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One-Pot Synthesis of 1,3,5-Triazine Derivatives via Controlled Cross-Cyclotrimerization of Nitriles: A Mechanism Approach

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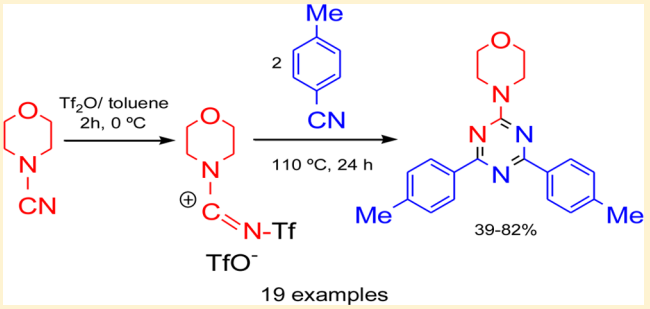
Supporting Information

ABSTRACT: The reaction of equimolecular amounts of a nitrile and triflic anhydride or triflic acid at low temperature produces an intermediate nitrilium salt that subsequently reacts with 2 equiv of a different nitrile at higher temperature to form 2,4-disusbstituted-6-substituted 1,3,5-triazines in moderate to good yields. This synthetic procedure has also been applied to the preparation of a 1,3,5-triazine having three different substituents. The results are explained in terms of a mechanism based on the relative stability of the intermediate nitrilium salts that are formed through a reversible pathway. The formation of a substituted isoquinoline using benzyl cyanide as the second nitrile supports the postulated mechanism as well as the structure of derivatives of the proposed intermediate when the reaction is carried out in the presence of different nucleophiles other than nitriles. Theoretical calculations and the monitoring of the reaction using ^{1}H and ^{13}C NMR spectroscopy are in agreement with the proposed mechanism pathway.



INTRODUCTION

The derivatives of 1,3,5-triazine are well-known compounds[1] of considerable interest because of their applications in many different fields. Thus, triazine derivatives have found applications as pharmaceuticals,[2] liquid crystals,[3] building blocks for supramolecular chemistry,[4] reactive dyes,[5] organic light-emitting diodes (OLEDs),[6] and chemical reagents for selected transformations.[7] Nevertheless, the preparation of polyfunctional 1,3,5-triazines is still a challenge. Several synthetic methods for their preparation have been reported, fundamentally based on the controlled stepwise nucleophilic displacement of the chlorine atoms of cyanuric chloride.[8] Additionally, the copper-catalyzed cross-coupling of Grignard reagents with monochloro azacycles leads to pyridine, pyrimidine, and 1,3,5-triazine derivatives.[9] Iodotriazines can undergo a Mg/I exchange for the preparation of mono- and dimagnesiated triazines.[10] Finally, nitriles and dicyanamides undergo [3 + 2] cycloaddition reactions affording triazines and tetrazoles under microwave irradiation.[11]

The *s*-1,3,5-triazines are well-known substances, but the direct synthesis of their derivatives with different substituents at each carbon atom presents several problems that have not been appropriately overcome so far. Because of the symmetry of the target compounds, the cyclization of three identical or different N−C units can provide access to these heterocycles. Nitriles,[11] imidates,[12] and amidine derivatives[13] are the units used in these procedures. The cyclization is a multistep process whose intermediates have not always been unambiguously identified, and the outcome of the reaction strongly depends on the reaction conditions.[1c] For example, the cyclotrimerization of nitriles is a very common route to symmetrical 1,3,5-triazine derivatives, but yields vary considerably and pressure and/or catalysts play a fundamental role.[14] Catalysts used have been protic and Lewis acids,[15] basic compounds,[16] solvent-free conditions,[17] and different lanthanide salts.[18]

On the other hand, different N−C units have been used for the preparation of azaheterocycles. Thus, the nucleophilic addition of nitriles to activated amines leads to the formation of pyrimidine derivatives,[19] while the reaction of nitriles and alkynes affords substituted pyridines and isoquinolines.[20] The use of cyanic acid derivatives and aminocarbonitriles instead of nitriles permits the preparation of pyrimidine derivatives bearing methylthio and amino moieties.[21]

During our investigations on the synthesis of pyrimidines and other azacycles from ketones and nitriles using triflic anhydride (Tf_2O), minor amounts of symmetrically trisubstituted 1,3,5-triazines were detected among the reaction products.[22] This led to a report of a synthetic procedure for the preparation of symmetrically trisubstituted 1,3,5-triazines from nitriles and triflic anhydride[23] and later from nitriles with large amounts of triflic acid (TfOH).[24] However, a mechanism for the reactions was unclear, and the

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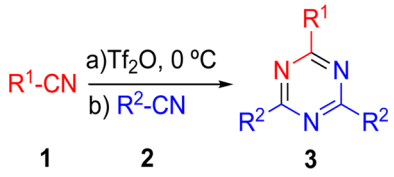
intermediates involved were not identified. Reported herein is the synthesis of 1,3,5-triazine derivatives via controlled cross-cyclotrimerization of nitriles. The process is examined to provide a deeper understanding of the corresponding reaction mechanism.

RESULTS AND DISCUSSION

The one-pot reaction of a nitrile R^1CN (**1**) with Tf_2O or TfOH (depending on the reactivity of nitriles) at low temperature and subsequent addition of a 2-fold amount of a different nitrile R^2CN (**2**) followed by heating at 100 °C for 24 h affords 1,3,5-triazines (**3**) with two different substituents in moderate to good yields (Scheme 1 and Table 1).

Scheme 1. Synthesis of 2,4-Disubstituted-6-substituted 1,3,5-Triazines 3 from Nitriles and Tf_2O



1 2 3

Nitriles have been shown to react with methyl triflate to initially form nitrilium salts,[25] which are then converted into synthetically useful molecules by reaction with a variety of nucleophiles.[26] This led us to postulate that the first step of the mechanism pathway involves the initial formation of triflate nitrilium salt **4** from nitrile R^1CN (**1**) and Tf_2O (Scheme 2). The carbon atom of the salt's imino moiety undergoes nucleophilic attack by the second nitrile R^2CN (**2**) to form an immonium salt **5**. The excess nitrile **2** acts again as a nucleophile on **5** to form another immonium salt, intermediate **6**. A subsequent cyclization reaction forms the triazine ring **7**, which yields the triazine **3** upon basic hydrolysis. It is noteworthy that the *s*-triazines corresponding to the trimerization of nitriles **1** and **2** are detected albeit in very low yields. The near absence of trimers from either **1** or from **2** suggests than nitrile **1** and Tf_2O are completely consumed in the formation of the intermediate **4**. Only trace quantities of **1** remain to take the role of nitrile **2**, and consequently the trimerization of **1** very rarely occurs. When nitrile **2** (R^2CN) is added to the reaction mixture, little or no Tf_2O is available to react with **2** to form a trimer.

The reaction seems to be controlled by the stability of the intermediate nitrilium salt **4**. Thus, when pivalonitrile (nitrile **1**) reacts with Tf_2O at low temperature to form nitrilium salt **8** followed by the addition of 2 equiv of *p*-tolunitrile (nitrile **2**), triazine **3c** is obtained in 75% yield (entry 3 of Table 1, Scheme 3). However, when the nitriles are reversed and nitrilium salt **9** formed first followed by addition of pivalonitrile, only triazine **3c** was obtained and in poor yield instead of the expected triazine **10** (Scheme 4).

The exclusive formation of triazine **3c** in both reactions can be explained by a pathway in which the corresponding nitrilium salts are formed through a reversible process controlled by the relative stabilities of these intermediates. Thus, the addition of pivalonitrile to intermediate **9** shifts the equilibrium to form the more stable nitrilium salt **8** and regenerated *p*-tolunitrile, which in turn reacts with **8** affording **3c** (Scheme 4). Similar results were obtained in the preparation of **3e**, where methylthiocyanate unexpectedly reacts faster with Tf_2O than *p*-methoxybenzonitrile affording **3e** instead of the expected 2-(4-methoxyphenyl)-4,6-bis-(methylthio)-1,3,5-triazine **11** (Scheme 5 and Experimental Section).

To shed light on the proposed mechanism, the reversibility of its first step was explored. The corresponding 2,4,6-tris(4-ethylphenyl)-1,3,5-triazine (**13**) was prepared by reaction of Tf_2O and a 3-fold amount of **12** (see Experimental Section). The reaction of 4-ethylbenzonitrile (**12**) with Tf_2O was repeated under various reaction conditions. First, equimolecular amounts of **12** and Tf_2O were mixed at 0 °C, and the reaction was allowed to attain room temperature. An equimolecular amount of benzyl alcohol was added, and subsequent heating afforded a mixture of *o*- and *p*-benzyltoluene (**15** and **16**) in a molecular ratio of 40:60, respectively, and 64% overall yield (Scheme 6). The formation of these compounds can be explained by an initial equilibrium between 4-ethylbenzonitrile (**12**) and Tf_2O to form the nitrilium salt **14**. The addition of the benzyl alcohol shifts the initial equilibrium to the starting stage (nitrile **12** and Tf_2O). Because alcohols are more reactive than nitriles toward Tf_2O, benzyl triflate is formed rather than **14**.[27] The benzyl triflate formed in situ easily generates a very reactive benzyl cation that reacts with toluene to form **15** and **16** via an electrophilic aromatic substitution. Significant amounts of nitrile **12** were recovered, while triazine **13** was detected in very low yield.

In addition, the intermediate nitrilium salt **14** was trapped by quenching the reaction mixture with nucleophiles other than nitriles or alcohols. The equilibrium reaction of **12**, Tf_2O, and the nitrilium salt **14** was quenched with 1,3,5-trimethoxybenzene as nucleophile reagent (Scheme 7). This time, the intermediate reacts with the aromatic substrate affording the substituted benzophenone **17**. Also formed was sulfone **18**, a consequence of the attack of the trimethoxybenzene at the electrophilic sulfur atom of the triflic anhydride. It is important to note that only minor amounts of the triazine **13** were obtained in this reaction. This fact clearly points to an initial equilibrium between nitrile, Tf_2O, and the nitrilium salt. The nitrilium salt intermediate is stable at low temperature until the addition of either nitriles or activated arenes acting as nucleophiles. Thus, the addition of a second nitrile leads to the formation of triazines, while the presence of activated arenes results in electrophilic aromatic substitution reactions. Similar processes are reported in the literature. For example, the reaction of aromatic nitriles and arenes in the presence of triflic anhydride affords diarylketones albeit in low yields.[28]

Dialkyl cyanamides (Table 1, entries 6−13) are ideal reagents (nitriles **1**) to react with Tf_2O because they easily form nitrilium salts that can react with alkyl or aryl nitriles. To demonstrate the versatility of the synthetic procedure, an equilibrium mixture of dimethylcyanamide, Tf_2O, and nitrilium salt was treated with an equimolecular mixture of 4-chloro- and 4-methylbenzonitrile. The main product (58%) was the triazine **19** having three different substituents, although small amounts of the different *s*-triazines were detected (Scheme 8). This result illustrates the enormous potential of this reaction for the synthesis of substituted triazines by simply controlling the addition order of the reactants and utilizing the relative reactivities of the nitriles toward the triflic anhydride.

