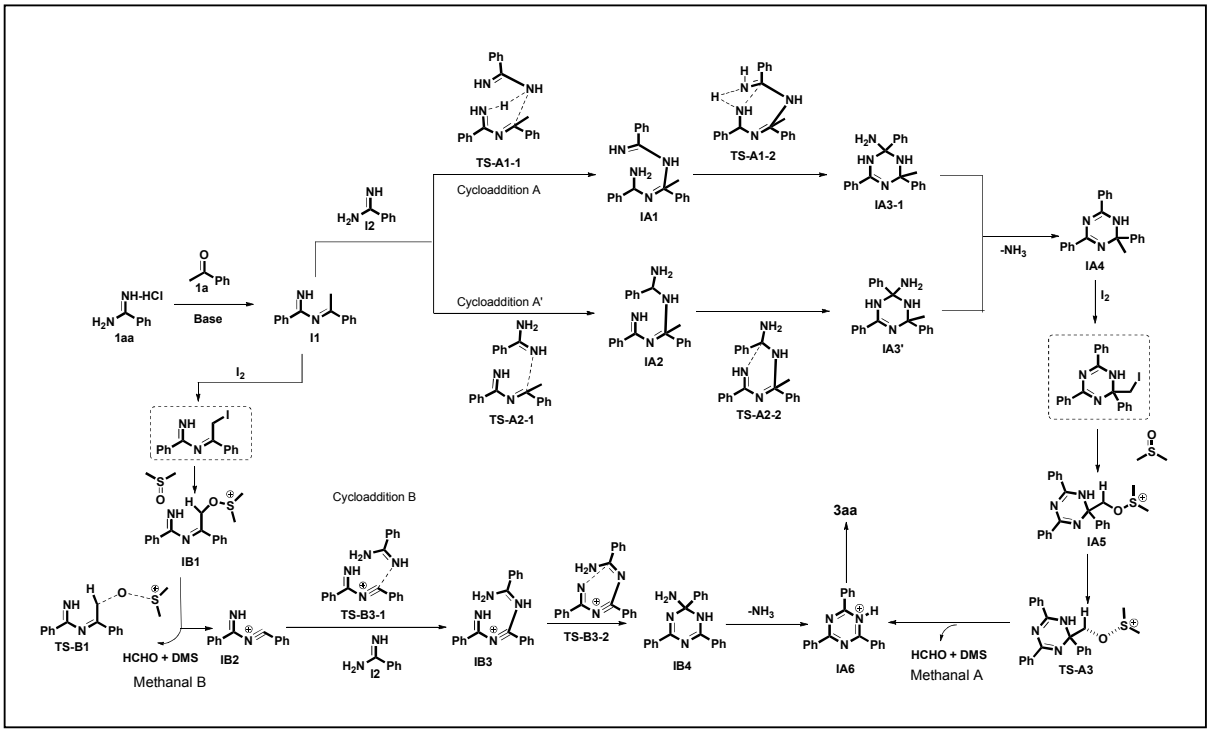


The participation of iodine in the mechanistic pathway is crucial for this reaction as it helps in the functionalization of sp^3 C-H bond of acetophenones *via* HCHO and DMS elimination. It is not certain, however, whether iodination takes place right at the beginning of the reaction giving α-iodo acetophenone or does it get involved at some later stage. To conclude this intriguing question, a series of control experiments were carried out (Scheme 3). The α-iodo acetophenone (**1aa**), was made to react with benzamidine hydrochloride (**2a**) and it furnished a five membered ring product **4aa** as a major product (confirmed by GCMS, m/z = 220)[20] in very good yield along with the desired product (**3aa**) as a minor product. The same result was observed irrespective of the presence or absence of I_2 (15 mol %). However, no such five membered ring formation was noted during optimization of the reaction conditions. This clearly suggests that the formation of α-iodo acetophenone does not take place during the progress of reaction and iodine would participate at a later stage, only after the formation of an imine intermediate (**I1**). Hence, on the basis of these control experiments and previous reports, a plausible reaction mechanism for formation of **3aa** from **1a** with **2a** has been depicted in scheme 4. The reaction is believed to proceed through formation of imine

intermediate (**I1**), which on coupling with DMSO forms **IA5** in pathway A and **IB1** in pathway B. Elimination of dimethyl sulfide and formaldehyde from both of these intermediates lead to formation of **IA6**, which on dehydrogenative aromatization produces **3aa**.

The mechanistic pathway followed by the reaction has further been investigated. A density functional theory (DFT) based study has thus been carried out, which provide insights at the molecular level.

Scheme 4. Plausible Reaction Pathways



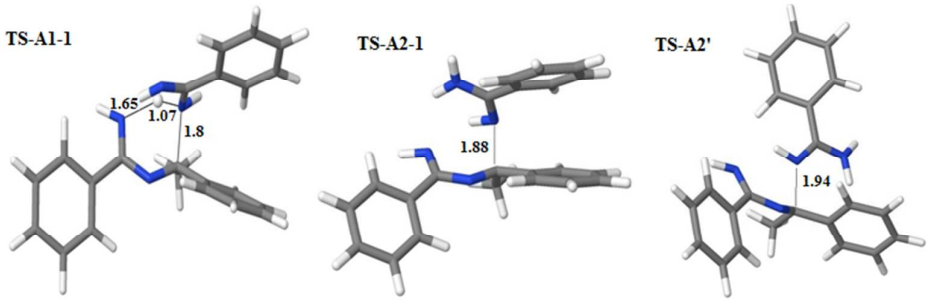


Figure 1. Transition States Involved in The First Stage of Cycloaddition A. Bond Distances are in Angstroms.

