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Reaction of Aldehydes/Ketones with Electron-Deficient 1,3,5-Triazines Leading to Functionalized Pyrimidines as Diels–Alder/Retro-Diels–Alder Reaction Products: Reaction Development and Mechanistic Studies

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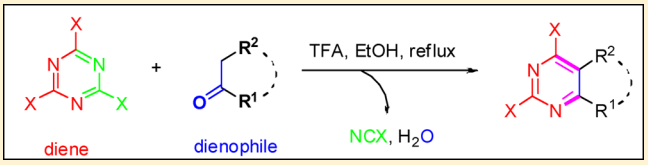
Supporting Information

ABSTRACT: Catalytic inverse electron demand Diels–Alder (IEDDA) reactions of heterocyclic aza-dienes are rarely reported since highly reactive and electron-rich dienophiles are often found not compatible with strong acids such as Lewis acids. Herein, we disclose that TFA-catalyzed reactions of electron-deficient 1,3,5-triazines and electron-deficient aldehydes/ketones can take place. These reactions led to highly functionalized pyrimidines as products in fair to good yields. The reaction mechanism was carefully studied by the combination of experimental and computational studies. The reactions involve a cascade of stepwise inverse electron demand hetero-Diels–Alder (*ih*DA) reactions, followed by retro-Diels–Alder (*r*DA) reactions and elimination of water. An acid was required for both *ih*DA and *r*DA reactions. This mechanism was further verified by comparing the relative reactivity of aldehydes/ketones and their corresponding vinyl ethers in the current reaction system.



INTRODUCTION

Improvement of existing methodologies in organic synthesis is an ongoing focus for chemists, and success in this field empowers chemists with tools for rapid synthesis of natural products and/or biologically important compounds for medicinal chemistry projects. For example, the metal-catalyzed coupling reactions for C–C and C–heteroatom bond formation reactions produced profound impacts to both organic and medicinal chemistry.[1] Traditionally, the more reactive aryl bromide or iodide are most often reported and thought to be required for most coupling reactions; later on, aryl chloride was introduced to expand the scope of coupling reactions.[2] However, direct arene couplings via C–H activation were discovered against the traditional way of thinking, which revolutionized our understanding about coupling reactions.[3] The inverse electron demand Diels–Alder (IEDDA) reactions of aza-dienes (such as triazines and tetrazines) have been widely used for the synthesis of diverse nitrogen-containing heterocycles including natural products and bioactive compounds (Scheme 1a).[4] Traditionally, aza-diene IEDDA reactions require electron-rich dienophiles, such as enamines, ynamines, amidines, and electron-rich heterocycles.[4,5] It is, therefore, not surprising to observe that most attempts of using Lewis acids to active aza-dienes often failed due to the nonproductive consumption of the electron-rich dienophiles (during the preparation of this manuscript, Boger et al. published their results of solvent (perfluoroalcohols) catalyzed reactions[6]). On the other hand, the development of IEDDA reactions of 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine has led to the total syntheses of bleomycin A_2, P-3A (Scheme 1b),[7] and the syntheses of many other bleomycin-related agents.[8] Recently, we disclosed that hydrazones could function as productive dienophiles in IEDDA reactions with 1,3,5-triazine, which avoids the needs to prepare air- and moisture-sensitive dienophiles such as enamines, ynamines, and amidines (Scheme 1c).[9] This improvement to aza-diene IEDDA reactions expanded the scope of dienophiles and gave chemists the flexibility to store a variety of hydrazone dienophiles and conduct IEDDA reactions on demand, without the inconvenience to freshly prepare those moisture-sensitive dienophiles.[9] It would be a further improvent of this methodology if we could utilize directly the readily available ketones and aldehydes as dienophiles without convertion to their corresponding hydrazones. However, vinyl ethers have been tested as dienophiles with the relatively unreactive 1,3,5-triazines unsuccessfully (Scheme 1d), indicating that the enol form of aldehydes/ketones alone might not be reactive enough to function as productive dienophiles. On the other hand, Haddadin, Schubert, and Li found that aldehydes/ketones could react with those highly reactive 1,2,4,5-tetrazines and 1,2,4-triazines (Scheme 1e),[10] which provided encouragement for the further investigation of aldehydes/ketones as