Alkyl cyanides other than acetonitrile and pivalonitrile are unreactive toward Tf_2O and are recovered unaltered even

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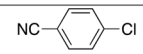
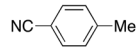
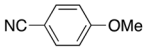
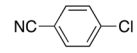
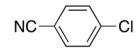
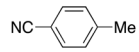
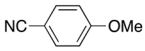
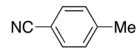
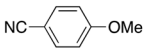
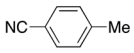
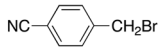
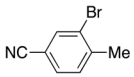
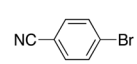
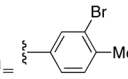
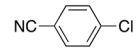
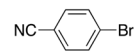
Table 1. Synthesized Triazines 3 from Nitriles 1 and 2

Entry	Nitrile 1 (R^1)	Nitrile 2 (R^2)	**3** Yield (%)[a]
1	MeCN		**3a**, R^1= Me, R^2 = *p*-Cl-C_6H_4 (67%),
2	MeCN	$Me(CH_2)_7CN$	**3b**, R^1= Me, R^2 = $Me(CH_2)_7$ (42%)
3	$(Me)_3C$-CN		**3c**, R^1= *t*Bu, R^2 = *p*-Me-C_6H_4 (75%)
4	$(Me)_3C$-CN	MeSCN	**3d**, R^1= *t*Bu, R^2 = SMe (69%)
5	MeSCN		**3e**, R^1= SMe, R^2 = *p*-OMe-C_6H_4 (51%)
6			**3f**, R^1=  , R^2 = *p*-Cl-C_6H_4 (82%)
7		$(Me)_3C$-CN	**3g**, R^1=  , R^2 = *t*Bu (67%)
8	$(Me)_2NCN$		**3h**, R^1= NMe_2, R^2 = *p*-Cl-C_6H_4 (76%)
9	$(Me)_2NCN$		**3i**, R^1= NMe_2, R^2 = *p*-Me-C_6H_4 (81%)
10	$(Me)_2NCN$		**3j**, R^1= NMe_2, R^2 = *p*-OMe-C_6H_4 (77%)
11			**3k**, R^1=  , R^2 = *p*-Me-C_6H_4 (80%)
12			**3l**, R^1=  , R^2 = *p*-OMe-C_6H_4 (77%)
13			**3m**, R^1=  , R^2 = cyclohexyl (59%)
14		$MeCH_2CN$	**3n**, R^1= *p*-Me-C_6H_4 , R^2 = $MeCH_2$ (49%)
15		PhCN	**3o**, R^1= *p*-$BrCH_2$-C_6H_4, R^2 = Ph (50%)
16[b]			**3p**, R^1=  , R^2 = *p*-Br-C_6H_4 (41%)
17[b]			**3q**, R^1=  , R^2 = *p*-Cl-C_6H_4 (45%)
18[b]			**3r**, R^1= 1-naphtyl, R^2 = *p*-Br-C_6H_4 (39%)

[a]Yield of isolated product. [b]Using TfOH.

after prolonged reaction times and harsh conditions. However, this lack of reactivity permits the use of these compounds as nitriles **2** (entries 2, 13, and 14). On the other hand, aromatic nitriles of reduced reactivity toward Tf_2O can be used as nitriles **1** if the reaction is carried out with triflic acid (TfOH) instead of Tf_2O (entries 16–18).

Unsubstituted benzyl cyanide shows a particularly interesting reactivity. Thus, when the nitrilium salt formed from pivalonitrile and Tf_2O, is treated with benzyl cyanide, the expected dibenzyl-substituted triazine **20** is not found. Instead, the substituted isoquinoline **21** was obtained in 41% reaction yield (Scheme 9). In this case, the cyclization step of the

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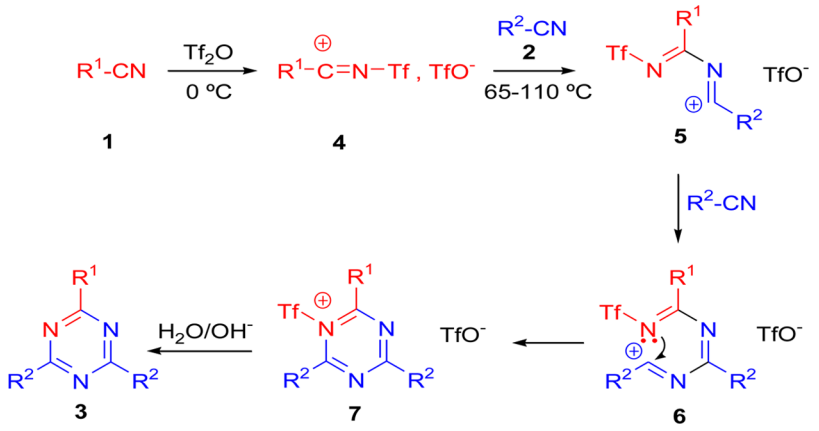
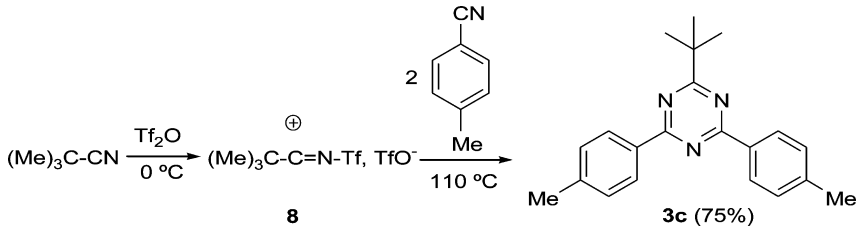
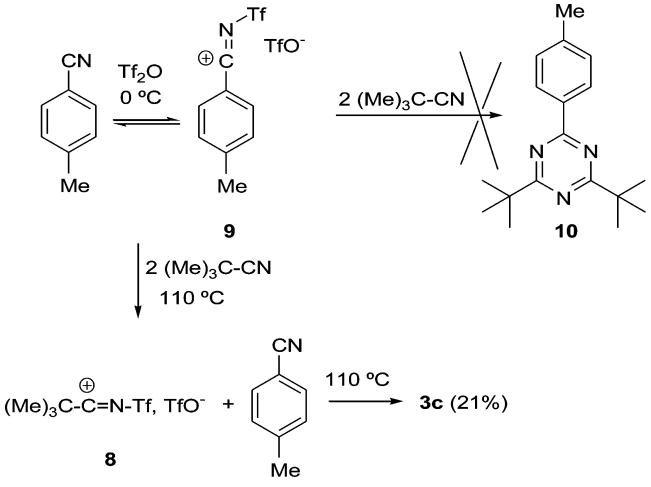
Scheme 2. Proposed Mechanism for the Synthesis of Triazines 3 from Nitriles 1 and 2



Scheme 3. Synthesis of Triazine 3c



Scheme 4. Formation of Triazine 3c Instead of Triazine 10



general proposed mechanism (Scheme 2) takes place at the activated *ortho* position of the phenyl ring of the benzyl cyanide. Moreover, the absence of triazine ring also precludes the elimination of the trifluoromethylsulfenyl group (Tf) in the last step of the process. The presence of the N-Tf moiety in the final product **21** supports the proposed mechanism outlined in Scheme 9.

Nuclear Magnetic Resonance Experiments. To test the proposed mechanism outlined in Scheme 2, we monitored the process using NMR techniques. In this regard, the reaction of 4-ethylbenzonitrile (**12**) with Tf_2O was selected. In its ^1H NMR spectrum this compound exhibits the typical signals of a deceptively simple AA′XX′ spin system corresponding to the protons of the *para*-substituted benzene ring. The same spin system is found in the triazine **13**, and the chemical shifts are sufficiently distinct to distinguish the species during the monitoring (Scheme 10). We used 1,1,2,2-tetrachloroethane-d_2 as solvent (undeuterated portion δ 6.00 ppm) to avoid signal overlap in the aromatic region and to facilitate the recording of the spectra at variable temperature.

Thus, the reaction of **12** with Tf_2O at 50 °C was monitored in a sample tube with ^1H NMR spectra at different times and temperatures. Figure 1 collects selected spectra of the aromatic region. The starting nitrile **12** (spectrum A, Figure 1) displays aromatic signals at 7.30 and 7.57 ppm (black arrows). The addition of an equimolecular amount of Tf_2O and heating at 50 °C during 2 h produces a new AA′XX′ spin system (spectrum B, Figure 1, red arrows). The chemical shifts for compounds **12** and **13** in the reaction mixture are quite different than those of the pure compounds (Scheme 10) due to the presence of triflic anhydride and the possible formation of traces of TfOH that modify the pH of the reaction mixture. The new AA′ portion resonates at 8.56 ppm while the corresponding XX′ portion appears at 7.55 ppm, practically overlapped with a signal of the starting nitrile. This new spin system can reasonably be assigned to the postulated nitrilium salt **14**. Theoretical calculations of the ^1H chemical shits for intermediate **14** are in agreement with the observed values, despite the difference of the solvent. Continuous monitoring of the reaction reveals a new aromatic system (7.44 and 7.98 ppm) corresponding to the protonated final product **13** (spectrum C, Figure 1, green arrows). Since the product triazine **13** (Scheme 2) is protonated in the crude mixture, its spectrum (spectrum C, Figure 1) is different from that of pure triazine **13** (spectrum D, Figure 1). It is noteworthy that the chemical shift differences for the aromatic protons between pure triazine and protonated triazine (reaction mixture) are higher for the protons of the AA′ portion than for the XX′ portion because the deshielded protons are closer to the protonated nitrogen atom. The increase of the signal intensities for the triazine **13** is