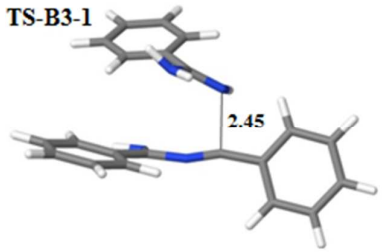


Figure 2. Transition State for The First Cycloaddition Step Between Diene IB2 and Dienophile I2 in Cycloaddition B. The bond Distance is in Angstroms.

Pathway A, assumes that the [4+2] cycloaddition, involving a diene (**I1**) and a dienophile (**I2**) is the first step, followed by the elimination of formaldehyde and DMS yielding the product **IA4** (Scheme 4, Methanal A). Pathway B, on the other hand, proposes the elimination of formaldehyde and DMS as the leading step, pursued by a cycloaddition step between the diene (**IB2**) and the dienophile (**I2**). The energy profiles of the respective pathways have been shown in figures 3-5. Figure 3 represents the relative Gibbs free energy profile for the cycloaddition step of Pathway A (Scheme 4, cycloaddition A). The free energy profile for the later part of the mechanism involving formaldehyde and DMS extrusion, a step following the cycloaddition A step has been shown separately in Figure 4. Figure 5, on the other hand, depicts the combined free energy profile for the cycloaddition and formaldehyde elimination steps (Scheme 4, cycloaddition B and Methanal B) of the pathway B.

To begin with, the nature of the two diene moieties (**I1** and **IB2**) and the dienophile (**I2**), participating in the cycloaddition step, across the two pathways, have been analyzed using global reactivity descriptors. These descriptors have been calculated using PyGlobal[21] and presented in Table 2. For the pathway A, the difference in the nucleophilicity and the electrophilicity indices for the diene (**I1**) and the dienophile (**I2**) is marginal. Both the reactants may fairly be classified as moderate nucleophiles (2.0 eV < N < 3.0 eV) as well as electrophiles (ω < 1.5 eV), within the scales proposed by Domingo and co workers.[22c] Further, the dienophile (**I2**) is less electrophilic and more nucleophilic, compared to the diene (**I1**) thereby implying a reverse charge transfer in the transition state. The higher chemical potential of the dienophile (**IB2**) also lends credence to this prediction. In case of pathway B, the diene **IB2**, as seen from the mechanism, being cationic in nature, possess a very high electrophilicity value, and in turn an extremely low nucleophilicity value. The considerable difference in chemical potential between the reactants **I2** and **IB2** suggest a possibility for rapid charge transfer in the transition state, resulting in a considerably lower energy barrier for this cycloaddition than that in pathway A. The highly electrophilic nature of the diene

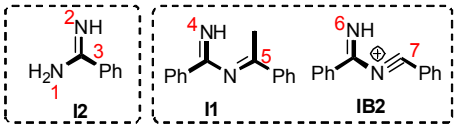
once again implies a reversal in the charge transfer similar to that seen between **I1** and **I2** of the earlier pathway. Thus, this reaction between the electron poor dienes (**I1** and **IB2**) and the electron rich dienophile (**I2**) can be classified as an inverse electron demand Diels Alder (iEDDA) reaction. The regioselectivity within dienes and the dienophile has also been investigated by calculating the local reactivity indices for the pertinent atoms of all the reactants involved. The local reactivity indices characterize the most electrophilic and nucleophilic centers of the reactant. These indices can be determined by employing the

Table 2. Global Reactivity Descriptors for the Reactants Involved in Reaction Pathways[a]

Molecules	χ	μ	η	S	ω	N
I1	4.52	-4.52	7.26	0.14	1.41	2.66
I2	4.13	-4.13	7.89	0.13	1.08	2.74
IB2	8.87	-9.87	6.09	0.16	6.46	-1.1

[a] All values are in eV

Table 3. Electrophilic and Nucleophilic Parr Functions Obtained Through Mulliken and Hirshfeld Population Analysis for The Labeled Atoms



Dienophile Dienes

		P_k^+ (Mulliken)	P_k^+ (Hirshfeld)	P_k^- (Mulliken)	P_k^- (Hirshfeld)
I2	N1	0.014	0.043	0.105	0.073
	N2	0.189	0.162	0.562	0.457
	C3	0.129	0.119	-0.153	-0.008
I1	N4	0.191	0.147	0.477	0.374
	C5	0.224	0.164	-0.107	0.006
IB2	N6	0.269	0.211	0.202	0.158
	C7	0.342	0.232	-0.006	-0.005

'condensed to atom method' to obtain the Fukui functions, which characterize the most reactive sites in polar chemical reactions**.** The recently proposed Parr functions can also be used for the same purpose.