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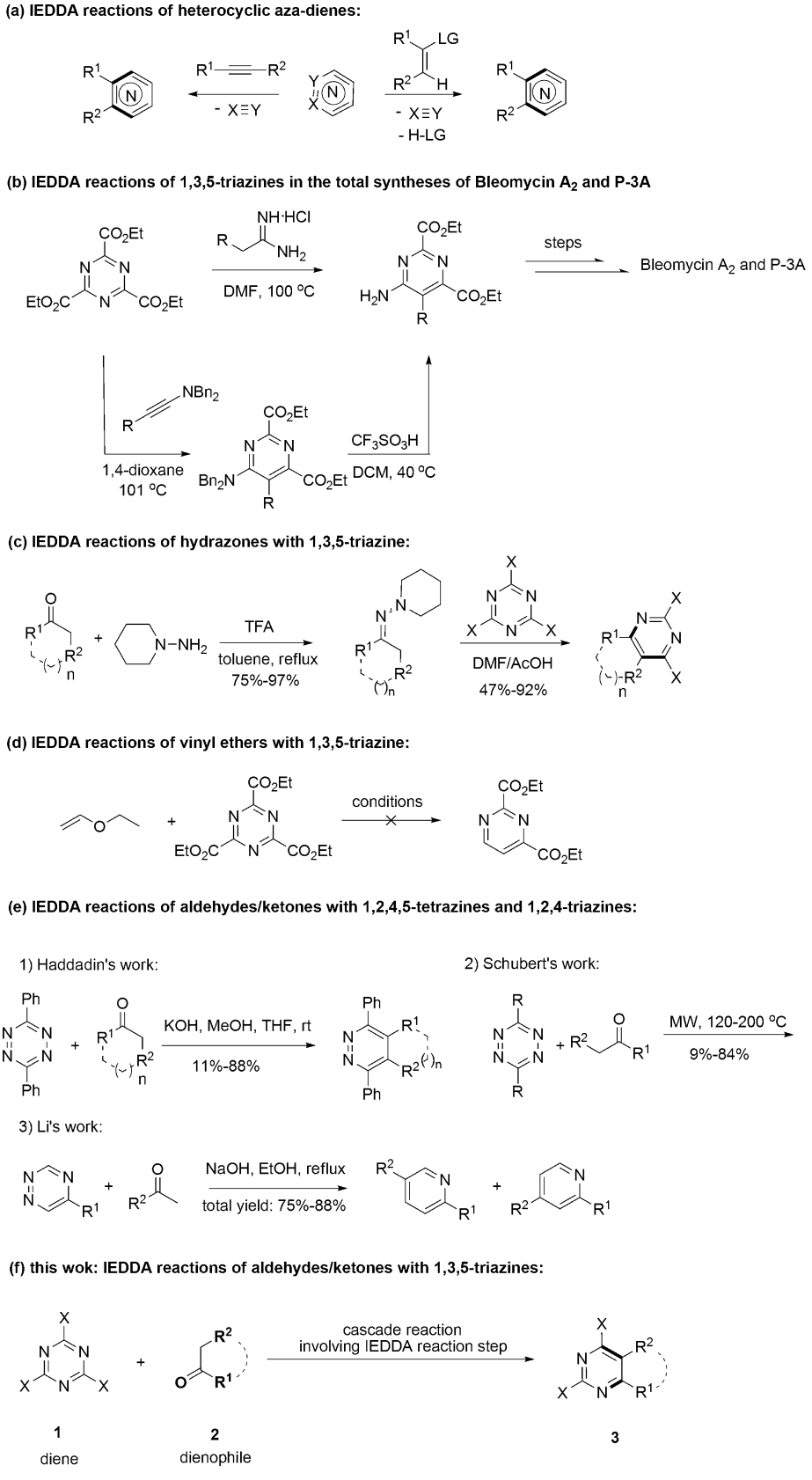
Scheme 1. Design of IEDDA Reactions of Aldehydes/Ketones with 1,3,5-Triazines



potential dienophiles with 1,3,5-triazines. With the contradictory implications in mind, we endeavored the investigations of the direct reaction of aldehydes/ketones with the less reactive and electron-deficient 1,3,5-triazines. Herein, we report the successful development of reaction conditions that enable aldehydes/ketones to react with 1,3,5-triazines directly, leading

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to IEDDA products in high yields (Scheme 1f). Moreover, investigation of the mechanism of this new reaction processes was carried out via both experimental and theoretical studies to provide further insights into this new cascade reaction.

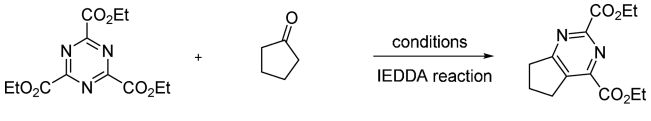
RESULTS AND DISCUSSION

Investigations of Direct Reactions of Aldehydes/Ketones with 1,3,5-Triazines. Ketone **2a** was studied with triazine **1a** under various reaction conditions, and the results are summarized in Table 1. We envisioned that there are two ways to increase the probability of success for aldehydes/ketones to function as productive dienophiles: one way is to facilitate the enolization of aldehydes/ketones, and the other is to increase the reactivity of 1,3,5-triazines. To promote enolization of aldehydes/ketones, strong basic conditions have been used in the IEDDA reactions of 1,2,4-triazines and 1,2,4,5-tetrazines.[10] However, only a trace amount of desired IEDDA product **3a** was detected (entries 1−3) and prolonged heating led to decomposition of triazine **1a**, which was consistent with our previous observations that 1,3,5-triazines are not stable under basic conditions.[9] To enhance the reactivity of 1,3,5-triazines, acids might be needed, which act as either a catalyst or an additive. We reasoned that protonation of 1,3,5-triazines could decrease LUMO energies of triazines, and this would promote/speed up IEDDA reactions.[5−9]

Considering our past success with TFA in IEDDA reactions of 1,3,5-triazines, we began to use TFA as either a catalyst or an additive to promote the desired reaction, and explore other reaction conditions with DMF as the solvent (Table 1, entries 5−7). To our delight, the first reaction conditions tested using 10 mol % TFA as a catalyst produced pyrimidine **3a** in 72% yield after 2 days of heating (entry 5). An increase of the amount of TFA did not lead to higher yields nor shorter reaction time, suggesting that substoichiometric acid is preferred by the current reaction (entries 6 and 7). A Lewis acid, boron trifluoride etherate, was also tested, but only moderate yield of the desired IEDDA product was obtained (entry 8). After the identification of TFA as an effective acid catalyst, various solvents were screened to see if the reaction time could be shortened (entries 9−13). Traditionally polar solvents are preferred for aza-diene IEDDA reactions, likely due to their polar transition states of the cascade reactions.[11] Among the polar solvents tested, ethanol truly stood out since higher yield and shorter reaction time were observed (entry 12). The current reaction was slower and gave lower yield in DMSO compared to ethanol, which is surprising since the reaction was carried out at 20 °C higher temperature and DMSO is more polar than ethanol (Table 1, entry 13). Moreover, TFA was also confirmed as a useful catalyst in ethanol (Table 1, entry 14). With the optimized reaction conditions (entry 12 in Table 1) in hand, the scope of this new IEDDA reaction was explored, and results are summarized in Table 2.