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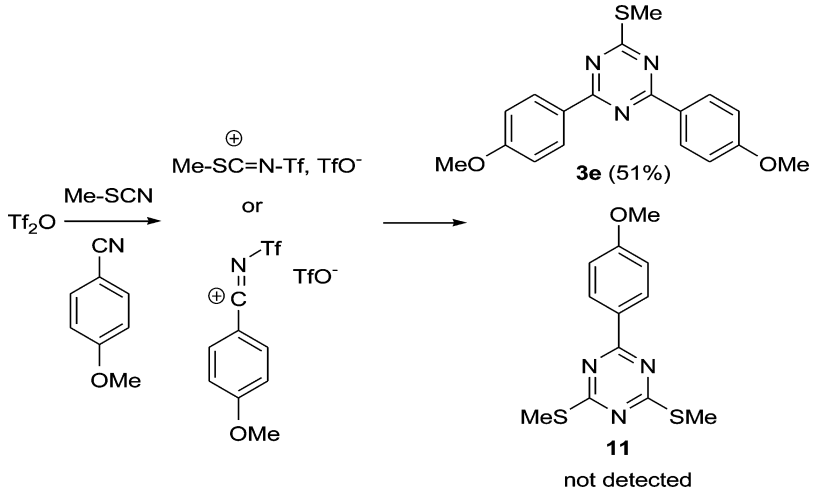
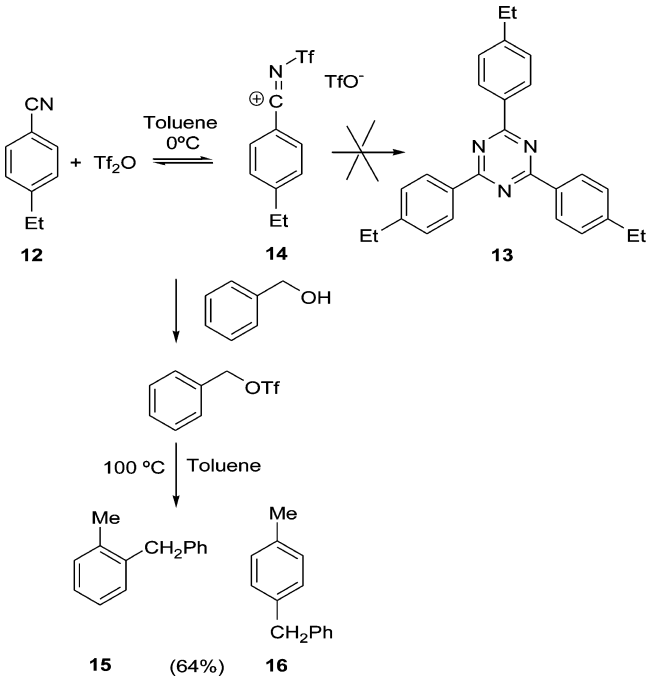
Scheme 5. Formation of Triazine 3e



Scheme 6. Reaction of Nitrile 12 and Tf_2O with Addition of Benzyl Alcohol and Formation of Compounds 15 and 16

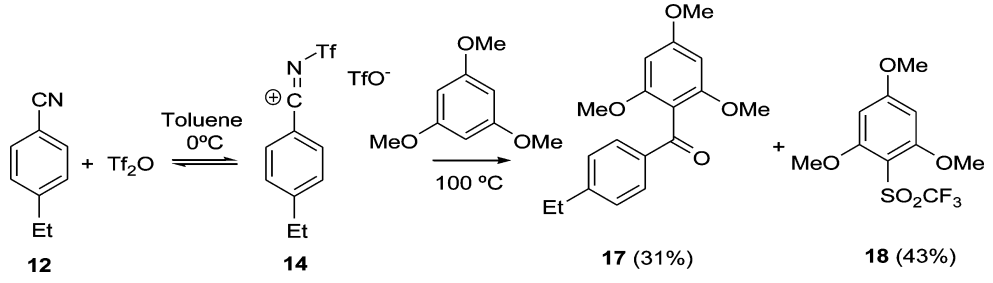


commensurate with the decrease of those for the starting nitrile and the corresponding intermediate.

The same results were obtained when the reaction was monitored by ^{13}C NMR. Chemical shifts of compounds **12**, **13**, and intermediate **14** are shown in Scheme 11. Figure 2 collects selected spectra recorded from the region between 110 and 170 ppm. The starting nitrile **12** (spectrum A, Figure 2) shows the signal assigned to C4 at 150.0 ppm (black arrow). Addition of an equimolecular amount of Tf_2O and heating at 50 °C during 2 h produces new signals, some of them overlapped, making assignments of these peaks more complicated. Among these, two important signals at 168 and 156 ppm (spectrum B, Figure 2) are indicated by red arrows. The broad signal of low intensity at 168 ppm can be more easily assigned with an HMBC spectrum (Figure 3). The observed correlations over three bonds with the aromatic protons of the AA′ portion (8.55 ppm) point to an unambiguously assignment of the peak at 168 ppm to the imino carbon atom of intermediate **14**. The new signal at 156 ppm corresponds to the C4 of the intermediate **14**. The peaks for the protonated triazine **13** are observed after 10 h of reaction (spectrum C, Figure 2). The carbon atom of the protonated triazine ring resonates at 174 ppm, while the C4 of this compound appears at 155 ppm (green arrows). The spectrum of the pure triazine **13** is displayed as spectrum D in Figure 2. As was the case in the ^1H NMR spectra, there are differences in the ^{13}C chemical shifts between protonated triazine (reaction mixture) and pure triazine **13**. Figure 4 shows the two overlapped quadruplets ($^1J_{C,F}$ = 323 Hz) assigned to the two CF_3 groups of nitrilium salt **14** underpinning the structure of the proposed intermediate.

Theoretical Calculations. To gain further insight into the cyclization process leading to the formation of triazines, a computational (DFT) study was carried out. The computed reaction profile (PCM-B3LYP/6-31+G(d)) is shown in Figure

Scheme 7. Reaction in the Presence of 1,3,5-Trimethoxybenzene and Formation of Compounds 17 and 18



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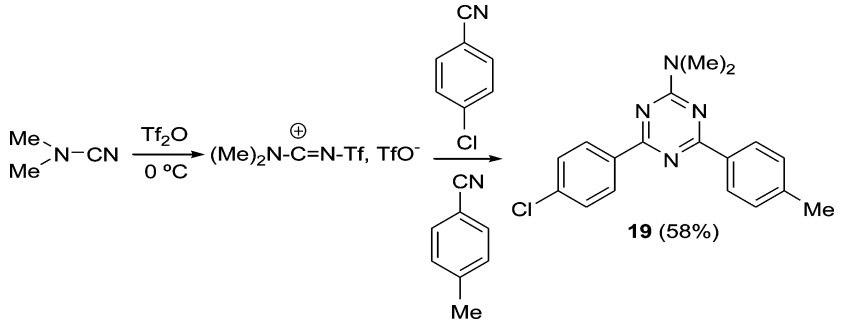
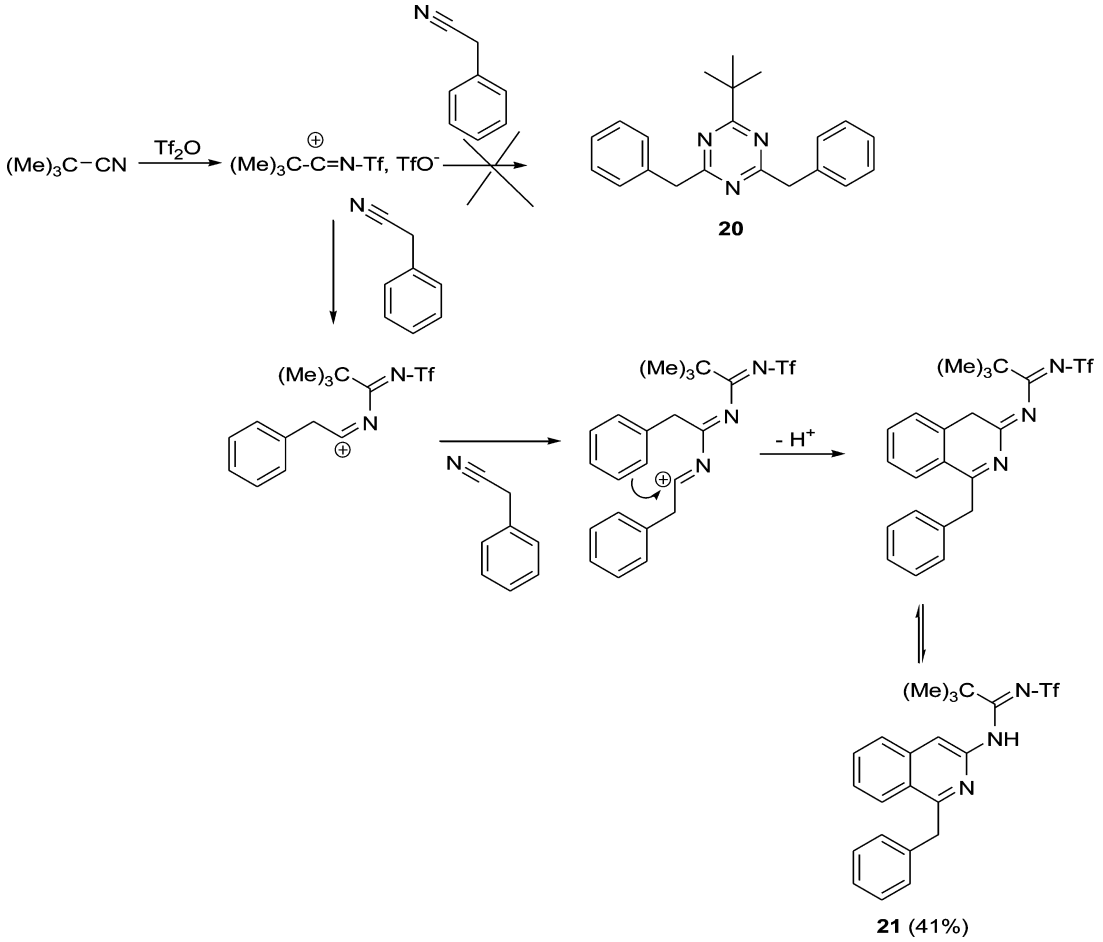
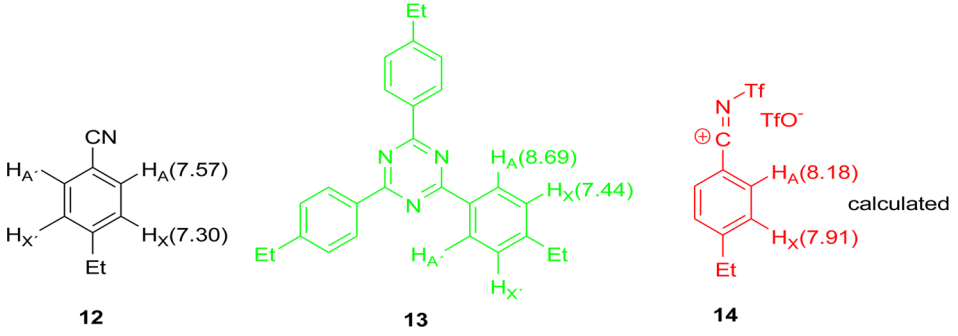
Scheme 8. Synthesis of Trisubstituted Triazine 19