Table 3 presents the electrophilic and nucleophilic Parr functions for the selected atomic centers of the dienes (**I1** and **IB2)** and dienophile (**I2)**. While the study concentrates on primary and secondary nitrogens as potential local nucleophilic centers of **I2**, the nitrogens (N4 and N6) and carbon (C1) turn out to be interesting centers in **I1** and **IB2**, to explore the local electrophilicity. The value for the most electrophilic center in each of molecules has been highlighted in red while the most nucleophilic atoms have been shown in blue. As may be seen from the data presented in Table 3, the Parr function calculated across Mulliken and Hirshfeld population analysis converge to the secondary nitrogen (Table 3, N2) as the strongest nucleophilic center in the dienophile **I2**. In the case of the dienes **I1** and **IB2**, calculated Parr function P_k^+ indicate C2 atomic center to be the most electrophilic in nature. The calculated Fukui functions show consistent result with Parr function while predicting the nucleophilic center in **I2**, though it comes across a disagreement in the results for the electrophilic center in **I1** and **IB2**. Calculated Fukui functions have been reported in the supplementary material.

Pathway A

As mentioned at the beginning of this study, the two pathways differ with respect to the sequence of cycloaddition and elimination reactions. Pathway A assumes the [4+2] cycloaddition to be the primary step. The presence of two nucleophilic centers in the dienophile **I2** leads to two possibilities for the cycloaddition step itself, labeled **A** and **A'**, between **I1** and **I2**. With two nucleophilic centres (N1 and N2) in **I2**, capable of forming a bond with the atom C5 in **I1**, separate transition states corresponding to the attack of the nucleophilic centers on C5 have been located. These structures along with some selected structural parameters can be seen in Figure 1. **TS-A1-1** involves the concerted proton migration between the primary nitrogen (N1) of **I2** and the secondary nitrogen (N4) in **I1** along with its nucleophilic attack on the benzylic carbon (C5). The shorter bond distance for the proton migration (1.65 Å) indicates its preferential formation over the C-N bond formation (1.8 Å). A subsequent IRC analysis confirms this hypothesis. In case of a possibility of nucleophilic attack by the secondary nitrogen (N2), two transition states (Figures 4 and Figure 5, **TS-A2-1** and **TS-A2'**) have been located. These two transition states differ in the orientation of the phenyl ring of **I2** with respect to that of **I1**. In **TS-A2-1**, the

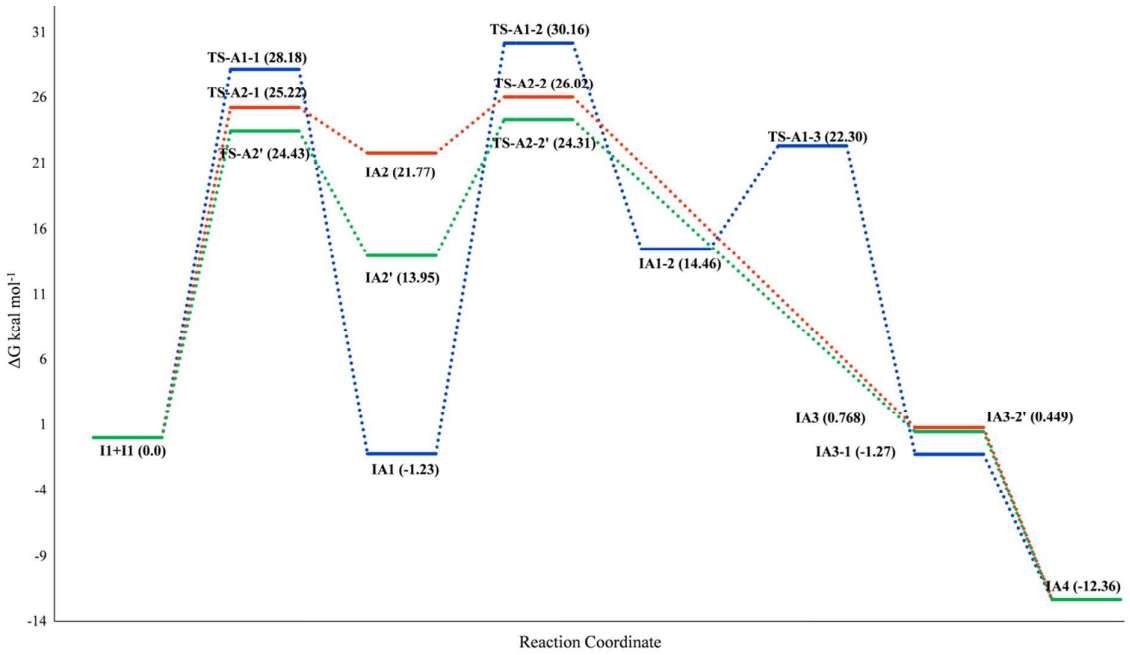


Figure 3. Plot of Gibbs Free Energy Change Across The Cycloaddition A and Cycloaddition A' Step of Pathway A