As evident from Table 2, almost all the tested ketones were good substrates for the current IEDDA reaction, leading to

Table 1. Exploration of IEDDA Reaction Conditions of 1a with 2a[a]

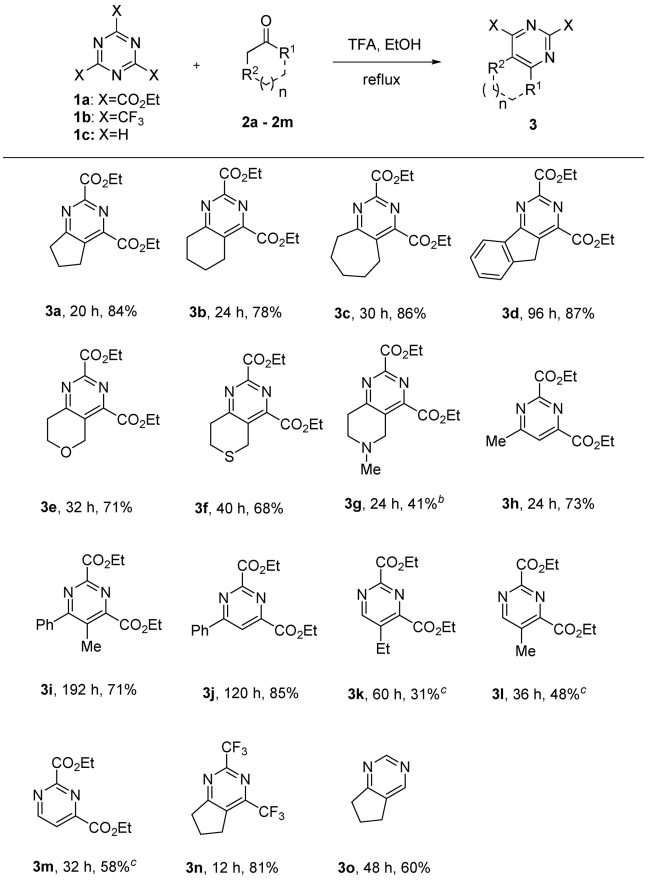


1a 2a 3a

entry	conditions	time	yield, %
1	KOH (0.1 equiv), EtOH, reflux	1 day	0
2	KOH (1.0 equiv), EtOH, reflux	8 h	0
3	*t*-BuOK (1.0 equiv), EtOH, reflux	1 day	0
4	DMF, 100 °C	4.5 days	57
5	TFA (0.1 equiv), DMF, 100 °C	3 days	72
6	TFA (0.5 equiv), DMF, 100 °C	2 days	66
7	TFA (1.0 equiv), DMF, 100 °C	1.7 days	61
8	$BF_3{\cdot}Et_2O$ (0.1 equiv), 1,4-dioxane, 100 °C	8 days	56
9	TFA (0.1 equiv), 1,4-dioxane, 100 °C	2.5 days	80
10	TFA (0.1 equiv), CH_3CN, reflux	4 days	83
11	TFA (0.1 equiv), DCE, reflux	12 days	45
12	TFA (0.1 equiv), EtOH, reflux	20 h	85
13	TFA (0.1 equiv), DMSO, 100 °C	5 days	50
14	EtOH, reflux	2 days	76

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), additive, and solvent (1 mL) were stirred at the indicated temperature under a nitrogen atmosphere, and monitored by LC-MS until all **1a** was consumed.

Table 2. IEDDA Reaction of Aldehydes/Ketones 2 with 1,3,5-Triazines 1[a]



[a]Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), and TFA (0.1 mmol) were stirred in EtOH (2 mL) at reflux under a nitrogen atmosphere until complete consumption of **1** as indicated by LC-MS. Reaction time and yields of isolated product are given. [b]2.1 mmol of TFA was used. [c]Reactions were conducted using **1a** (1.0 mmol) and aldehyde **2** (2.0 mmol) in EtOH (2 mL) at reflux under a nitrogen atmosphere, and after 24 h, an additional 2.0 mmol of aldehyde **2** was added.

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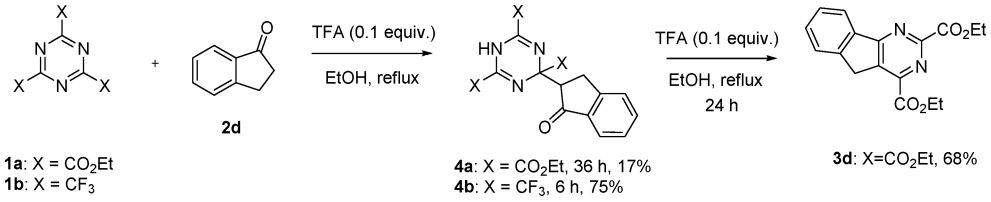
Scheme 2. Isolation of Intermediates 4a and 4b



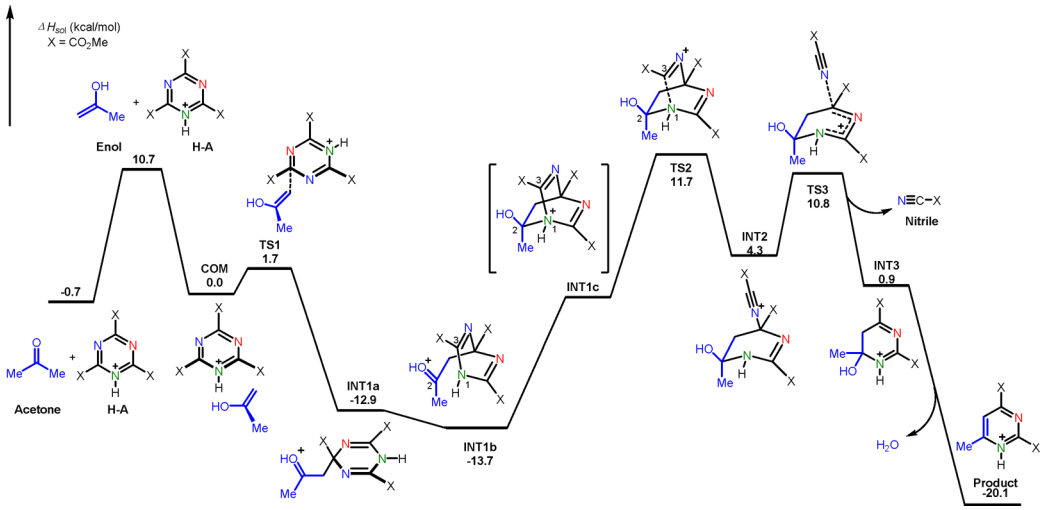


Figure 1. Energy profiles of the IEDDA reaction between **H-A** and acetone calculated at the MP2/6-311+G(d,p)-SMD(EtOH)//B3LYP/6-31G(d)-SMD(EtOH) level of theory.

moderate to high yields of the desired IEDDA products. Carbocyclic ketones (**2a**−**2d**) gave high yields of the desired IEDDA products (**3a**−**3d**), while heterocyclic ketones (**2e**−**2g**) produced the desired products (**3e**−**3g**) in moderate to high yields (41−87%). The presence of a basic amine group in ketone **2g** led to only 28% of **3g** under the current conditions. Increasing the amount of TFA to 2.1 equiv improved the yield to 41% (**3g**). Acyclic ketones (**2h**−**2j**), including even the low-boiling acetone (**2h**), were good substrates to produce the highly functionalized pyrimidines (**3h**−**3j**) in good to excellent yields (71−85%), together with excellent control of regiochemistry outcomes.