Scheme 9. Proposed Mechanism for the Formation of Isoquinoline 21



Scheme 10. Observed ^{1}H Chemical Shifts for the AA′XX′ Spin Systems for 4-Ethylbenzonitrile 12 and Triazine 13 in 1,1,2,2-Tetrachloroethane-d_2 and Calculated Chemical Shifts for Nitrilium Salt 14 in $CDCl_3$



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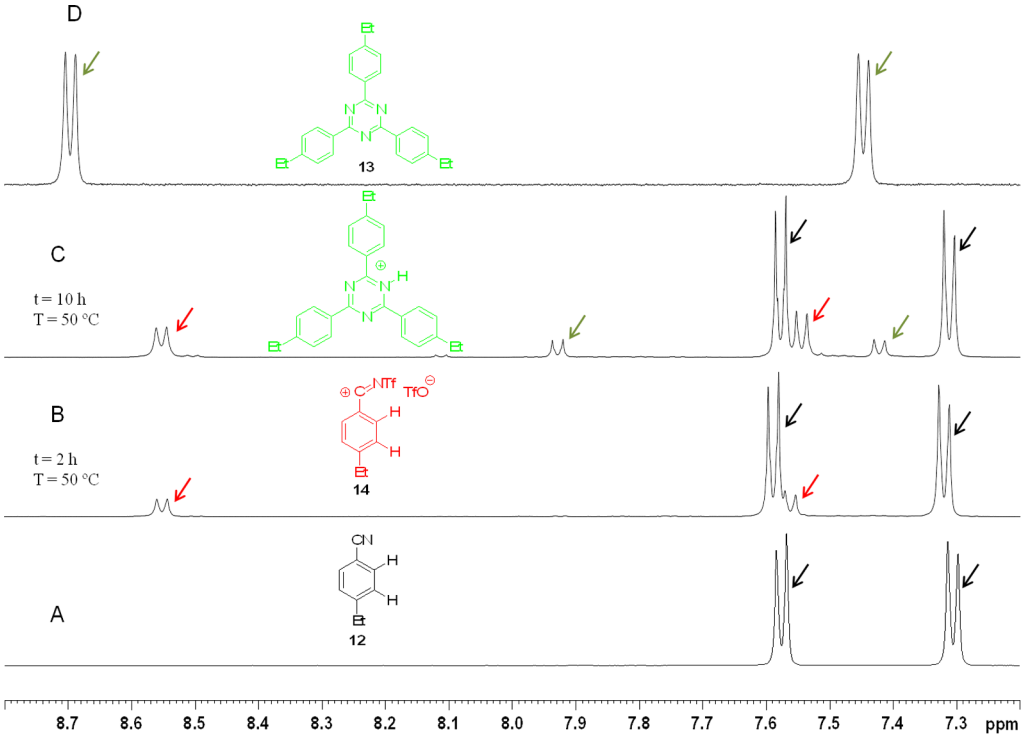
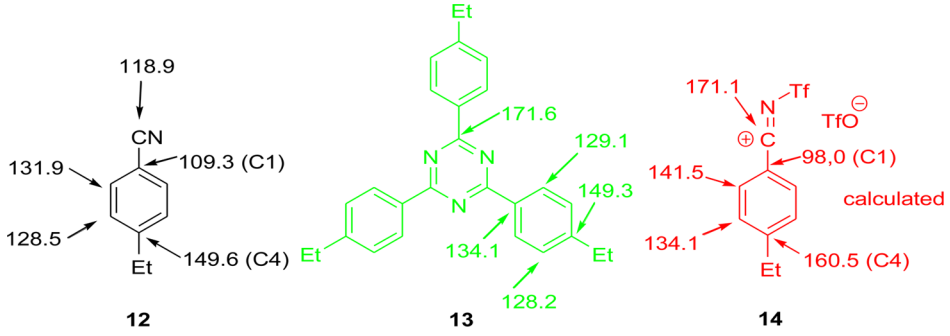


Figure 1. ^{1}H NMR monitoring (aromatic region) of the reaction of 4-ethylbenzonitrile **12** and Tf_2O in 1,1,2,2-tetrachloroethane-d_2.

Scheme 11. Observed ^{13}C Chemical Shifts for 4-Ethylbenzonitrile 12 and Triazine 13 in 1,1,2,2-tetrachloroethane-d_2 and Calculated Chemical Shifts for Nitrilium Salt 14 in $CDCl_3$



5, which shows the corresponding free energies (computed at 298 K) in toluene solution.

As reported previously,[25] the reaction starts from the nitrilium cation **INT0** formed by reaction of Tf_2O and MeCN. In the presence of a new molecule of nitrile (MeCN as model in the calculations), a weakly bonded van der Waals complex **INT1** is formed in a slightly endergonic ($\Delta G_{R,298}$ = 2.0 kcal/mol) reaction. Subsequent nucleophilic attack of the lone-pair of the nitrile at the highly electrophilic carbon atom of the nitrilium cation **INT0** produces the new cationic intermediate **INT2** through the transition state **TS1**. Figure 5 shows that this saddle point is associated with the formation of the new C···N bond with a computed activation barrier of 8.7 kcal/mol (from the initial weakly bonded complex **INT1**). Then, a second nucleophilic addition on **INT2** by a new molecule of nitrile leads to the formation of the cation **INT3**. This step is clearly endergonic ($\Delta G_{R,298}$ = 6.6 kcal/mol) with an associated activation barrier of 8.4 kcal/mol (via the saddle point **TS2**). At this point **INT3**, undergoes a ring closure to form triazine **INT4** by an easy intramolecular nucleophilic addition (computed activation barrier of only 3.8 kcal/mol) of the nitrogen atom attached to the triflic substituent to the carbocationic center in **INT3**. The gain in aromaticity in the readily formed triazine **INT4** explains the highly exergonic nature of this transformation ($\Delta G_{R,298}$ = −13.0 kcal/mol), and therefore this last step is the driving-force of the process. Finally, basic hydrolysis of **INT4** provides the experimentally obtained neutral triazines **3**.

■ CONCLUSIONS

We have developed a synthetic procedure for the preparation of 2,4-disubstituted-6-substituted 1,3,5-triazines using a one-pot reaction. The process is controlled by the initial formation of a nitrilium salt intermediate. Further reaction with 2 equiv of a different nitrile produces the corresponding triazines. Reactions carried out in the presence of different nucleophiles and followed with ^{1}H and ^{13}C NMR reaction monitoring support the reversible formation of a nitrilium salt in the first step of the proposed mechanism. Theoretical calculations are also in agreement with the postulated mechanism pathway. In

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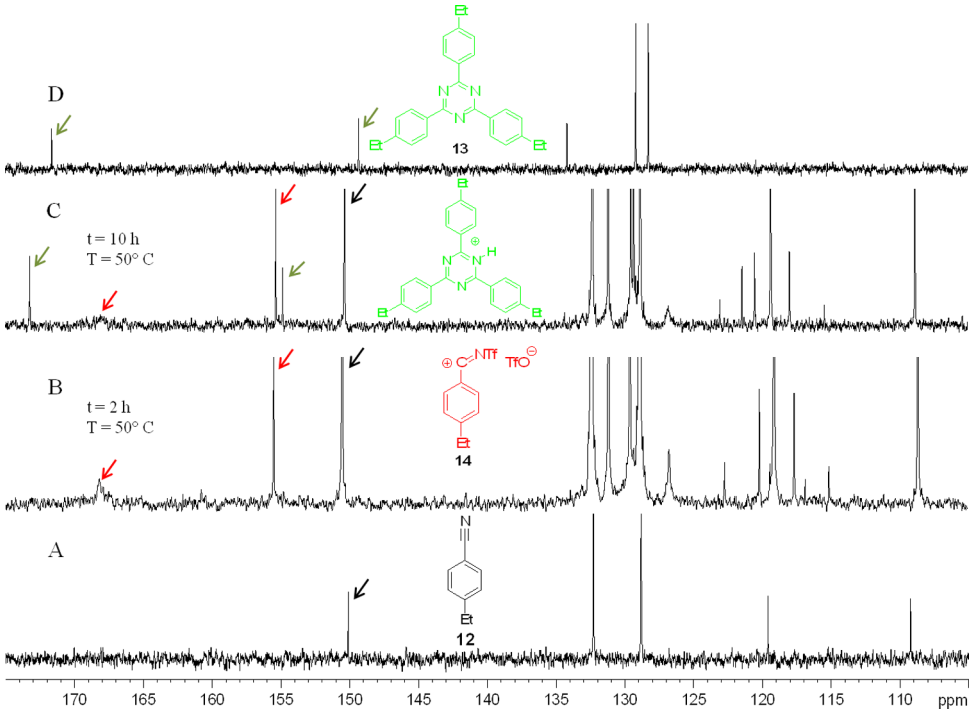

Figure 2. ^{13}C NMR monitoring (aromatic region) of the reaction of 4-ethylbenzonitrile **12** and Tf_2O in 1,1,2,2-tetrachloroethane-d_2.

conclusion, a variety of triazines can be prepared from two different nitriles, which cyclotrimerize by the action of triflic anhydride.

EXPERIMENTAL SECTION

All chemicals and solvents were purchased from commercial suppliers. Triflic anhydride was distilled over P_2O_5 before use. All reactions were carried out under argon atmosphere. The ^1H NMR and ^{13}C NMR spectra were recorded in solution of $CDCl_3$, *N*,*N*-dimethylformamide-d_7, CD_2Cl_2, and 1,1,2,2-tetrachloroethane-d_2 at 300, 500, and 700 MHz for ^1H and 57, 125, and 176 MHz for ^{13}C, respectively. Spectra were referenced to 7.26 and 77.0 ppm for chloroform, 8.01 and 166.5 ppm for DMF-d_7, 5.32 and 53.5 ppm for CD_2Cl_2, and 6.00 and 74.2 ppm for $C_2D_2Cl_4$, respectively. ^1H NMR spectra often include a water signal. Assignment of ^{13}C NMR signals was based on DEPT, HMBC, and HMQC spectra. High resolution mass spectra (FT-ICR) were recorded under electrospray ionization (ESI) in a 7 T FT-ICR spectrometer. Melting points were uncorrected.