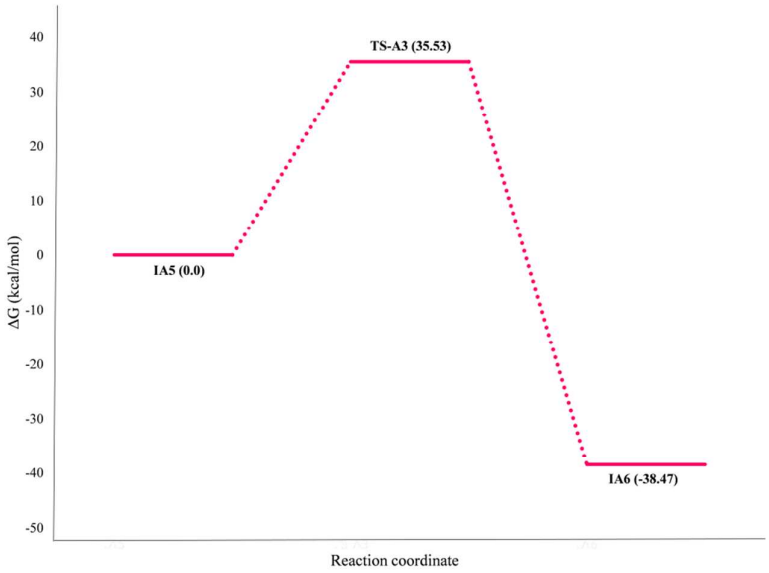


Figure 4. Plot of Gibbs Free Energy Change for Methanal A Step of Pathway A

two rings nearly eclipse each other with a transient bond length of 1.88 Å. For the second orientation **TS-A2'**, the transient bond distance turns out to be 1.94 Å. The greater incipient bond distance in the latter case implies that the interaction between the respective centers involved in the bond formation occurs earlier than in the former case. Figure 3 reveals that **TS-A2**' is the most stable transition state, whereas **TS-A1-1** has the highest energy among

the three. This may partly be explained through the earlier discussed electrophilic and nucleophilic Parr functions, where the secondary nitrogen (N2) was found to be the better nucleophilic centre compared to the primary nitrogen, thereby indicating feasible nucleophilic attack from secondary nitrogen at a lower energy expense.

Following the first step of the cycloaddition, each of the above discussed three transition states give three subsequent intermediates (Figure 3). Among these, the intermediate arising from the concerted proton transfer (**IA1**) is found to be the most stable. The next step involves the bond formation between the Carbon C3, of the former dienophile fragment and N2 of the former diene fragment. The corresponding transition states along the proposed pathways arising from **IA2** and **IA2'** have been located and once again **TS-A2-2'**, having the uneclipsed phenyl rings of the former fragments, turns out to be lower. As may be seen, the corresponding intermediates **IA3** and **IA3-2'** marginally differ in energies. It can be seen from Scheme 4 that the conversion of **IA1** to **IA3-1** involves another concerted transition state **TS-A1-2**. Several attempts to locate this however, failed. Instead a transition state involving only the proton transfer step was found. This has been labeled as **TS-A1-2** on the reaction coordinate and has a barrier of ~31 kcal/mol which is much greater than that of its **TS-A2-2** counterparts shown in Figure 3. The ring cyclization then involves another transition state (**TS-A1-3** in Figure 3) ultimately leading to the **IA3-1** intermediate. The cyclization is, thus, complete with the formation of the respective **IA3** intermediates. Following the extrusion of ammonia, the cycloaddition mechanism converges at **IA4**, which is the starting moiety for the next stage of the pathway. The subsequent alpha iodination step and its related intermediates (shown in square, Scheme 4) have been skipped from the DFT study, which intends to investigate the dominant pathway among the cycloaddition and the methanal elimination. The iodination and subsequent attack by DMSO on **IA4** yields the cationic intermediate, **IA5**. The barrier for the elimination of the DMS and formaldehyde fragments from **IA5** turns out to be around 35.53 kcal/mol (Figure 4). This collapses to the protonated triazine intermediate, **IA6** common to both the pathways.

Pathway B

As seen in Scheme 4, Pathway B commences with the extrusion of DMS and formaldehyde from the sulfonated intermediate **IB1**. The transition state (**TS-B1**) located for this particular elimination is found to have a very high energy value of 50.13 kcal/mol above its reactant (Figure 5). On comparing, it turns out to be almost twice of the energy of the transition state

TS-A2' of the cycloaddition A pathway. Further, it is also found to be higher in energy by ~15 kcal/mol