It was known that aldehydes generally have a higher propensity to enolize compared to ketones.[12] We expected that aldehydes should be more reactive than ketones in the 1,3,5-triazine IEDDA reactions. However, we found that aldehydes gave much lower yields than ketones in the current IEDDA reaction (**3k**−**3m**). We suspected that aldehydes might be unstable under the thermal and acidic conditions, which may account for the lower observed yields. Therefore, we decided to explore the optimal reaction conditions for the IEDDA reaction of aldehydes **2l** with 1,3,5-triazine **1a**. The optimal reaction conditions for aldehydes are heating **1a** and 4.0 equiv of **2l** (which was added by two portions) in EtOH without acidic additive (details of this optimization are summarized in the Supporting Information). Then, these conditions were applied to other aldehydes to produce the pyrimidine products in low to moderate yields (**3k**−**3m**, 31−58%).[10b] Other 1,3,5-triazines (**1b**−**1c**) were also explored and found to be suitable dienes for the current IEDDA reactions, leading to **3n** and **3o** in 81% and 60%, respectively.

Through the above investigations, we demonstrated that aldehydes/ketones can react directly with the relatively unreactive 1,3,5-triazines, leading to highly functionalized pyrimidines as IEDDA products. Considering that aldehydes and ketones are electron-deficient, it is counterintuitive to observe them as productive dienophiles in IEDDA reactions with electron-deficient 1,3,5-triazines, which prompted us to carry out both experimental and computational studies of the mechanism of the present reaction.[13]

Isolation of Reaction Intermediates and Stepwise Reaction Process. It is well established that IEDDA reactions of 1,3,5-triazines are cascade reactions.[4] Therefore, if some of the intermediates could be isolated and identified, it will help us elucidate the reaction mechanism. To this end, we selected the less reactive ketone **2d** and deliberately terminated its reactions with triazine **1a** and **1b** before completion. Fortunately, two intermediates were detected by TLC and were isolated (**4a** and **4b**, Scheme 2). Furthermore, the structure of intermediate **4b** was unambiguously assigned based on the X-ray crystallography analysis (ORTEP drawing of **4b** is shown in the Supporting Information).[14]

To confirm that compounds **4a** and **4b** are relevant intermediates, not just side products, we subjected compound **4a** to the current reaction conditions and obtained the corresponding IEDDA product **3d** in 68% yield (Scheme 2). It was further determined that an acid was required for ketone **2d** to function as a productive dienophile in the IEDDA reaction with triazine **1a**, since, after 1 week of heating in EtOH, only a trace amount of intermediate **4a** (<5%) (but no final product **3d**) was detected by TLC and LC-MS. These results suggested that the acid is essential for the initial formation of intermediate **4a**. Furthermore, heating of **4a** in refluxing ethanol for 2 days did not produce any trace of compound **3d**, which indicated that the presence of an acid was required for the subsequent conversion of the intermediate **4a**

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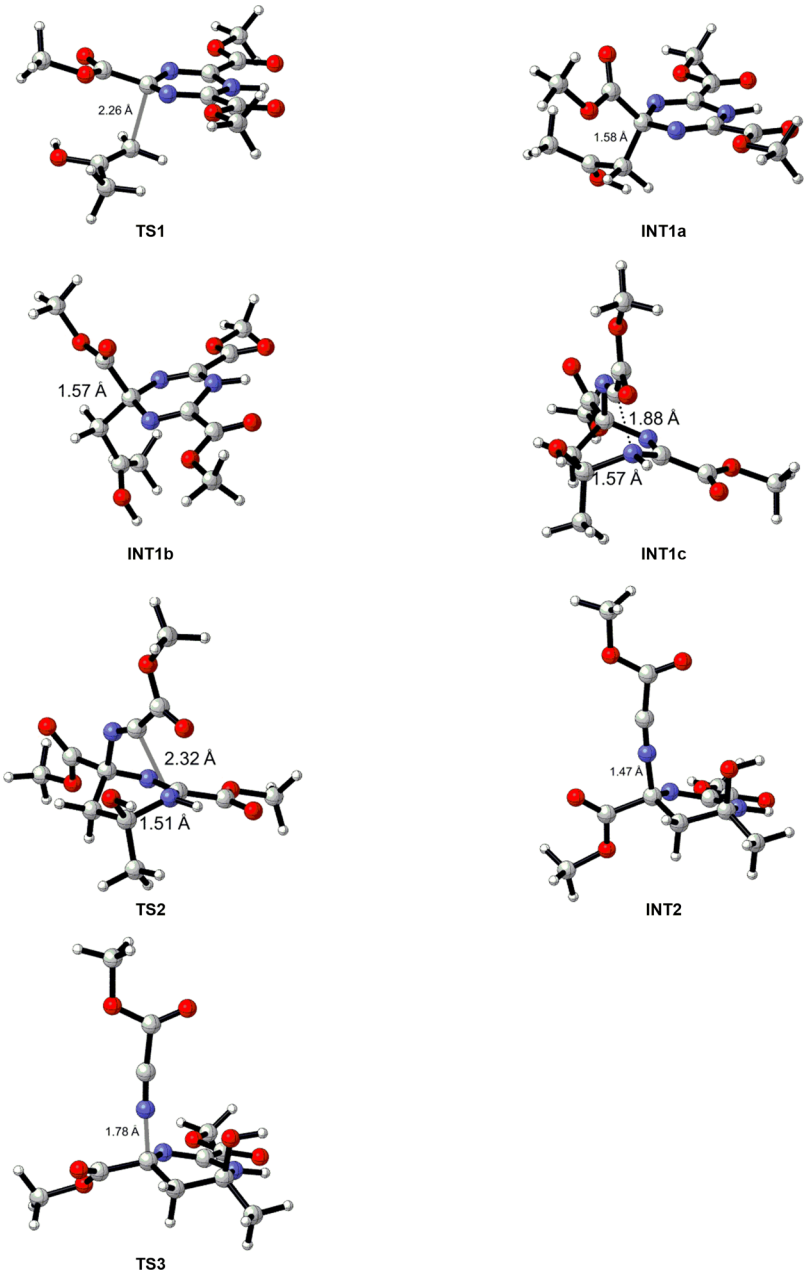