In order to monitor the reaction by NMR, a solution of 4-ethylbenzonitrile **12** (50.0 mg, 0.38 mmol) in 0.6 mL of $C_2D_2Cl_4$ was prepared in a standard 5 mm NMR tube. ^1H NMR and ^{13}C NMR spectra of the prepared solution were recorded at 50 ± 1 °C as references. To this, triflic anhydride (128.0 mg, 0.45 mmol) was added, and the tube was transferred to the NMR spectrometer. Further spectra were recorded under the same conditions over 20 h.

General Procedure A. A solution of 2.82 g (10 mmol) of triflic anhydride in 15 mL of toluene was added dropwise to a solution containing 10 mmol of nitrile **1** in 15 mL of toluene at 0 °C. The resulting solution was stirred 3 h at 0 °C, then a solution of 20 mmol of nitrile **2** in 15 mL toluene was added, and the reaction mixture was heated at reflux for 24 h. The progress of the reaction was monitored by TLC. The reaction mixture was quenched with aqueous sodium hydrogen carbonate until the pH was basic, washed with water, and dried over magnesium sulfate. The solvent was removed, and the residue was fractionated by column chromatography using hexane/ethyl acetate 9:1 as eluent. The triazine obtained was purified by recrystallization or distillation.

General Procedure B. A solution of 1.50 g (10 mmol) of triflic acid in 15 mL of toluene was added dropwise to a solution containing 10 mmol of nitrile **1** in 15 mL of toluene at 0 °C. The resulting solution was stirred 3 h at 0 °C, then a solution of 20 mmol of nitrile **2** in 15 mL toluene was added, and the reaction mixture was heated at reflux for 24 h. The progress of the reaction was monitored by TLC. The reaction mixture was quenched with aqueous sodium hydrogen carbonate until the pH was basic, washed with water, and dried over magnesium sulfate. The solvent was removed, and the residue was fractionated by column chromatography using hexane/ethyl acetate 9:1 as eluent. The triazine obtained was purified by recrystallization or distillation.

2,4-Bis(4-chlorophenyl)-6-methyl-1,3,5-triazine (3a). This compound was synthesized according to the general procedure A using acetonitrile as nitrile **1** and 4-chlorobenzonitrile as nitrile **2** as a white solid (2.11 g, 67% yield): mp 198−199 °C (EtOH), lit.[29] mp 200−202 °C; FTIR (KBr) ν 1581 (w), 1527 (s), 1367 (w), 1090 (w), 801 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.78 (s, 3H, CH_3), 7,50, 8.60 (AA′XX′ system, 8H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ 26.0 (CH_3), 128.9 (C *meta*), 130.2 (C *ortho*) 134.2 (C *ipso*) 138.9 (C-Cl) 170.3 (C-2, C-4), 177.3 (C-6) ppm; HRMS (ESI) $[M + H]^+$ 316.04028, calcd for $C_{16}H_{12}Cl_2N_3$ 316.04083.

2,6-Dioctyl-4-methyl-1,3,5-triazine (3b). This compound was prepared according to general procedure A using acetonitrile and nonanenitrile as nitriles **1** and **2**, respectively, (1.34 g, 42% yield): bp 200 °C (1 mbar); FTIR (film) ν 2926 (m), 2859 (w), 1540 (s), 1119 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (t, J = 7.5 Hz, 6H, $C\underline{H}_3CH_2$), 1.18 (m, 20 H, CH_2), 1.72 (m, 4H, CH_2), 2.77 (t, J = 7.5 Hz, 4H, CH_2Ar), 2.79 (s, 3H, CH_3Ar) ppm; ^{13}C NMR ($CDCl_3$) δ 14.5 ($\underline{C}H_3CH_2$), 23.0 ($CH_3\underline{C}H_2$), 27.0 (CH_3Ar), 28.2 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 32.2 (CH_2), 39.2 (CH_2Ar), 179.5 (C-2, C-6), 180.5 (C-4) ppm; HRMS (ESI) $[M + H]^+$ 320.30498, calcd for $C_{20}H_{38}N_3$ 320.30602.

2-*tert*-Butyl-4,6-bis(4-methylphenyl)-1,3,5-triazine (3c). This compound was prepared according general procedure A using pivalonitrile as nitrile **1** and 4-tolunitrile as nitrile **2** as a white solid (2.37 g, 75% yield): mp 127−128 °C (MeOH); FTIR (KBr) ν 1519 (s), 1370 (m), 813 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52 (s, 9H, CH_3), 2.47 (s, 6H, CH_3), 7.34, 8.60 (AA′XX′ system, 8H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ 22.1 (CH_3-Ar), 30.1 [$(\underline{C}H_3)_3C$], 39.6

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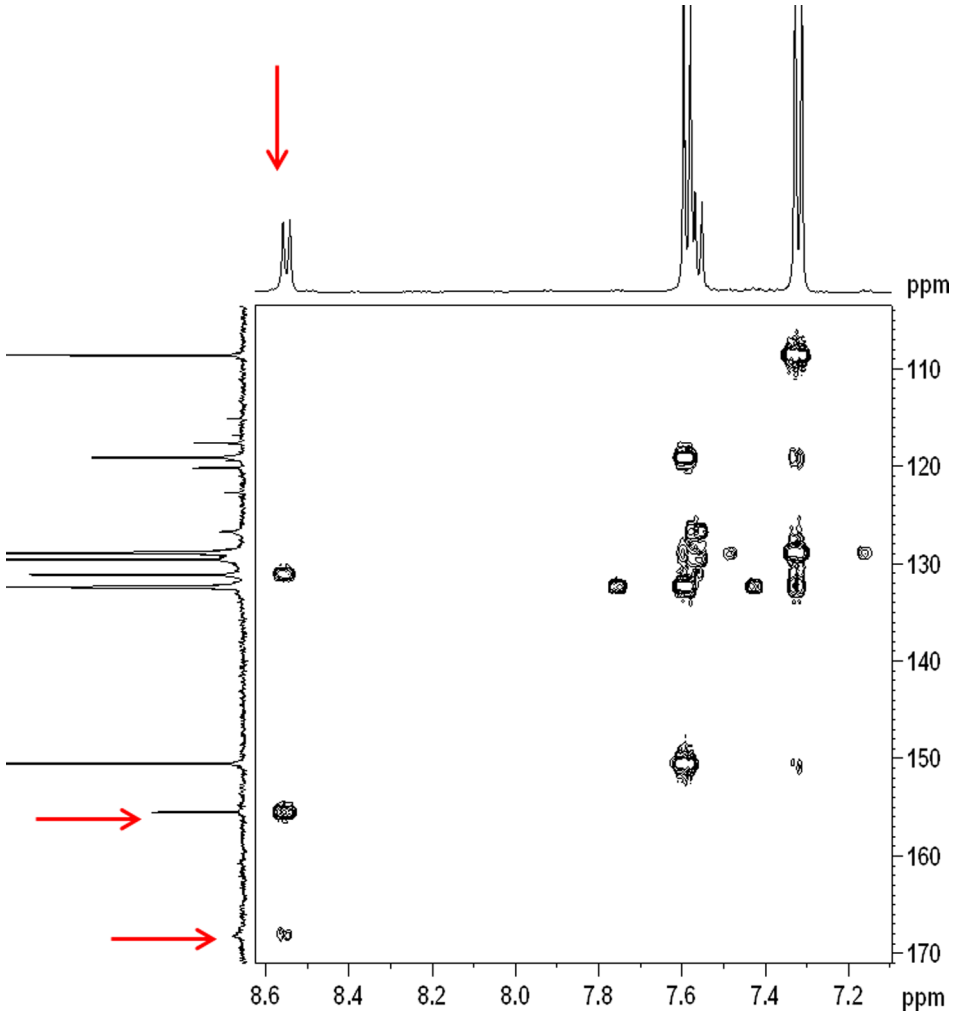

Figure 3. HMBC spectrum of the reaction mixture (10 h at 50 °C) showing the correlations over three bonds for the imino carbon atom (168 ppm, 8.55 ppm) and C4 (156 ppm, 8.55 ppm) of intermediate **14**.

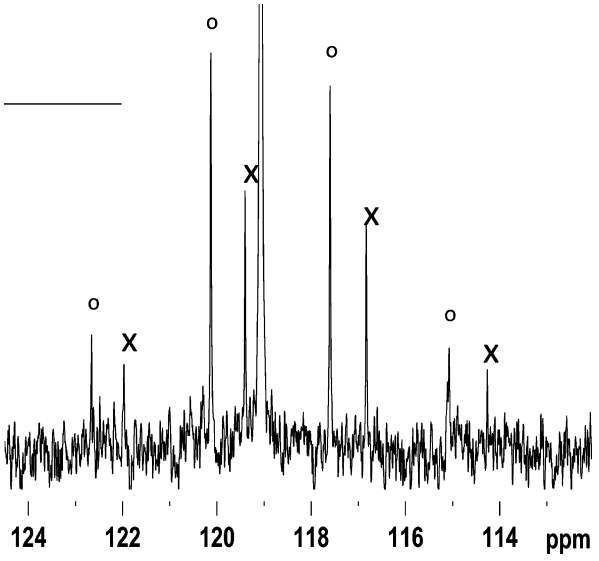

Figure 4. Overlapped quadruplets for the two CF_3 groups of intermediate **14** (118.8 and 117.4 ppm respectively, $^1J_{C,F}$ = 323 Hz).

$[(CH_3)_3\underline{C}]$, 128.8 (C *meta*), 129.2 (C *ortho*), 133.9 (C *ipso*), 142.6 ($C\text{-}CH_3$), 170.8 (C-4, C-6), 185.5 (C-2) ppm; HRMS (ESI) $[M + H]^+$ 318.19596, calcd for $C_{21}H_{24}N_3$ 318.19647.

