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3-Substituted Benzo[e][1,2,4]triazines: Synthesis and Electronic Effects of the C(3) Substituent

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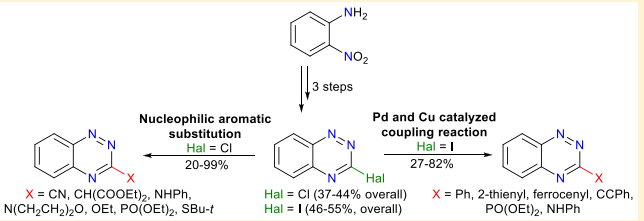
Supporting Information

ABSTRACT: A series of 19 structurally diverse C(3)-substituted derivatives of benzo[e][1,2,4]triazine were synthesized from 3-chloro- (**1c**) and 3-iodobenzo[e][1,2,4]triazine (**1d**) obtained in three steps from 2-nitroaniline in 37−55% yields. Nucleophilic aromatic substitution and metal-catalyzed (Pd, Cu) reactions led to functional derivatives that include alkyl (C_5H_{11}), (het)aryl (Ph, 2-thienyl, ferrocenyl), ArC≡C, amine (NHPh and morpholine), $PO(OEt)_2$, sulfanyl (SBu-*t*), alkoxide (OEt, OMe), and CN. The synthesis of C(3)−CF_3 derivative **1g** via the Ruppert reaction with **1d** and its 1-oxide analogue **2d** led to the substitution followed by formal addition of HCF_3 to the C=N bond. Pd-catalyzed carbonylation reactions of **1d** and **2d** did not give the corresponding C(3)-carboxylic acids. Therefore, acid **1f** was obtained through hydrolysis of the CN. The substituent effect on the electronic structure of the benzo[e][1,2,4]triazine ring was investigated by spectroscopic methods (UV−vis and NMR) augmented with density functional theory calculations. Results show significant effect of the C(3) substituent on the $\pi-\pi^*(1)$ transition energy and good correlation of the ^{1}H NMR chemical shift with the substituent constant σ_p. Molecular and crystal structures of six derivatives were established with the single-crystal X-ray diffraction method, and the substituent impact on the molecular geometry was investigated.



INTRODUCTION

In the past two decades, an increased interest has been observed in chemistry and applications of derivatives of the benzo[e][1,2,4]triazine[1] (**1a**, Figure 1) in pharmacology and material science. For instance, 3-aminobenzo[e][1,2,4]triazines posses antimalarial activity[2] and can act as *Src* kinase inhibitors with antitumor activity[3,4] and inhibitors of *Abl* and *Abl*-T315I enzymes.[5] Other derivatives have been described as PARP[6] and sodium-glucose co-transporter 2 inhibitors,[7] microbicides,[8] and antiviral agents.[9] One of the most biologically important classes of benzo[e][1,2,4]triazine derivatives are 3-aminobenzo[e][1,2,4]triazine-1,4-dioxides, which act as bioreductive antitumor agents and are selectively toxic to oxygen-deprived (hypoxic) cells.[10−12] On the other hand, benzo[e][1,2,4]triazine has been used as a structural element of organic materials, such as organic and electrochemical light emitters,[13] and its derivatives are convenient precursors to exceptionally stable benzo[e][1,2,4]triazinyl radicals.[14]

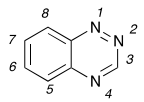


Figure 1. Parent benzo[e][1,2,4]triazine (**1a**) with the numbering scheme.

In spite of such a broad application of benzo[e][1,2,4]triazine derivatives, there are surprisingly few investigations of their molecular and electronic structures. Thus, only five experimental solid-state structures have been reported to date,[15−19] and UV−vis spectroscopy has been limited to the parent[20,21] and a few members of 3-phenyl,[22] 3-aryl,[23] 3-amino,[24] and 3-alkyl[21] derivatives. There has been no systematic investigation of the effect of 3-substituent on the electronic properties of the benzo[e][1,2,4]triazine ring. Our interest in this class of heterocycles stems from understanding of the electronic effects of the C(3) substituent and accessing C(3)-substituted benzo[e][1,2,4]triazinyl radicals.