Figure 2. Key structures calculated at the B3LYP/6-31G(d)-SMD(EtOH) level of theory.

to the final IEDDA product **3d**. Therefore, these results provide strong experimental evidence that the current IEDDA reaction occurred through a stepwise mechanism and an acid is required to catalyze both steps of reactions.[11]

Quantum Chemical Calculations of the Stepwise Pathways of IEDDA Reaction between Protonated Triazine and Acetone. Quantum chemical calculations[15] with the B3LYP functional[16] and 6-31G(d) basis set in ethanol solution using SMD model[17] were carried out to understand the detailed process of the IEDDA reaction between triazine and ketones/aldehydes.[11,18] Then, energy evaluations were performed using MP2 single point energy calculations[19] using the 6-311+G(d,p) basis set[20] in ethanol solvent using the SMD model, since B3LYP was found to overestimate the aromatization energy for aromatic compounds.[11] More discussions of computational methods are given in the Supporting Information. The discussed energies here are enthalpies in ethanol solution.

To simplify the calculations, trimethyl 1,3,5-triazine-2,4,6-tricarboxylate (**A**) and acetone **2h** were chosen as the model substrates. Considering the fact that substoichiometric TFA was used in the current reaction, we hypothesized that protonated 1,3,5-triazine-2,4,6-tricarboxylate (**H-A**) is the real reactive species for the cascade reaction. This hypothesis was supported by our calculations given in Figures 1 and 2 (see more discussions in the Supporting Information). On the basis of quantum chemical calculations, we proposed that the cascade reaction started from the formation of a complex, **COM**, between **Enol** and **H-A**, which is exothermic by 10.7 kcal/mol (here, we did not consider the complex formation of acetone and **H-A**). The subsequent C−C bond formation (via transition state **TS1**) is facile with an activation enthalpy of only 1.7 kcal/mol, and this step is exothermic by 12.9 kcal/mol,

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giving rise to intermediate **INT1a**. Then, **INT1a** is converted to a more stable intermediate, **INT1b**, via rapid C−C bond rotation. Initially, we proposed that **INT1b** could be converted to **INT1c** via the C2−N1 bond formation; then, **INT1c** underwent C3−N1 bond cleavage to give **INT2**. We successfully located C3−N1 bond cleavage transition state **TS2**, but failed to locate intermediate **INT1c**, which is not a stationary point. IRC calculations from **TS2** suggested that this transition state is connected by **INT1b** and **INT2**. During the process from **TS2** to **INT1b**, intermediate **INT1c** was observed in the IRC calculation (if an alcohol is present nearby, this intermediate can be located; see Figure S5 of the Supporting Information). This suggests that, once **INT1a** is formed, it then undergoes a series of transformations of **INT1a** → **INT1b** → **INT1c** → **TS2** → **INT2**.

The followed step in the cascade reaction is the liberation of nitrile from **INT2** via transition state **TS3**, which needs an activation enthalpy of 6.5 kcal/mol and generates **INT3**. Finally, elimination of water from **INT3** gives the protonated cycloadduct, and this step is exothermic by 21.0 kcal/mol.

The above calculations showed that the rate-determining step is the C3−N1 bond cleavage step and an overall activation enthalpy is 25.4 kcal/mol (from **INT1b** to **TS2**). This suggests that **INT1b**, which is the most stable intermediate in the potential energy surface, could be isolated if it is deprotonated. This DFT-located intermediate was supported by the observation of **4a** in the experiment (actually, the existence of **INT1b** predicted by calculations was before the experimental isolation of **4a** intermediate).

Crossover Experiment. On the basis of the above studies, we considered that aldehydes/ketones underwent enolization before participation in the current IEDDA reaction. We reasoned that vinyl ethers locked in the presumed reactive forms should be more reactive than corresponding aldehydes/ketones. Therefore, it would be interesting to compare the relative reactivities of vinyl ethers and aldehydes/ketones in the current reaction to verify this hypothesis.

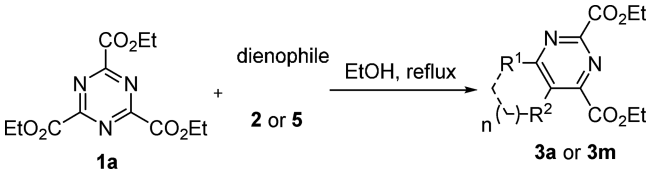
Since heating 1,3,5-triazine **1a** and aldehydes in EtOH without acidic additive is the optimal reaction conditions for aldehydes, and vinyl ethers were not stable in acids (results of reactions of vinyl ethers with **1a** under acidic conditions are summarized in the Supporting Information), the relative reactivities of vinyl ethers and aldehydes/ketones were compared under the same neutral conditions, and the results are summarized in Table 3.

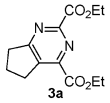
Even though vinyl ethers **5a** and **5b** are locked in the presumed reactive forms, they proved to be significantly less reactive than their corresponding ketones and aldehydes **2a**/**2m** (entries 1−4). This observation was surprising to us and must be explained.

On the basis of the above observations, we hypothesized that, under neutral conditions, triazine **1a** could function as a base to promote the enolization of ketone/aldehyde **2a**/**2m**, and during the process triazine **1a** becomes protonated and the protonated triazine serves as the reactive diene for the IEDDA reaction to proceed smoothly (Scheme 3). Moreover, this self-activation process of the triazine-ketone/aldehyde system does not require high concentration of the protonated triazine since the proton is not consumed during the reaction sequence (Figure 1).