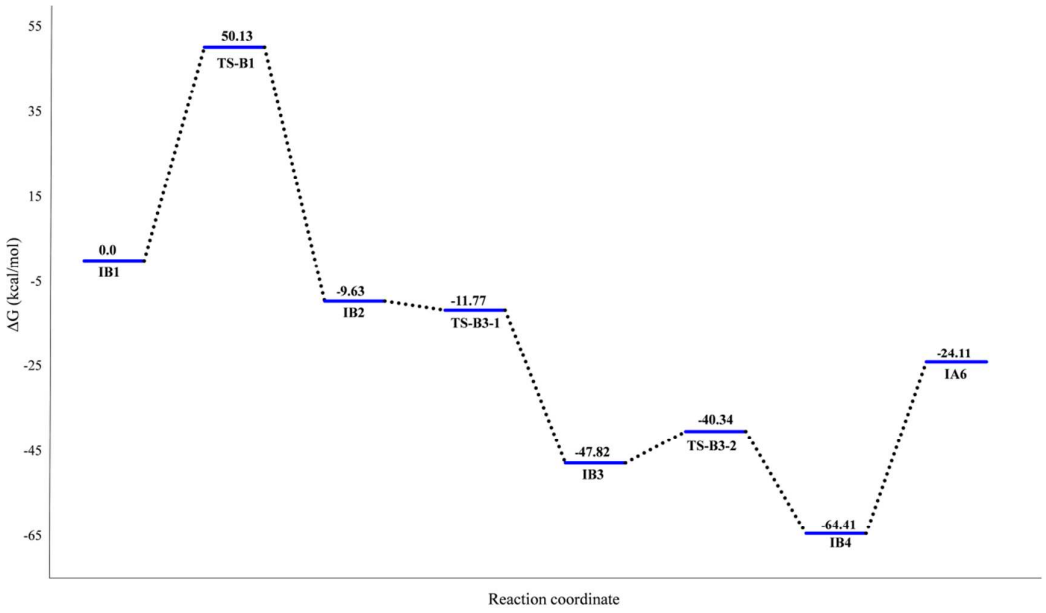


Figure 5. Reaction Profile for Pathway B in DMSO Leading up to Intermediate IA6 Common to Both The Pathways.

with respect to equivalent methanal elimination step (Methanal A) of pathway A. Following the elimination step, the cationic diene IB2, is obtained which undergoes a barrierless nucleophilic attack by the common dienophile I2, and a further cycloaddition step leading to IB4. The extremely electrophilic nature of IB2, as predicted by the global reactivity descriptor calculations, might have resulted in the slight lowering of energy for the transition complex, TS-B3-1 in comparison with its reactants. Its optimized geometry can be seen in Figure 2. The incipient bond distance of 2.45 Å is now even greater than all of its counterparts in the other competitive pathway. Thus, as with the earlier TS-A2', the same implication about the earliness of the bond forming interaction can be made in this case. After the formation of IB4, the cationic intermediate IA6 is once again obtained following the loss of an ammonia molecule with the consequent gain of conjugation in the 1,3,5-triazine nucleus.

CONCLUSIONS

In conclusion, a facile and efficient synthetic methodology for the preparation of 1,3,5-trizines from acetophenones and amidines has been achieved. The functionalization of sp^3 C-H bond of Acetophenones is accomplished using a catalytic amount of molecular Iodine. This

is a simple and efficient methodology for the synthesis of 1,3,5-triazines in good to excellent yields under transition metal-free and peroxide-free conditions. A series of 1,3,5-triazines were synthesized in excellent to good yields. Moreover, the synthesis of 1,3,5-triazines can be achieved at gram scale level. The reaction is believed to takes place *via* an in situ iodination-based oxidative elimination of formaldehyde. The multi-step mechanism was studied using both experiments and DFT calculations. The two Gibbs free energy profiles investigated, highlight interesting aspects about the mechanistic pathway to be followed. The first step of Pathway A is cycloaddition while the one with Pathway B is methanal formation. A comparison of the energy barrier faced by these two respective steps across the two pathways indicate Pathway A to prevail over Pathway B. While the energy barrier for the cycloaddition step in the pathway A is 24.4 kcal.mol^{-1}, a similar energy barrier faced during methanal formation step of pathway B is as high as 50 kcal.mol^{-1}. Global reactivity descriptor analysis classifies the cycloaddition as an inverse electron demand Diels Alder (iEDDA) reaction. The local reactivity descriptor analysis carried out within Pathway A suggest that the imine Nitrogen N2 of dienophile **I2** is more nucleophilic than its primary amine counterpart. The first cycloaddition step is thus predicted to occur from this centre. This hypothesis has been confirmed by comparing the energies of their corresponding transition states. Furthermore, the barrier for the second cycloaddition step of the intermediate arising from nucleophilic attack via N1, is found to be considerably higher and along with this the presence of a third transition state required for the final ring cyclization leads us to discard this particular route.

EXPERIMEMTAL SECTION

General Information

All chemicals and solvents were purchased with high purities and used without further purification. The progress of the reaction was monitored by gas chromatography (GC) Perkin Elmer Clarus 400. GC equipped with a flame ionization detector (FID) with a capillary column (30 m × 0.25 mm × 0.25 μm) and thin layer chromatography (using Merck silica gel 60 F-254 plates. The products were visualized with a 254 nm UV lamp. GC-MS-QP 2010 instrument (Rtx-17, 30 m × 25 mm ID, film thickness (df = 0.25 μm) (column flow 2 mL min-^{1} 80 °C to 240 °C at 10 °C min^{-1} rise) was used for the mass analysis of the products. Products were purified by column chromatography on 100-200 mesh silica gel. The ^{1}H NMR spectras were recorded on 400 MHz and 500 MHz spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. The ^{13}C NMR spectras were recorded on

100 MHz and 125 MHz in $CDCl_3$. Chemical shifts were reported in parts per million (δ) relative to tetramethylsilane (TMS) as an internal standard. Coupling constant (J) values were reported in hertz (Hz). Splitting patterns of proton are described as s (singlet), d (doublet), dd (doublet of doublet), t (triplet) and m (multiplet). The products were confirmed by GCMS, HRMS, ^1H and ^{13}C NMR spectroscopic analysis. All the products are well known in literature.