Following the general procedure A, a solution of 2.82 g (10 mmol) of triflic anhydride in 15 mL of toluene was added dropwise to a solution containing 1.17 g (10 mmol) of 4-methylbenzonitrile in 15 mL of toluene at 0 °C. The resulting solution was stirred 3 h at 0 °C, then a solution of 1.66 g (20 mmol) pivalonrile in 15 mL toluene was added, and the reaction mixture heated at reflux for 24 h. After the above-reported workup, compound **3c** (0.66 g, 21% yield) was obtained.

2-*tert*-Butyl-4,6-bis(methylthio)-1,3,5-triazine (3d). This compound was prepared according to general procedure A using pivalonitrile and methylthiocyanate as nitriles **1** and **2**, respectively, (1.58 g, 69% yield): bp 150 °C (10 mbar); FTIR (film) ν 1495 (s), 1267 (s), 820 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 9H, CH_3), 2.55 (s, 6H, SCH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 13.7 (SCH_3), 28.1 $[(CH_3)_3\underline{C}]$, 29.2 $[(\underline{C}H_3)_3C]$, 181.3 (C-4, C-6), 182.9 (C-2) ppm; HRMS (ESI) $[M + H]^+$ 230.07870, calcd for $C_9H_{16}N_3S_2$ 230.07802.

2,4-Bis(4-methoxyphenyl)-6-(methylthio)-1,3,5-triazine (3e). This compound was prepared according general procedure A using methylthiocyanate and 4-methoxybenzonitrile as starting materials **1** and **2**, respectively, as a white solid (1.79 g, 53% yield): mp 134–135 °C (EtOH), lit.[30] mp 132 °C; FTIR (KBr) ν 1605 (w), 1495 (s), 1365 (m), 1251 (s, C-O-C), 1171 (m), 852 (m), 806 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.62 (s, 3H, SCH_3), 3.83 (s, 6H, OCH_3), 6.95, 8.50 (AA′XX′ system, 8H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ 13.6 (SCH_3), 55.5 (OCH_3), 114.0 (C *meta*), 128.3 (C *ipso*), 131.0 (C *ortho*), 163.4 ($C\text{-}OCHH_3$), 169.3 (C-2, C-4), 181.1 (C-6) ppm; HRMS (ESI) $[M + H]^+$ 340.11044, calcd for $C_{18}H_{17}N_3O_2S$

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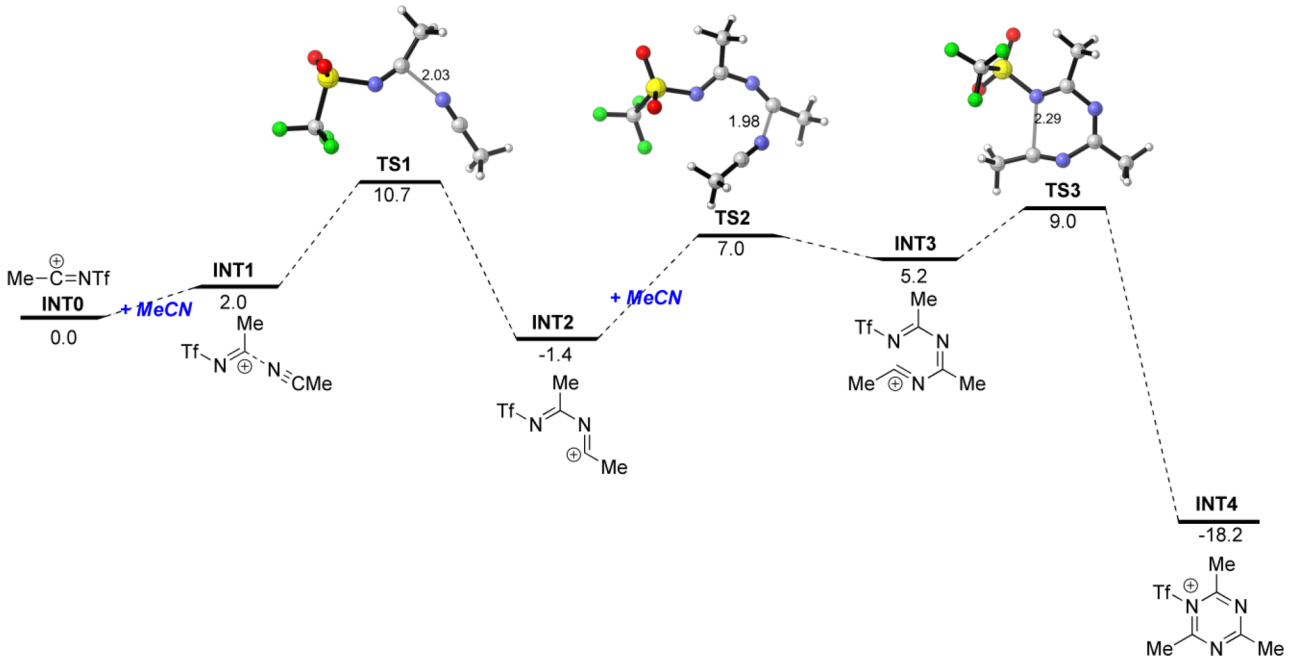

Figure 5. Computed reaction profile for the transformation of **INT0** into **INT4**. Bond lengths are given in angstroms, and relative free energies (ΔG_{298}, in toluene) are in kcal/mol. All data have been computed at the PCM-B3LYP/6-31+G(d) level.

340.11142; $[2M + Na]^+$ 701.19205, calcd for $C_{36}H_{34}N_6NaO_4S_2$ 701.19752.

A solution of 2.82 g (10 mmol) of triflic anhydride in 15 mL of toluene was added dropwise to a solution containing 1.33 g (10 mmol) of 4-methoxybenzonitrile and 0.73 g (10 mmol) of methylthiocyanate in 30 mL of toluene at 0 °C. The resulting solution was stirred 3 h at 0 °C and heated 24 h at 100 °C. After hydrolysis and purification of the crude product, compound **3e** (0.25 g, 15%) was obtained.

2,4-Bis(4-chlorophenyl)-6-piperidin-1-yl-1,3,5-triazine (3f). This compound was prepared according general procedure A using piperidine-1-carbonitrile and 4-chlorobenzonitrile as starting nitriles **1** and **2**, respectively, as a white solid (3.14 g, 82% yield): mp 196–197 °C (hexane/chloroform); FTIR (KBr) ν 2933 (m), 2854 (w), 1588 (m), 1546 (s), 1511 (s), 806 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (m, 4H, CH_2), 1.78 (m, 2H, CH_2), 4.04 (t, J = 5 Hz, 4H, NCH_2), 7.48, 8.52 (AA′XX′ system, 8H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ 25.2 (CH_2), 26.3 (CH_2), 44.8 (NCH_2), 128.9 (C *meta*), 130.3 (C *ortho*), 136.0 (C *ipso*), 138.2 (C-Cl), 165.0 (C-2, C-4), 170.4 (C-6) ppm; HRMS (ESI) $[M + H]^+$ 385.09890, calcd for $C_{20}H_{19}Cl_2N_4$ 385.09813.

2,6-Di-*tert*-butyl-6-piperidin-1-yl-1,3,5-triazine (3g). This compound was prepared according general procedure A using piperidine-1-carbonitrile and pivalonitrile as nitriles **1** and **2**, respectively, as an undistillable oil (1.85 g, 67% yield): FTIR (film) ν 2935 (m), 2859 (m), 1550 (s), 1522 (s), 1398 (w), 1362 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (s, 9H, CH_3), 1.62 (m, 4H CH_2), 1.72 (m, 2H, CH_2), 3.86 (t, J = 5 Hz, 4H, NCH_2) ppm; ^{13}C NMR ($CDCl_3$) δ 25.3 (CH_2), 26.1 (CH_2), 29.2 (CH_3), 39.6 (C), 44.2 (NCH_2), 165.1 (C-6), 184.5 (C-2, C-4) ppm; HRMS (ESI) $[M + H]^+$ 277.23785, calcd for $C_{16}H_{29}N_4$ 277.23867.

4,6-Bis(4-chlorophenyl)-*N*,*N*-dimethyl-1,3,5-triazin-2-amine (3h). This compound was prepared according general procedure A using dimethylcyanamide and 4-chlorobenzonitrile as starting materials **1** and **2** as a white solid (2.61 g, 76% yield): mp 216–217 (chloroform/MeOH); FTIR (KBr) ν 1585 (m), 1522 (m), 1378 (m), 1089 (w), 804 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.43 (s, 6H, NCH_3), 7.50, 8.55 (AA′XX′ system, 8H, Ar-H)ppm; ^{13}C NMR ($CDCl_3$) δ 36.7 (NCH_3), 128.2 (C *meta*), 130.55 (C *ortho*), 136.0 (C-Cl), 138.5 (C *ipso*), 165.9 (C-2), 170.3 (C-4, C-6) ppm; HRMS (ESI) $[M + H]^+$ 345.06614, calcd for $C_{17}H_{15}Cl_2N_4$ 345.06683.

4,6-Bis(4-methylphenyl)-*N*,*N*-dimethyl-1,3,5-triazin-2-amine (3i). This compound was prepared according general procedure A using dimethylcyanamide and 4-tolunitrile as starting nitriles **1** and **2**, respectively, as a white solid (2.46 g, 81% yield): mp 193–194 °C (chloroform/EtOH); FTIR (KBr) ν 2920 (w), 1589 (m), 1510 (s), 1376 (w), 800 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47 (s, 6H, CH_3-Ar), 3.40 (s, 6H, NCH_3), 7.32, 8.51 (AA′XX′ system, 8H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ 22.0 (Ar-CH_3), 36.7 (NCH_3), 128.9 (C *ortho*), 129.4 (C *meta*), 134.9 (C-CH_3), 142.3 (C *ipso*), 166.1 (C-2), 171.0 (C-4, C-6) ppm; HRMS (ESI) $[M + H]^+$ 305.17525, calcd for $C_{19}H_{21}N_4$ 305.17662.

4,6-Bis(4-methoxyphenyl)-*N*,*N*-dimethyl-1,3,5-triazin-2-amine (3j). This compound was prepared according general procedure A using dimethylcyanamide and 4-methoxybenzonitrile as starting materials **1** and **2**, respectively, as a white solid (2.58 g, 77% yield): mp 159–160 °C (MeOH); FTIR (KBr) ν 1580 (m), 1505 (s), 1379 (s), 1251 (s, C-O-C), 1167 (m), 813 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.38 (s, 6H, NCH_3), 3.92 (s, 6H, OCH_3), 7.03, 8.58 (AA′XX′ system, 8H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ 36.6 (NCH_3), 55.8 (OCH_3), 114.0 (C *ortho*), 114.4 (C *ipso*), 130.3 (C *meta*), 163.0 (C-$OCHH_3$), 166.0 (C-2), 170.4 (C-4, C-6) ppm; HRMS (ESI) $[M + H]^+$ 337.16590, calcd for $C_{19}H_{21}N_4O_2$ 337.16590.