On the other hand, when vinyl ethers **5a** and **5b** were used as dienophiles, triazine **1a** could not be activated via protonation and the vinyl ethers themselves are not electron-rich enough to undergo the traditional [4 + 2] cycloaddition reactions with free-base form triazine (entries 2 and 4, Table 3). If the above hypothesis is correct, then addition of aldehydes/ketones to the vinyl ether reaction system could help to catalyze/promote the IEDDA reactions with vinyl ethers. Indeed, addition of substoichiometric aldehyde **2m** into the reaction of vinyl ether **5b** and triazine **1a** produced the desired IEDDA product **3m** in comparable yield as the reaction with **2m** as the dienophile (entry 5); albeit the reaction took longer time to go to completion. A crossover study was also conducted with vinyl ether **5a**, and aldehyde **2m** also showed catalytic activity for the IEDDA reaction of vinyl ether **5a** with triazine **1a**, leading to the desired product **3a** (entry 6). In order to demonstrate that the observed effect is not simple due to the presence of a carbonyl group, but an enolizable carbonyl group capable of delivering a proton, the reaction was conducted with benzophenone, which is not enolizable and thus cannot provide a proton. We found that benzophenone cannot catalyze/promote the IEDDA reaction of **1a** with **5b** (details of this reaction are summarized in the Supporting Information). These experiments supported our hypothesis and the proposed reaction mechanism (Figure 1 and Scheme 3).

Table 3. Reactivity Comparison among 2a, 2m, 5a, 5b in the IEDDA Reaction[a]



entry	dienophile	product	time, d	yield[b] ,%
1	 2a	 3a	2	72
2	 5a	**3a**	7	<5[c]
3	Me−CHO 2m	 3m	3/2.8[d]	45/36[d]
4	 5b	**3m**	7	<5[c]
5	**5b+2m**[e]	**3m**	6.5	54
6	**5a+2m**[e]	**3a**	8.5	46

[a]Unless specified, 0.5 mmol of **1a**, 1.0 mmol of **2a**/**5a**, or 2.0 mmol of **2m**/**5b** were used. [b]Yields of isolated product. [c]**1a** remained. [d]4.0 mmol of **2m**. [e]0.05 mmol of **2m**.

CONCLUSION

In summary, the inverse electron demand Diels−Alder (IEDDA) reactions of electron-deficient 1,3,5-triazines and electron-deficient aldehydes/ketones have been developed and can be used to synthesize highly functionalized pyrimidines. In

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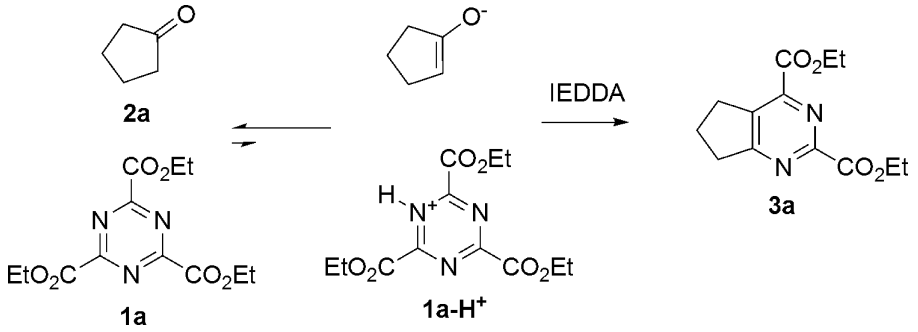
Scheme 3. Self-Activation within the Triazine-Ketone System



this reaction, aldehydes/ketones are directly introduced as productive dienophiles for the IEDDA reactions. The reaction mechanism was carefully studied by the combination of experimental investigation and computational studies. The experimental results indicated that the *ih*DA reactions occurred through a stepwise mechanism and an acid was required for both *ih*DA and *r*DA reactions. Quantum chemical calculations showed that aldehydes/ketones first protonated triazine to give enol and protonated triazine, which are the real reactants for the DA reaction. The DA reaction is stepwise and starts from C−C bond formation via **TS1**, which is then followed by cleavage of the C3−N1 bond and release of nitrile (Figure 1). The rate-determining step is the C3−N1 bond cleavage step via **TS3**, and the overall activation energy is 25.4 kcal/mol. This mechanism was further supported by the discovery that aldehydes/ketones can provide a proton to activate triazines, which can then take part in the otherwise difficult IEDDA reaction with nonproductive vinyl ethers. Our studies should break the dogma and traditional thinking that electron-rich dienophiles are required for the IEDDA reaction with 1,3,5-triazines. The discovery of this new reaction should provide impetus for chemists to rethink the classical IEDDA reactions, which may open new areas/directions for IEDDA reactions. On the basis of the results and observation from these studies, other IEDDA reactions with aldehydes/ketones will be designed and developed.

EXPERIMENTAL SECTION

General Methods. Acetonitrile (CH_3CN), *N*,*N*-dimethylformamide (DMF), and dichloroethane (DCE) were dried with CaH_2 and distilled. 1,4-Dioxane and ethanol (EtOH) were dried with Na and distilled. DMSO was dried with $MgSO_4$ and distilled. All other commercial reagents were used as received without additional purification. The melting point was uncorrected. Mass spectra were obtained using the ESI method. ^{1}H NMR and ^{13}C NMR spectra were recorded on 300 and 75 MHz spectrometers, respectively, with TMS as the internal standard, using $CDCl_3$ or DMSO-d_6 as solvents. Data for ^{1}H NMR spectra are reported as follows: chemical shift δ (ppm), referenced to TMS; multiplicities are indicated as the following: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; coupling constants (Hz) and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift δ (ppm) relative to residual solvent peak ($CDCl_3$: 77.16 ppm; DMSO-d_6: 39.50 ppm). HRMS was recorded on an LC TOF (ES). Compounds **3a**−**3c**, **3e**−**3f**, **3i**−**3j**, **3o** are known compounds and have been reported in the previous references.[5b,9,21]

General Procedure for the Synthesis of Pyrimidines from Ketones. To a stirred mixture of **1** (1.0 mmol) and ketone **2** (2.0 mmol) in EtOH (2.0 mL) was added TFA (8.0 μL, 0.1 mmol) under a nitrogen atmosphere. The resulting solution was stirred for the corresponding time under reflux and then cooled to room temperature, and quenched with saturated $NaHCO_3$ (10 mL). The aqueous layer was separated and extracted with DCM (3 × 10 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuum. Purification of the resulting residue by flash column chromatography (eluting with PE/EtOAc 5:1 to 2:1, v/v) afforded the product **3**.