General experimental procedure to prepare 1,3,5-triazines (3)

To an oven dried reaction vial containing mixture of acetophenones (**1**, 0.75 mmol) and amidine hydrochloride (**2,** 1.0 mmol) dissolved in DMSO (2 mL), Cs_2CO_3 (1.1 mmol), 15 mol% of molecular iodine was added and stirred at room temperature for 5 min and then heated at 110 ^oC for 16 h. After completion of the reaction, the reaction mixture was cooled to room temperature. The reaction mixture was diluted with 5 mL of water and the product was extracted with ethyl acetate (10 × 3mL). The product was purified by silica gel column chromatography by using ethyl acetate (EA)/ petroleum ether (PE).

*2,4,6-triphenyl-1,3,5-triazine (**3aa**)*[18a]

The product was obtained following the general procedure and was purified by silica gel chromatography (5% EA/PE). White solid, Yield 93% (143.85 mg). m.p. 171-173 ^oC.^1H NMR (400 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 8.0, 1.5 Hz, 6H), 7.60 – 7.56 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 136.2, 132.5, 128.93, 128.6. GCMS (EI, 70 eV): m/z (%): 309. HR-MS (ESI) m/z calcd for $C_{21}H_{16}N_3$ $[M+H]^+$ 310.1344, found 310.1317.

*2,4-diphenyl-6-(p-tolyl)-1,3,5-triazine (**3ba**)*[18b]

The product was obtained following the general procedure and was purified by silica gel chromatography (5% EA/PE). White solid, Yield 96% (155.22 mg). m.p. 199-201^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 8.1, 1.6 Hz, 4H), 8.65 (d, *J* = 8.2 Hz, 2H), 7.63 – 7.52 (m, 6H), 7.35 (d, *J* = 8.0 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 171.5, 142.9, 136.4, 133.6, 132.3, 129.3, 129.8, 128.9, 128.5, 21.71. HR-MS (ESI) m/z calcd for $C_{22}H_{18}N_3$ $[M+H]^+$ 324.1501, found 324.1475.

*2-(4-methoxyphenyl)-4,6-diphenyl-1,3,5-triazine (**3ca**)*[18b]

The product was obtained following the general procedure and was purified by silica gel chromatography (15% EA/PE). White solid, Yield 96% (162.9 mg). m.p. 160-162^oC. ^1H NMR (400 MHz, CDCl3) δ 8.76 – 8.71 (m, 6H), 7.59 – 7.53 (m, 6H), 7.04 (d, J = 8.9 Hz,

2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 173.1, 163.3, 136.4, 132.3, 130.8, 128.8, 128.7, 128.5, 113.9, 55.4. HR-MS (ESI) m/z calcd for $C_{22}H_{18}N_3O$ $[M+H]^+$ 340.1450, found 324.1434.

2-(4-chlorophenyl)-4,6-diphenyl-1,3,5-triazine (***3da***)[18b]

The product was obtained following the general procedure and was purified by silica gel chromatography (10% EA/PE). White solid, Yield 89% (153 mg). m.p. 200 -203 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 – 8.80 (m, 6H), 7.73 – 7.63 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 170.7, 138.8, 136.2, 136.0, 134.7, 132.6, 130.3, 128.9, 128.6. HR-MS (ESI) m/z calcd for $C_{21}H_{15}N_3Cl$ $[M+H]^+$ 344.0955, found 344.0932.

2-(3-chlorophenyl)-4,6-diphenyl-1,3,5-triazine (***3ea***)[18b]

The product was obtained following the general procedure and was purified by silica gel chromatography (10% EA/PE). White solid, Yield 88% (151.27 mg). m.p. 198-200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 – 8.63 (m, 6H), 7.61-7.49 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 170.5, 138.1, 135.9, 134.8, 132.7, 132.4, 129.9, 129.0, 128.9, 128.67, 127.0. HR-MS (ESI) m/z calcd for $C_{21}H_{15}N_3Cl$ $[M+H]^+$ 344.0955, found 344.0925.

2-(4-fluorophenyl)-4,6-diphenyl-1,3,5-triazine (***3fa***)[18b]

The product was obtained following the general procedure and was purified by silica gel chromatography (10% EA/PE). White solid, Yield 85% (139.12 mg). m.p. 245-248 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 – 8.73 (m, 4H), 7.61 – 7.54 (m, 4H), 7.23 (dd, J = 11.2, 6.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 170.6, 165.5 (d, J = 252 Hz), 136.06, 132.6, 132.4, 131.3, 128.9, 128.6, 115.7, 115.5. HR-MS (ESI) m/z calcd for $C_{21}H_{15}N_3F$ $[M+H]^+$ 328.1250, found 328.1262.

2-(4-nitrophenyl)-4,6-diphenyl-1,3,5-triazine (***3ga***)[18b]

The product was obtained following the general procedure and was purified by silica gel chromatography (10% EA/PE). Yellow solid, Yield 76% (134.73 mg). m.p. 217-222 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, J = 8.9 Hz, 2H), 8.74 (dd, J = 8.2, 1.3 Hz, 3H), 8.62 (d, J = 6.9 Hz, 1H), 8.38 (d, J = 6 Hz, 2H), 7.65-7.51 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 166.7, 142.0, 135.6, 132.3, 132.2, 129.8, 129.0, 128.9, 128.7, 123.72. HR-MS (ESI) m/z calcd for $C_{21}H_{15}N_4O_2$ $[M+H]^+$ 355.1195, found 355.1211.