2,4-Bis(4-methylphenyl)-6-morpholin-4-yl-1,3,5-triazine (3k). This compound was prepared according general procedure A using morpholine-4-carbonitrile and 4-tolunitrile as nitriles **1** and **2**, respectively, as a white solid (2.76g, 80% yield): mp 219–220 °C (EtOH); FTIR (KBr) ν 1546 (m), 1510 (s), 1381 (m), 801 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47 (s, 6H, CH_3), 3.85 (t, J = 5.0 Hz, 4H, NCH_2), 4.10 (t, J = 5.0 Hz, 4H, OCH_2), 7.32, 8.48 (AA′XX′ system, 8H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ 22.0 (CH_3-Ar), 44.0 (NCH_2), 67.3 (OCH_2), 129.1 (C *ortho*), 129.5 (C *meta*), 134.7 (C-CH_3), 142.6 (C *ipso*), 165.5 (C-6), 171.4 (C-2, C-4) ppm; HRMS (ESI) $[M + H]^+$ 347.18479, calcd for $C_{21}H_{23}N_4O$ 347.18664.

2,4-Bis(4-methoxyphenyl)-6-morpholin-4-yl-1,3,5-triazine (3l). This compound[31] was prepared according general procedure A using morpholine-4-carbonitrile and 4-methoxybenzonitrile as nitriles **1** and **2**, respectively, as a white solid (2.91g, 77% yield): mp 190–192 °C (MeOH); FTIR (KBr) ν 1534 (m), 1510 (s), 1385 (m), 1255 (s, C-O-C), 814 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85 (t, J = 4.9 Hz, 4H, NCH_2), 3.93 (s, 6H, OCH_3), 4.09 (t, J = 4.9 Hz, 4H,

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OCH_2), 7.02, 8.56 (AA′XX′ system, 8H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ 44.0 (NCH_2), 55.8 (OCH_3), 67.3 (OCH_2), 114.0 (C *meta*), 129.7 (C *ipso*), 131.2 (C *ortho*), 162.9 (C-$OCHH_3$), 165.3 (C-6), 171.0 (C-2, C-4) ppm; HRMS (ESI) $[M + H]^+$ 379.17617, calcd for $C_{21}H_{23}N_4O_3$ 379.17647.

2,4-Dicyclohexyl-6-morpholin-4-yl-1,3,5-triazine (3m). This compound was prepared according general procedure A using morpholine-4-carbonitrile and cyclohexanecarbonitrile as nitriles **1** and **2**, respectively, as an undistillable oil (1.94 g, 59% yield): FTIR (film) ν 2930 (m), 2856 (w), 1545 (s), 1250 (s), 1028 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55−1.92 (m, CH_2, 20 H), 2.55 (m, 2H, CH), 3.74 (t, J = 4.9 Hz, 4H, NCH_2), 3.89 (t, J = 4.9 Hz, 4H, OCH_2) ppm; ^{13}C NMR ($CDCl_3$) δ 26.3 (CH_2), 26.4 (CH_2), 31.8 (CH_2), 43.9 (NCH_2), 47.1 (CH), 67.1 (OCH_2), 165.0 (C-6), 181.8 (C-2, C-4) ppm; HRMS (ESI) $[M + H]^+$ 331.25043, calcd for $C_{19}H_{31}N_4O$ 331.24924.

2,4-Diethyl-6-(4-methylphenyl)-1,3,5-triazine (3n). This compound was prepared according general procedure A using 4-tolunitrile and propanenitrile as starting materials **1** and **2**, respectively, as a liquid (1.11 g, 49% yield): bp 100 °C (1 mbar); FTIR (film) ν 3037 (m), 2977 (w), 1533 (s), 1385(m), 822 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (t, J = 7.6 Hz, 6H, $CH_2C\underline{H}_3$), 2.50 (s, 3H, Ar-CH_3), 3.05 (q, J = 7.6 Hz, 4H, $C\underline{H}_2CH_3$), 7.30, 8.50 (AA′XX′ system, 4H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ 11.9 ($\underline{C}H_3CH_2$), 21.8 (Ar-CH_3), 32.7 ($\underline{C}H_2CH_3$), 129.1 (C *meta*), 129.7 (C *ortho*), 133.8 (C *ipso*), 143.3 (C-CH_3), 171.1 (C-2, C-6), 180.5 (C-4) ppm; HRMS (ESI) $[M + H]^+$ 228.14981, calcd for $C_{14}H_{18}N_3$ 228.14952.

2-[4-(Bromomethyl)phenyl]-4,6-diphenyl-1,3,5-triazine (3o). This compound was prepared according general procedure A using 4-(bromomethyl)benzonitrile and benzonitrile as starting materials **1** and **2**, respectively, as a white solid (2.00 g, 50% yield): mp 200−201 °C (toluene); lit.[32] mp 201−203 °C; FTIR (KBr) ν 1519 (s), 1366 (m), 739 (w), 689 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.61 (s, 2H, CH_2Br), 7.60 (m, 8H, Ar-H), 8.55 (m, 6H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ 33.2 (CH_2Br), 129.1 (CH), 129.4 (CH), 129.8 (CH), 129.9 (CH), 133.0 (CH), 136.5 (C), 136.7 (C), 142.5 (C), 171.4 (C-2), 172.1 (C-4, C-6) ppm; HRMS (ESI) $[M + H]^+$ 402.06137, calcd for $C_{22}H_{17}BrN_3$ 402.06004.

2-(3-Bromo-4-methylphenyl)-4,6-bis(4-bromophenyl)-1,3,5-triazine (3p). This compound was prepared according general procedure B using 3-bromo-4-methylbenzonitrile and 4-bromobenzonitrile as starting materials **1** and **2**, respectively, as a white solid (2.28 g, 41% yield): mp 267−268 °C (chloroform/MeOH); FTIR (KBr) ν 1516 (s), 1357 (m), 803 (m), 772 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.57 (s, 3H, Ar-CH_3), 7.45 (d, J = 7.7 Hz, 1H, Ar-H), 7.75, 8.63 (AA′XX′ system, 8H, Ar-H), 8.58 (m, 1H, Ar-H), 8.88 (d, J = 1.4 Hz, 1H, Ar-H) ppm; ^{13}C NMR (45 °C, $CDCl_3$) δ 23.6 (Ar-CH_3), 125.4 (C-Br), 127.8 (C-Br), 130.5 (C *ortho*), 131.1 (CH), 132.1 (C *meta*), 132.8 (CH), 134.9 (C), 135.5 (C), 142.9 (C), 143.0 (C), 170.8 (C-2), 171.2 (C4, C-6) ppm; HRMS (ESI) $[M + H]^+$ 557.88383, calcd for $C_{22}H_{15}Br_3N_3$ 557.88106.

2,4-Bis(4-chlorophenyl)-6-(2-thienyl)-1,3,5-triazine (3q). This compound was prepared according general procedure B using thiophene-2-carbonitrile and 4-chlorobenzonitrile as starting materials **1** and **2**, respectively, as a white solid (1.72 g, 45% yield): mp 288−289 °C (chloroform); FTIR (KBR) ν 1585 (w), 1518 (s), 1404 (m), 806 (w) cm^{-1}; ^1H NMR (DMF-d_7) δ 7.58 (dd, J = 4.9 Hz, J = 3.9 Hz, 1H, H-4, 2-thienyl ring), 7.92, 8.93 (AA′XX′ system, 8H, Ar-Cl), 8.25 (dd, J = 4.9 Hz, J = 1.1 Hz, 1H, H-3, 2-thienyl ring), 8.66 (dd, J = 3.9 Hz, J = 1.1 Hz, H-5, 2-thienyl ring) ppm; ^{13}C NMR (DMF-d_7) δ 129.6 (C-4 of 2-thienyl ring), 129.8 (CH, Ar-Cl), 131.2 (CH, Ar-Cl), 133.1 (C-5 of 2-thienyl ring), 134.5 (C-3 of 2-thienyl ring), 135.1 (C, Ar-Cl), 139.2 (C-Cl), 141.9 (C-2 of 2-thienyl ring), 169.0 (C-6), 171.4 (C-2, C-4) ppm; HRMS (ESI) $[M + O]^{\bullet+}$ 398.98916, calcd for $C_{19}H_{11}Cl_2N_3OS$ 398.99997.

2,4-Bis(4-bromophenyl)-6-(1-naphthyl)-1,3,5-triazine (3r). This compound was prepared according general procedure B using naphthalene-1-carbonitrile and 4-bromobenzonitrile as starting materials **1** and **2**, respectively, as a white solid (2.00 g, 39% yield): mp 199−200 °C (chloroform/MeOH); FTIR (KBr) ν 1584 (w), 1517 (s), 1369 (w), 801 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63 (t, J = 7.2 Hz, 1H), 7.66 (t, J = 7.2 Hz, 1H), 7.72 (t, J = 7.2 Hz, 1H), 7.74, 8.66 (AA′XX′ system, 8H, Br-Ar-H), 8.01 (d, J = 8.6 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 8.53 (d, J = 7.2 Hz, 1H), 9.01 (d, J = 8.8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 126.3 (C-Br), 126.6, 127.8, 128.3, 129.7, 131.0, 131.3, 131.7, 132.5, 133.0, 134.0, 134.7, 135.3, 171.3 (C-4), 175.0 (C-2, C-6) ppm; HRMS (ESI) $[M + H]^+$ 515.97184, calcd for $C_{25}H_{16}Br_2N_3$ 515.97055.