*Diethyl 6,7-Dihydro-5H-cyclopenta[d]pyrimidine-2,4-dicarboxylate (**3a**).*[21] (222 mg, 84%); yellow solid, mp: 43−44 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58−4.46 (m, 4H), 3.39 (t, J = 7.8 Hz, 2H), 3.21 (t, J = 7.8 Hz, 2H), 2.30−2.19 (m, 2H), 1.49−1.43 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.2, 164.3, 163.5, 155.9, 150.2, 138.5, 62.9, 62.6, 34.3, 30.7, 22.2, 14.31, 14.27. MS (ESI): m/z 265.1 [M + H^+].

*Diethyl 5,6,7,8-Tetrahydroquinazoline-2,4-dicarboxylate (**3b**).*[21] (217 mg, 78%); yellow solid, mp: 41−42 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57−4.43 (m, 4H), 3.10−2.99 (m, 4H), 1.98−1.83 (m, 4H), 1.47−1.41 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 164.8, 163.5, 155.8, 153.8, 131.5, 62.8, 62.5, 33.0, 25.4, 21.7, 21.6, 14.3, 14.2. MS (ESI): m/z 279.1 [M + H^+].

*Diethyl 6,7,8,9-Tetrahydro-5H-cyclohepta[d]pyrimidine-2,4-dicarboxylate (**3c**).*[21] (251 mg, 86%); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56−4.43 (m, 4H), 3.22−3.18 (m, 2H), 2.96−2.92 (m, 2H), 1.93−1.89 (m, 2H), 1.77−1.71 (m, 4H), 1.47−1.40 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.3, 165.4, 163.5, 156.2, 154.0, 135.3, 62.8, 62.5, 39.0, 32.9, 29.2, 26.7, 25.7, 14.3, 14.2. MS (ESI): m/z 293.1 [M + H^+].

*Diethyl 5H-Indeno[1,2-d]pyrimidine-2,4-dicarboxylate (**3d**).* (271 mg, 87%); yellow solid, mp: 142−144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36−8.33 (m, 1H), 7.71−7.53 (m, 3H), 4.63−4.53 (m, 4H), 4.37 (s, 2H), 1.54−1.49 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 164.3, 163.9, 156.9, 149.9, 146.0, 137.5, 136.5, 132.6, 128.0, 125.6, 123.5, 62.9, 62.7, 35.5, 14.3. HRMS (ESI-TOF): calcd. for $C_{17}H_{17}N_2O_4$ [M + H]$^+$ 313.1188; found 313.1191.

*Diethyl 7,8-Dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-dicarboxylate (**3e**).*[9] (199 mg, 71%); yellow solid, mp: 82−83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13−5.12 (m, 2H), 4.58−4.45 (m, 4H), 4.10 (t, J = 6.0 Hz, 2H), 3.24−3.20 (m, 2H), 1.49−1.43 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 164.1, 163.2, 154.9, 151.3, 132.0, 65.7, 64.2, 63.1, 63.0, 32.3, 14.3, 14.2. MS (ESI): m/z 281.1 [M + H^+].

*Diethyl 7,8-Dihydro-5H-thiopyrano[4,3-d]pyrimidine-2,4-dicarboxylate (**3f**).*[9] (201 mg, 68%); yellow solid, mp: 50−51 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57−4.45 (m, 4H), 4.08 (s, 2H), 3.40 (t, J = 6.3 Hz, 2H), 3.03 (t, J = 6.3 Hz, 2H), 1.48−1.42 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 164.3, 163.1, 154.4, 154.2, 129.6, 63.0, 62.9, 34.3, 26.3, 25.2, 14.2, 14.1. MS (ESI): m/z 297.1 [M + H^+].

*Diethyl 6-Methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-dicarboxylate (**3g**).* (120 mg, 41%); yellow solid, mp: 124−125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66−4.36 (m, 4H), 3.94 (s, 2H), 3.25 (t, J = 5.9 Hz, 2H), 2.85 (t, J = 5.9 Hz, 2H), 2.55 (s, 3H), 1.48−1.42 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 164.3, 163.3, 154.4, 152.6, 130.5, 62.9, 62.7, 54.3, 51.1, 45.8, 33.0, 14.2, 14.1. HRMS (ESI-TOF): calcd. for $C_{14}H_{20}N_3O_4$ [M + H]$^+$ 294.1448; found 294.1456.

*Diethyl 6-Methylpyrimidine-2,4-dicarboxylate (**3h**).* (174 mg, 73%); yellow solid, mp: 37−38 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 4.53 (m, 4H), 2.76 (s, 3H), 1.59−1.33 (m, 6H). ^{13}C

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NMR (75 MHz, $CDCl_3$) δ 171.1, 163.7, 163.3, 157.3, 155.8, 122.1, 63.0, 62.9, 24.6, 14.2, 14.1. HRMS (ESI-TOF): calcd. for $C_{11}H_{15}N_2O_4$ $[M + H]^+$ 239.1026; found 239.1038.

*Diethyl 5-Methyl-6-phenylpyrimidine-2,4-dicarboxylate (**3i**).*[9] (223 mg, 71%); yellow solid, mp: 83−84 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63−7.59 (m, 2H), 7.53−7.48 (m, 3H), 4.56−4.47 (m, 4H), 2.52 (s, 3H), 1.48−1.43 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 165.1, 163.4, 158.3, 154.3, 136.9, 130.0, 129.2, 128.7, 128.6, 62.8, 62.6, 16.1, 14.2, 14.1; MS (ESI): m/z 315.1 $[M + H^+]$.