Analysis of the literature indicates that there are several classes of benzo[e][1,2,4]triazine derivatives, each accessible through a separate pathway (Figure 2). One of the most convenient methods in the synthesis of the benzo[e][1,2,4]-triazine skeleton is condensation of 2-nitroanilines with

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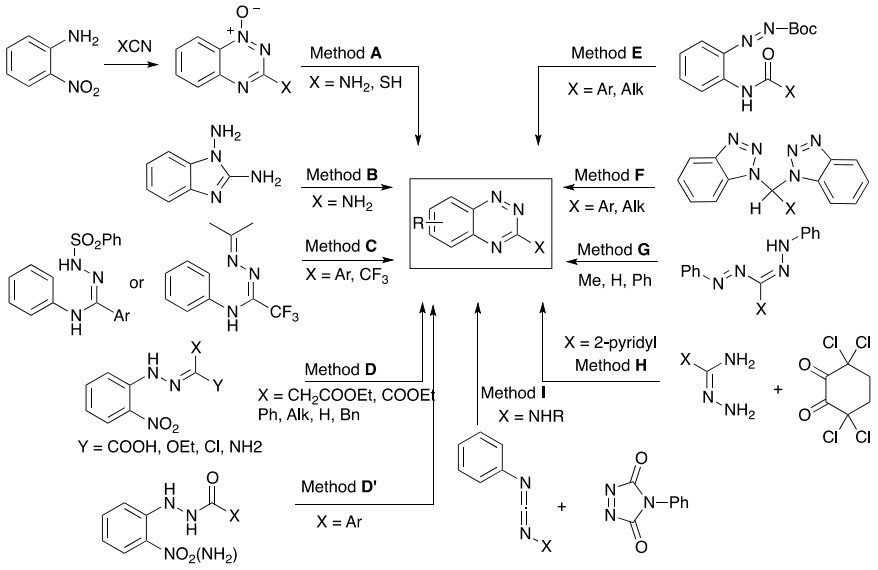

Figure 2. General methods for construction of the benzo[*e*][1,2,4]triazine skeleton.

cyanamide[25] followed by reductive deoxygenation of the resulting 3-aminobenzo[*e*][1,2,4]triazine-1-oxides, achieving 67−80% yield (method A, Figure 2).[2,5,10,26,27] Alternatively, using KSCN and benzoyl chloride in the condensation with 2-nitroanilines, 3-mercapto derivatives are obtained.[28] Oxidation of 1,2-diaminobenzimidazoles with $Pb(OAc)_4$ or $PhI(OAc)_2$ gives the corresponding 3-aminobenzo[*e*][1,2,4]triazines in good yields (method B, Figure 2).[29,30] On the other hand, oxidation of 2-NHPh and 2-NHMe derivatives of 1-aminobenzimidazole with $Pb(OAc)_4$ affords the corresponding benzo[*e*][1,2,4]triazines in low yields (up to 25%).[24] Another method involves the formation of benzo[*e*][1,2,4]triazine ring via oxidative cyclization of the corresponding *N*-arylbenzamidrazones (method C, Figure 2).[23,31,32] Although the reaction allows for the formation of a wide range of 3-aryl[23] and 3-trifluoromethyl-substituted[32] benzo[*e*][1,2,4]triazines in moderate yields, the method suffers from demanding synthesis of amidrazones and use of HgO.[23]

Another method for the preparation of the benzo[*e*][1,2,4]-triazine ring relies on reductive cyclization of 2-nitrophenylhydrazones,[21,22] 2-nitrophenylhydrazono esters,[33] and 2-nitrophenylhydrazides[34] (method D, Figure 2). This route allows for the formation of benzo[*e*][1,2,4]triazine derivatives with H, Me, Et, CH_2Ph, Ph, and CH_2COOEt groups at C(3) position in low to moderate yields. Also, the preparation of C(3)−COOR derivatives follows a similar pathway starting with appropriate hydrazonoyl chlorides (Y = Cl), which are transformed to the corresponding amidrazones (Y = NH_2).[35]

A direct synthesis of 3-arylbenzo[*e*][1,2,4]triazines was achieved through a Cu_2O-catalyzed reaction of 2-iodoanilines and aryl hydrazides[16] (method D', Figure 2), resulting in 22−75% yield. Cyclization of azo compounds, obtained by Cu-catalyzed coupling of 2-hydrazino acetanilides and *N*-Boc-protected hydrazine, provides 3-alkyl and 3-aryl (e.g., Ph and 2-thienyl)-substituted benzo[*e*][1,2,4]triazines in excellent yields (method E, Figure 2).[36] A recent report of an unprecedented rearrangement of bis(benzotriazol-1-yl)methylarenes in the presence of allylsamarium bromide demonstrates the formation of the corresponding 3-arylbenzo[*e*][1,2,4]triazines in moderate yields (method F, Figure 2).[37,38]

Another route to 3-aryl derivatives is based on an intramolecular cyclization of formazones in sulfuric acid[20,39,40] or in BF_3/AcOH[9,41] (method G, Figure 2). Benzo[*e*][1,2,4]-triazines with 2-pirydyl substituent at C(3) position were obtained using method H by condensation of 2-picolinoamidrazone with tetrachloro-1,2-cyclohexanedione.[42]