2-(3-nitrophenyl)-4,6-diphenyl-1,3,5-triazine (***3ha***)[18a]

The product was obtained following the general procedure and was purified by silica gel chromatography (10% EA/PE). Yellow solid, Yield 78% (138.2 mg). m.p. 201-202 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 9.02 (d, *J* = 7.8 Hz, 1H), 8.71 (d, *J* = 7.1 Hz, 4H), 8.40 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.71 (t, *J* = 7.9 Hz, 1H), 7.63-7.54 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 169.5, 148.7, 138.03, 135.5, 134.5, 132.9, 129.6, 129.0, 128.7, 126.7, 123.73. HR-MS (ESI) m/z calcd for $C_{21}H_{15}N_4O_2$ $[M+H]^+$ 355.1195, found 355.1214.

4-(4,6-diphenyl-1,3,5-triazin-2-yl)benzonitrile (***3ia***)[19b]

The product was obtained following the general procedure and was purified by silica gel chromatography (15% EA/PE). White solid, Yield 61% (102 mg). m.p. 230-232 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 8.7 Hz, 2H), 8.74 (dd, *J* = 8.3, 1.4 Hz, 4H), 7.84 (d, *J* = 8 Hz, 2H), 7.62 – 7.55 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 140.32, 135.6, 132.9, 132.3, 129.3, 129.0, 128.7, 118.5. HR-MS (ESI) m/z calcd for $C_{22}H_{15}N_4$ $[M+H]^+$ 335.1297, found 335.1322.

2-phenyl-4,6-di-p-tolyl-1,3,5-triazine (***3ab***)[18b]

The product was obtained following the general procedure and was purified by silica gel chromatography (5% EA/PE). White solid, Yield 95% (160.27 mg). m.p. 236-238 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 8.0, 1.6 Hz, 2H), 8.64 (d, *J* = 8.2 Hz, 4H), 7.59 – 7.53 (m, 3H), 7.34 (d, *J* = 8.0 Hz, 4H), 2.46 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 171.33, 142.9, 136.4, 133.6, 132.3, 129.32, 128.90, 128.87, 128.52, 21.71. HR-MS (ESI) m/z calcd for $C_{23}H_{20}N_3$ $[M+H]^+$ 338.1657, found 338.1718.

*2-(4-methoxyphenyl)-4,6-di-p-tolyl-1,3,5-triazine (**3cb**)*[18a]

The product was obtained following the general procedure and was purified by silica gel chromatography (5% EA/PE). White solid , Yield 96% (176.37 mg). m.p. 196-198 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 8.6 Hz, 2H), 8.62 (d, *J* = 7.9 Hz, 4H), 7.34 (d, *J* = 7.9 Hz, 4H), 7.04 (d, *J* = 8.6 Hz, 2H), 3.90 (s, 3H), 2.45 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 170.8, 163.1, 142.7, 133.7, 130.7, 129.2, 128.9, 128.8, 113.8, 77.3, 55.4, 21.7. HR-MS (ESI) m/z calcd for $C_{24}H_{23}N_3O$ $[M+2H]^+$ 369.1841, found 369.1824.

*2-(4-chlorophenyl)-4,6-di-p-tolyl-1,3,5-triazine (**3db**)*[18b]

The product was obtained following the general procedure and was purified by silica gel chromatography (5% EA/PE). White solid, Yield 91% (169.19 mg). m.p. 196-198 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 8.4 Hz, 2H), 8.60 (d, *J* = 8.2 Hz, 4H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 4H), 2.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 170.4, 143.1, 138.52, 134.91, 133.4, 130.2, 129.4, 128.9, 128.9, 21.7. HR-MS (ESI) m/z calcd for $C_{23}H_{19}N_3Cl$ $[M+H]^+$ 372.1268, found 372.1292.

2,4-bis(4-bromophenyl)-6-(4-methoxyphenyl)-1,3,5-triazine (***3cc***)[18b]

The product was obtained following the general procedure and was purified by silica gel chromatography (10% EA/PE). White solid, Yield 86% (213.78 mg). m.p. 290-292 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 – 8.53 (m, 5H), 7.66 – 7.64 (m, 5H), 7.05 – 7.01 (m, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 165, 136.3, 132.3, 131.8, 130.9, 130.4, 128.9, 128.6, 113.9, 55.5. HR-MS (ESI) m/z calcd for $C_{22}H_{17}N_3Br_2O$ $[M+2H]^+$ 496.9738, found 497.9685.

*2,4-bis(4-fluorophenyl)-6-phenyl-1,3,5-triazine (**3ad**)*[16d]

The product was obtained following the general procedure and was purified by silica gel chromatography (10% EA/PE). White solid, Yield 80% (138.13 mg). m.p. 253-255 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 – 8.73 (m, 6H), 7.64 – 7.57 (m, 3H), 7.27 (s, 1H), 7.24 (d, *J* = 8.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 170.7, 163.4 (d, *J* = 345 Hz) 132.6, 132.3, 131.3, 131.2, 128.9, 128.7, 115.8, 115.6. HR-MS (ESI) m/z calcd for $C_{21}H_{14}F_2N_3$ $[M+H]^+$ 346.1156, found 346.1176.