*Diethyl 6-Phenylpyrimidine-2,4-dicarboxylate (**3j**).*[21] (255 mg, 85%); yellow solid, mp: 115−116 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.28−8.25 (m, 2H), 7.59−7.54 (m, 3H), 4.60−4.52 (m, 4H), 1.52−1.47 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 164.0, 163.5, 158.0, 156.8, 135.1, 132.3, 129.3, 127.8, 117.8, 63.1, 62.9, 14.2. MS (ESI): m/z 301.1 $[M + H^+]$.

*2,4-Bis(trifluoromethyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (**3n**).* (207 mg, 81%); yellow oil; ^1H NMR (300 MHz,$CDCl_3$) δ 3.29−3.19 (m, 4H), 3.37−2.27 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.3, 135.2, 34.2, 28.8, 22.3. HRMS (ESI-TOF): calcd. for $C_9H_7F_6N_2$ $[M + H]^+$ 257.0508; found 257.0501.

*6,7-Dihydro-5H-cyclopenta[d]pyrimidine (**3o**).*[5b] (73 mg, 60%); yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.52 (s, 1H), 3.05−2.96 (m, 4H), 2.21−2.11 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 152.1, 34.2, 28.5, 22.6. MS (ESI): m/z 121.0 $[M + H^+]$.

General Procedure for the Synthesis of Pyrimidines from Aldehydes. A mixture of **1a** (1.0 mmol) and aldehyde **2** (2.0 mmol) in EtOH (2.0 mL) was stirred in EtOH (2 mL) at reflux under a nitrogen atmosphere. After 24 h, an additional 2.0 mmol of aldehyde **2** was added. The resulting solution was stirred for the corresponding time at reflux and then cooled to room temperature, and quenched with saturated $NaHCO_3$ (10 mL). The aqueous layer was separated and extracted with DCM (3 × 10 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuum. Purification of the resulting residue by flash column chromatography (eluting with PE/EtOAc 8:1 to 4:1, v/v) afforded the product **3**.

*Diethyl 5-Ethylpyrimidine-2,4-dicarboxylate (**3k**).* (78 mg, 31%); yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 4.55−4.46 (m, 4H), 2.94 (q, J = 7.5 Hz, 2H), 1.52−1.40 (m, 6H), 1.31 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 163.0, 160.3, 155.9, 154.6, 137.7, 62.9, 62.7, 23.4, 14.9, 14.2, 14.1. HRMS (ESI-TOF): calcd. for $C_{12}H_{17}N_2O_4$ $[M + H]^+$ 253.1183; found 253.1185.

*Diethyl 5-Methylpyrimidine-2,4-dicarboxylate (**3l**).* (115 mg, 48%); yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 8.89 (d, J = 0.6 Hz, 1H), 4.58−4.46 (m, 4H), 2.59 (d, J = 0.6 Hz, 3H), 1.49−1.43 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 165.1, 163.4, 156.6, 153.8, 121.1, 62.4, 62.3, 22.3, 14.0, 13.9. HRMS (ESI-TOF): calcd. for $C_{11}H_{15}N_2O_4$ $[M + H]^+$ 239.1026; found 239.1038.

*Diethyl Pyrimidine-2,4-dicarboxylate (**3m**).* (130 mg, 58%); yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 9.16 (d, J = 4.8 Hz, 1H), 8.13 (d, J = 5.1 Hz, 1H), 4.60−4.49 (m, 4H), 1.51−1.44 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 162.6, 159.8, 157.1, 156.0, 122.2, 62.7, 13.9, 13.8. HRMS (ESI-TOF): calcd. for $C_{10}H_{13}N_2O_4$ $[M + H]^+$ 225.0870; found 225.0877.

General Procedure for the Synthesis of Intermediates 4a and 4b. To a stirred mixture of **1** (1.0 mmol) and ketone **2d** (2.0 mmol) in EtOH (2.0 mL) was added TFA (8 μL, 0.1 mmol) under a nitrogen atmosphere. The resulting solution was stirred for the corresponding time under reflux and then cooled to room temperature, and quenched with saturated $NaHCO_3$ (10 mL). The aqueous layer was separated and extracted with DCM (3 × 10 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuum. Purification of the resulting residue by flash column chromatography (eluting with PE/DCM/EtOAc 3:1:1 to 1:1:1, v/v) afforded the product **4**.

*Triethyl 4-(1-Oxo-2,3-dihydro-1H-inden-2-yl)-1,4-dihydro-1,3,5-triazine-2,4,6-tricarboxylate (**4a**).* (73 mg, 17%); yellow oil; ^1H NMR (300 MHz, DMSO-d_6) δ 10.15 (s, 1H), 7.68−7.55 (m, 3H), 7.43−7.38 (m, 1H), 4.32−4.17 (m, 6H), 3.74 (dd, J = 8.1, 4.8 Hz, 1H), 3.25 (dd, J = 17.4, 8.1 Hz, 1H), 2.89 (dd, J = 17.4, 8.1 Hz, 1H), 1.28−1.18 (m, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 203.3, 167.8, 159.62, 159.59, 153.5, 145.2, 144.7, 136.8, 134.7, 127.3, 126.7, 122.9, 81.1, 62.7, 62.6, 61.4, 54.9, 29.0, 13.8, 13.73, 13.68. HRMS (ESI-TOF): calcd. for $C_{21}H_{24}N_3O_7$ $[M + H]^+$ 430.1609; found 430.1627.

*2-(2,4,6-Tris(trifluoromethyl)-2,5-dihydro-1,3,5-triazin-2-yl)-2,3-dihydro-1H-inden-1-one (**4b**).* (311 mg, 75%); white solid oil; mp 95−96 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.94 (s, 1H), 7.74−7.64 (m, 3H), 7.45 (t, J = 7.5 Hz, 1H), 3.45 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 202.2, 153.0, 135.8, 135.4, 127.7, 126.6, 124.3, 123.2, 120.5, 52.2, 27.4. HRMS (ESI-TOF): calcd. for $C_{15}H_9F_9N_3O$ $[M + H]^+$ 418.0596; found 418.0605.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02570.

Crystal structure of **4b** (CIF)

Additional data for Tables 2 and 3 and quantum chemical calculations, the crystallographic data, and copies of the ^1H and ^{13}C NMR (PDF)

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Notes

The authors declare no competing financial interest.

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