The last method for the preparation of the benzo[*e*][1,2,4]-triazine skeleton involves the [4 + 2] cycloaddition of unsymmetrical carbodiimides to 4-phenyl[1,2,4]triazoline-3,5-dione. This two-step reaction allows for the formation of a series of 3-arylamino- and 3-alkylaminobenzo[*e*][1,2,4]-triazines in 59−95% yield (method I, Figure 2).[43]

The above-mentioned synthetic methods[44] are often specific for a particular class of substituents at the C(3) position and in many cases require multistep preparation of precursors for cyclization to the benzo[*e*][1,2,4]triazine skeleton. For instance, methods A, B, and I lead to 3-amino derivatives. Essentially all other methods are used mainly to obtain 3-aryl and 3-heteroaryl derivatives. Only several 3-alkyl derivatives have been obtained using methods D−G. The preparation of the parent benzo[*e*][1,2,4]triazine (**1a**) was demonstrated using methods D and G, while the CF_3 group was introduced at the C(3) position using method C.

Most useful derivatives for further functionalization in the context of pharmacological studies are those containing the NH_2, COOH, and CH_2COOH groups at the C(3) position. They can be transformed into carbonyl derivatives, such as amides and hydrazides, while the C(3)-amino derivatives (e.g., **1b**) can undergo condensation or diazotization reactions, e.g., to form C(3)−Cl derivative **1c**. The chloride **1c** appears to be a synthetically useful intermediate since, in principle, chlorine can be replaced with a number of nucleophiles in the S_NAr process, but only a handful of such transformations have been demonstrated to date: the synthesis of C(3)−$NHNH_2$,[26,45] C(3)−NH_2,[46] and C(3)−OEt derivatives.[45] It should be mentioned that 3-chlorophenanthro[9,10-*e*][1,2,4]triazine, a ring-condensed analogue of the benzo[*e*][1,2,4]triazine, was demonstrated to react with trialkyl phosphites to give phosphonate esters in good yields.[47] In another approach, nucleophilic substitution of the C(3)−SMe group[48] with secondary amines,[48] hydrazine,[28] and MeO[49] was described.

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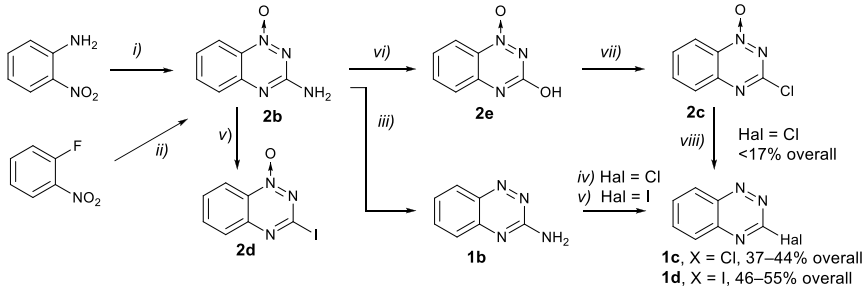
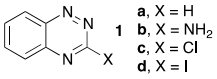
Scheme 1. Synthesis of 3-Halobenzo[*e*][1,2,4]triazines 1c and 1d[a]



[a]Reagents and conditions: (i) (1) NH_2CN, HCl, 100 °C; (2) NaOH, H_2O, 100 °C, 0.5 h, 82−85% yield; (ii) $HN{=}C(NH_2)_2{\cdot}HCl$, *t*-BuOK, tetrahydrofuran (THF), 70 °C, 6 h, 96% yield, ref 58; (iii) H_2, Pd/C, EtOH/EtOAc, room temperature (rt), overnight, >98%; alternatively $Na_2S_2O_4$, EtOH/H_2O, 33−63% yield; (iv) $CuCl_2{\cdot}2H_2O$, *t*-BuONO, MeCN, 60 °C, 0.5 h, 48−52% yield; (v) CuI, I_2, *t*-BuONO, THF, reflux, 2 h, 59−65% yield for **1d** and 41−51% for **2d**; (vi) $NaNO_2$, H_2SO_4/H_2O, 0 °C, 3 h then rt, overnight, 95% yield; (vii) $POCl_3$, reflux, 2 h, 57% yield; (viii) Zn, NH_4Cl, H_2O, rt, 48 h, <39% yield.