2,4,6-Tris(4-ethylphenyl)-1,3,5-triazine (13). This compound was prepared according general procedure A using 4-ethylbenzonitrile (**12**) (3.92 g, 30 mmol) in 50 mL of toluene and 2.82 g (10 mmol) of triflic anhydride in 15 mL of toluene. The reaction mixture was heated at 100 °C for 24 h. After usual workup, the compound was isolated (3.49 g, 89% yield): mp 114−115 °C (EtOH); FTIR (KBr) ν 1509 (s), 1370 (m), 815 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, J = 7.2 Hz, 9H, CH_3), 2.80 (q, J = 7.2 Hz, 6H, CH_2), 7.42 (AA′XX′ system, 6H), 8.71 (AA′XX′ system, 6H) ppm; ^1H NMR ($C_2D_2Cl_4$) δ 1.37 (t, J = 7.2 Hz, 9H, CH_3), 2.82 (q, J = 7.2 Hz, 6H, CH_2), 7.44 (AA′XX′ system, 6H), 8.69 (AA′XX′ system, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 1.58 (CH_3), 29.5 (CH_2), 128.5 (C *meta*), 129.4 (C *ortho*), 134.4 (C *ipso*), 149.6 (C *para*), 171.9 (C2, C4, C6) ppm; ^{13}C NMR ($C_2D_2Cl_4$) δ 15.2 (CH_3), 29.0 (CH_2), 128.2 (C *meta*), 129.1 (C *ortho*), 134.1 (C *ipso*), 149.3 (C *para*), 171.6 (C2, C4, C6) ppm; HRMS (ESI) $[M + H]^+$ 394.22884, calcd for $C_{27}H_{28}N_3$ 394.22777; $[2M + Na]^+$ 809.42681, calcd for $C_{54}H_{54}N_6Na$ 809.43020.

1-Benzyl-2-methylbenzene (15) and 1-Benzyl-4-methylbenzene (16). A solution of triflic anhydride (10 mmol) in 15 mL toluene was added dropwise to a solution containing 1.31 g (10 mmol) of 4-ethylbenzonitrile (**12**) in 15 mL of toluene at 0 °C. The resulting solution was stirred 3 h at 0 °C, then a solution of 1.08 g (10 mmol) of benzyl alcohol in 15 mL of toluene was added, and the reaction mixture was heated at reflux for 24 h. The reaction mixture was quenched with aqueous sodium hydrogen carbonate until the pH was basic, washed with water, and dried over magnesium sulfate. The solvent was removed, and the residue was fractionated by column chromatography using hexane/ethyl acetate 9:1 as eluent. After evaporation of solvent, the residue (1.16 g, 64% overall yield) was analyzed by GC−MS, ^1H and ^{13}C NMR.

Compound **15** (40% of mixture): ^1H NMR ($CDCl_3$) δ 2.29 (s, 3H, CH_3), 4.04 (s, 2H, CH_2), 7.10−7.35 (m, 5H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ 20.1 (CH_3), 40.0 (CH_2), 126.3, 126.9, 128.9, 129.2, 129.6, 130.9, 130.7 (C−H), 137.0, 139.4, 140.8 ppm; MS(EI, 70 eV) m/z (%B) 182 ($M^{\bullet+}$, 90), 165 (M-CH_3, 100), 165 (45), 152 (15), 104 (22).

Compound **16** (60% of mixture): ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H, CH_3), 4.00 (s, 2H, CH_2), 7.10−7.35 (m, 5H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ 21.5 (CH_3), 42.0 (CH_2), 126.4, 128.8, 129.1, 129.2, 129.6, (C−H), 135.9, 138.5, 141.8 ppm; MS(EI, 70 eV) m/z (%B) 182 ($M^{\bullet+}$, 90), 165 (M-CH_3, 100), 165 (33), 152 (20), 104 (21).

(4-Ethylphenyl)(2,4,6-trimethoxyphenyl)methanone (17) and 1,3,5-Trimethoxy-2-[(trifluoromethyl)sulfonyl]benzene (18). A solution of triflic anhydride (10 mmol) in 15 mL toluene was added dropwise to a solution containing 1.31 g (10 mmol) of 4-ethylbenzonitrile (**12**) in 15 mL of toluene at 0 °C. The resulting solution is stirred 3 h at 0 °C, then a solution of 1.68 g (10 mmol) of l,3,5-trimethoxybenzene in 15 mL of toluene was added, and the reaction mixture was heated at reflux for 24 h. The progress of the reaction can be monitored by TLC. The reaction mixture was quenched with aqueous sodium hydrogen carbonate until the pH was basic, washed with water, and dried over magnesium sulfate. The solvent was removed, and the residue was fractionated by column chromatography using hexane/ethyl acetate 9:1 as eluent.

Compound **17** (0.93 g, 31% yield): mp 110−111 °C (toluene/hexane); FTIR (KBr) ν 1666 (m), 1603 (s), 1128 (s) cm^{-1}; ^1H NMR (CD_2Cl_2) δ 1.17 (t, 3H, J = 9 Hz, CH_3), 2.62 (q, 2H, J = 9 Hz CH_2), 3.65 (s, 6H, OCH_3), 3.78 (s, 3H, OCH_3), 6.10 (s, 2H, Ar-H), 7.17 (2H, AA′XX′ system), 7.65 (2H, AA′XX′ system) ppm; ^{13}C

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NMR (CD_2Cl_2) δ 15.8 (CH_3), 29.7 (CH_2), 56.3 (OCH_3), 56.6 (OCH_3), 91.5 (C_{arom}–H), 111.9, 128.8 (C_{arom}–H), 130.2 (C_{arom}–H), 136.7, 151.0, 159.2 (C–$OCHH_3$), 163.1 (C–$OCHH_3$), 194.9 (CO) ppm; HRMS (ESI) $[M + H]^+$ 301.14349, calcd for $C_{18}H_{21}O_4$ 301.14344, $[M + Na]^+$ 323.12560, calcd for $C_{18}H_{20}O_4Na$ 323.12538.

Compound **18** (1.29 g, 43% yield): mp 92–93 °C (toluene/hexane); FTIR (KBr) ν 1594 (m), 1572 (s), 1345 (m, SO_2), 1116 (s, SO_2), 1074 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 3.92 (s, 6H, OCH_3), 3.93 (s, 3H, OCH_3), 6,19 (s, 2H, Ar-H) ppm; ^{13}C NMR (CD_2Cl_2) δ 55.9 (OCH_3), 56.6 (OCH_3), 91.5 (C-4, C-6), 100.6 (C-2), 120.3 (q, CF_3, J = 334 Hz), 163.8 (C-1, C-3), 168.0 (C-5) ppm; HRMS (ESI) $[M + Na]^+$ 323.01826, calcd for $C_{10}H_{11}F_3NaO_5S$ 323.01715.

4-(4-Chlorophenyl)-*N*,*N*-dimethyl-6-(4-methylphenyl)-1,3,5-triazin-2-amine (19). This compound was prepared according general procedure A using dimethylcyanamide as nitrile **1** and a mixture of equimolecular amounts of 4-chlorobenzonitrile and 4-tolunitrile as nitrile **2** (1.88g, 58% yield): mp 178–179 °C (EtOH); FTIR (KBr) ν 1591 (m), 1511 (s), 1377 (m), 801 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47 (s, 3H, CH_3-Ar), 3.39 (s, 6H, CH_3-N), 7.33, 8.49 (AA′XX′ system, CH_3-Ar-H), 7.48, 8.56 (AA′XX′ system, Cl-Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ 22.0 (CH_3-Ar), 36.7 (CH_3-N), 128.9, 129.0, 129.5, 130.4 (C–H), 134.6, 136.2, 138.1, 144.6, 166.0 (C-2), 170.0 (C-4), 171.1 (C-6) ppm; HRMS (ESI) $[M + H]^+$ 325.12194, calcd for $C_{18}H_{18}ClN_4$ 325.12145.

(1*Z*)-*N*-(1-Benzylisoquinolin-3-yl)-2,2-dimethyl-*N*′-[(trifluoromethyl)sulfonyl]propanimide (21). This compound was prepared according general procedure A using pivalonitrile and benzylcyanide as starting materials **1** and **2**, respectively, (1.84 g, 41% yield): mp 158–159 °C (chloroform/hexane); FTIR (KBr) ν 3413 (NH, w), 1523 (m), 1336 (m), 1210 (SO_2, s), 1188 (s), 752 (m), 708 (m), 620 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (s, 9H, CH_3), 4.63 (s, 2H, CH_2), 7.20–7.30 (m, 5H, Ar-H), 7.54 (t, J = 8.5 Hz, 1H, H-7 of isoquinoline ring), 7.70 (t, J = 8.5 Hz, 1H, H-6 of isoquinoline ring), 7.84 (d, J = 8.5 Hz, 1H, H-5 of isoquinoline ring), 8.12 (d, J = 8.5 Hz, 1H, H-8 of isoquinoline ring), 8.28 (s, 1H, H-4 of isoquinoline ring), 8.60 (bs, NH) ppm; ^{13}C NMR ($CDCl_3$) δ 28.0 (CH_3), 41.3 ($\underline{C}H_2$-C6H5), 41.3 [$(CH_3)_3\underline{C}$], 111.6 (C-4), 119.7 (q, J = 316 Hz, CF_3), 126.2 (C-8), 126.6 (C-8a), 126.9 (phenyl ring), 127.9 (C-7), 128.5 (C-5), 128.9 (phenyl ring), 129.0 (phenyl ring), 131.3 (C-6), 138.4 (C-4a), 139.0 (phenyl ring), 143.4 (C-3), 160.5 (C-1), 171.7 (C=N) ppm. To distinguish the quaternary carbon atom of the *tert*-butyl group in compound **22**, a selective INEPT experiment has been carried out because this nuclei and the CH_2 carbon atom of the benzyl group resonate closely at 41.35 and 41.37 ppm, respectively. NOE experiments show that the irradiation of the methyl groups of the *tert*-butyl moiety at 1.64 ppm produces a strong dipolar coupling with the NH proton and weak interactions with H-4 and H-5; HRMS (ESI) $[M + H]^+$ 450.14466, calcd for $C_{22}H_{23}F_3N_3O_2S$ 450.14576.

Computational Details. All calculations reported in this paper were obtained with the GAUSSIAN 09 suite of programs.[33] Electron correlation was partially taken into account using the hybrid functional usually denoted as B3LYP[34] using the double-ζ quality plus polarization and diffuse functions 6-31+G(d) basis set[35] for all atoms. Reactants and products were characterized by frequency calculations[36] and have positive definite Hessian matrices. Transition structures (TSs) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the intrinsic reaction coordinate (IRC) method.[37] Solvents effects were taken into account using the polarizable continuum model (PCM).[38] Geometry optimizations were performed at this level (PCM-B3LYP/6-31+G(d)) to estimate the change in the Gibbs energies in the presence of toluene as solvent.

■ ASSOCIATED CONTENT

Supporting Information

IR, ^1H NMR and ^{13}C NMR spectra (1D and 2D), crystallographic data for **3c**, including CIF files, as well the Cartesian coordinates and total energies of all the stationary points discussed in the manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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