*2,4-diphenyl-6-(pyridin-2-yl)-1,3,5-triazine (**3ja**)*[18a]

The product was obtained following the general procedure and was purified by silica gel chromatography (20 % EA/PE). White solid, Yield 84% (130.34 mg). m.p. 238-239 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (d, *J* = 7.9 Hz, 1H), 8.83 – 8.72 (m, 5H), 7.64 – 7.49 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 170.1, 152.8, 150.5, 136.2, 135.7, 132.8, 129.0, 128.7, 123.5. HR-MS (ESI) m/z calcd for $C_{20}H_{15}N_4$ $[M+H]^+$ 311.1297, found 311.1325.

*2,4-diphenyl-6-(pyridin-3-yl)-1,3,5-triazine (**3ka**)*[18a]

The product was obtained following the general procedure and was purified by silica gel chromatography (25% EA/PE). White solid, Yield 85% (131.89 mg). m.p. 265-270 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 8.95 (d, *J* = 7.9 Hz, 1H), 8.76 (t, *J* = 19.3 Hz, 5H),

7.64 – 7.52 (m, 6H), 7.48 (dd, *J* = 7.7, 4.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 170.1, 152.8, 150.5, 136.2, 135.7, 132.8, 131.8, 129.0, 128.7, 123.5. HR-MS (ESI) m/z calcd for $C_{20}H_{15}N_4$ $[M+H]^+$ 311.1297, found 311.1339.

*2-(furan-2-yl)-4,6-diphenyl-1,3,5-triazine (**3la**)*[18a]

The product was obtained following the general procedure and was purified by silica gel chromatography (25% EA/PE). White solid, Yield 76% (113.74 mg). m.p. 196 -198 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (d, *J* = 0.9 Hz, 1H), 8.64 – 8.63 (m, 5H), 7.60 – 7.53 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 166.7, 164.3, 135.5, 132.8, 128.94, 128.88, 128.7, 128.6. HR-MS (ESI) m/z calcd for $C_{19}H_{15}N_3O$ $[M+2H]^+$ 301.1215, found 301.1190.

*2,4-diphenyl-6-(thiophen-2-yl)-1,3,5-triazine (**3ma**)*[19d]

The product was obtained following the general procedure and was purified by silica gel chromatography (25% EA/PE). White solid, Yield 81% (127.73 mg). m.p. 250 -252 ^{o}C.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 8.3, 1.4 Hz, 4H), 8.38 – 8.37 (m, 1H), 7.62 – 7.55 (m, 7H), 7.25 – 7.24 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 168.1, 142.1, 135.9, 132.5, 131.5, 128.9, 128.6, 128.5. HR-MS (ESI) m/z calcd for $C_{19}H_{13}N_3S$ $[M+H]^+$ 316.0908, found 316.0939.

Computational Methods

All the starting geometries are constructed and refined using Avogadro software.[22] The M06-2X, exchange correlation functional in conjunction with the 6-31+G(d,p) set is used for further optimization and calculations with the GAUSSIAN 09 programme package.[23,24] Vibrational frequencies, computed at the same level of theory as above, are used to characterize each of the optimized stationary points. The optimized geometries and their 3D structures were obtained with the Jmol software.[25] All of the transition states are found to have a single imaginary frequency. These transition states have further been verified to connect to their respective reactant and product geometries by IRC calculations.[26] All frequencies for the reactant, intermediate or product structures are found to be positive, thus confirming their nature as local minima. The self-consistent reaction field (SCRF) Polarizable Continuum Model (PCM) was used to model the effect of DMSO solvent on the reaction profile.[27]

All Global reactivity descriptors such as the Chemical potential (μ), Electronegativity (χ), Global hardness (η), Global Softness (S), the Electrophilicity (ω) and Nucleophilicity Indices (N) were calculated using PyGlobal.[21a]

The recently proposed Parr functions, based upon the distribution of atomic spin densities in the respective radical cations and anions of molecules have also been evaluated.[28]

They can be defined as:

$P^{+}(\mathbf{r}) \equiv \rho_s(\mathrm{r})^{\mathrm{ra}}$ *and* $\mathrm{P_B^-(r)} \equiv \rho_s(\mathrm{r})^{\mathrm{rc}}$

Here, $\rho_s(\mathrm{r})^{\mathrm{ra}}$ gives the atomic spin density of the radical anion while, $\rho_s(\mathrm{r})^{\mathrm{rc}}$ gives the atomic spin density for the radical cation. These are used to obtain the local nucleophilic P_k^- and local electrophilic P_k^+ functions for each atom in a molecule. The atomic charges of the neutral molecules as well as the charges and spin densities of its associated radical cation and anion were calcuated from the Mulliken and Hirshfeld population analysis techniques. For the radical cation and anion, the UM062x formalism was used for the calculations.

ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR, HRMS spectra of the 1,3,5-triazine compounds (3). ZPE corrected energies and Cartesian coordinates of all intermediates and transition states along the reaction pathways. Fukui functions for **I1**, **I2**, **IB2**.

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