Surprisingly, neither chloride **1c** nor any other C(3) halides have been investigated in Pd-catalyzed C−C cross-coupling reactions, even though such a process could, in principle, provide an easy access to a variety of (het)aryl, alkyl, and other substituents at the C(3) position of the benzo[*e*][1,2,4]triazine ring. The analogous C(3)-bromide is only mentioned in the literature,[25] while the C(3)-iodide **1d** is unknown. On the other hand, 3-chloro-[26] (**2c**), 3-bromo-,[26,50] and 3-iodo-benzo[*e*]-[1,2,4]triazine-1-oxides[51] (**2d**) have been successfully used in Pd-catalyzed C−C coupling reactions with a dozen substituted aromatic and heteroaromatic boronic acids (Suzuki conditions)[50,52] and several organotin reagents (Et_4Sn, Me_4Sn, $Bu_3SnCH{=}CH_2$, and $Bu_3SnCH_2CH{=}CH_2$; Stille conditions).[51−53]

In the context of our investigation of functional benzo[*e*]-[1,2,4]triazin-4-yl radicals,[54−57] we are interested in an easy access to a variety of C(3)-substituted derivatives of **1a** available from a common precursor. For this purpose, we selected the 3-aminobenzo[*e*][1,2,4]triazine (**1b**), which can be converted to 3-chloro- (**1c**) and 3-iodobenzo[*e*][1,2,4]triazines (**1d**) to serve as reagents for the formation of C−N (amines), C−O (ether), C−S (sulfides), C−C (COOH, CN, alkyl, aryl, hetaryl, ethynyl, CF_3, acetic acid), and C−P (phosphonates) bonds either by nucleophilic aromatic substitution or through metal-catalyzed (Pd and Cu) coupling reactions. Selected benzo[*e*]-[1,2,4]triazine derivatives were characterized by X-ray diffraction (XRD) and spectroscopic methods, and the effect of the substituent at the C(3) position on NMR and electronic absorption spectra was investigated. The experimental data are supported with density functional theory (DFT) computational results.

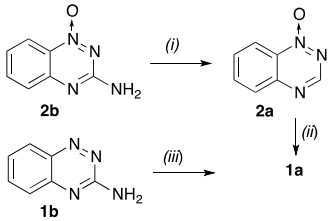


RESULTS AND DISCUSSION

Synthesis of Precursors and Reference Compounds. The requisite 3-halobenzo[*e*][1,2,4]triazines **1c** and **1d** were obtained in three steps from 2-nitroaniline in 37−44 and 46−55% overall yields, respectively, as shown in Scheme 1. Thus, a reaction of 2-nitroaniline and cyanamide in concentrated HCl gave 3-aminobenzo[*e*][1,2,4]triazine-1-oxide (**2b**) in 82−85% yield.[10,26] The reaction is exothermic and requires careful control in a large scale. An alternative preparation of **2b** involves a two-step process starting with a nucleophilic substitution of 2-fluoronitrobenzene, as shown in Scheme 1.[58] Subsequent catalytic hydrogenation (Pd/C) of the *N*-oxide **2b** in EtOH/AcOEt gave 3-aminobenzo[*e*][1,2,4]triazine (**1b**) in a nearly quantitative yield. This method is more convenient and efficient than the literature protocol[10] for deoxygenation of **2b** with $Na_2S_2O_4$ (33−63% yield). The resulting amine **1b** was converted to 3-halobenzo[*e*][1,2,4]triazines **1c** and **1d** via a substitutive deamination reaction, according to a general literature method[59] and a method for the preparation of 3-iodo derivative **2d**,[51] respectively. Thus, a reaction of **1b** with *t*-BuONO in the presence of $CuCl_2$ hydrate or CuI/I_2 afforded **1c** and **1d** in 54 and 62% yields, respectively (Scheme 1).

This strategy for the preparation of 3-chloro derivative **1c** constitutes a more efficient alternative to the literature procedure involving 3-hydroxy derivative **2e** and *N*-oxide **2c** (Scheme 1).[26] The main limitation of this method appears to be deoxygenation of *N*-oxide **2c** with Zn powder, which in our hands gave the desired **1c** in yields no greater than 39%. The 3-iodobenzo[*e*][1,2,4]triazine-1-oxide (**2d**) was obtained from amine **2b** in 41−51% yield according to the literature procedure (Scheme 1).[51] For comparison purposes, the parent benzo[*e*]-[1,2,4]triazine (**1a**) was prepared from amine **1b** by reductive deamination, according to a general literature procedure[60] (Scheme 2).

Scheme 2. Synthesis of Benzo[*e*][1,2,4]triazine (1a)[a]



[a]Reagents and conditions: (i) *t*-BuONO, dimethylformamide (DMF), 60 °C, 2 h; (ii) H_2, Pd/C, EtOH/EtOAc, rt, overnight, 48% overall; (iii) *t*-BuONO, DMF, 60 °C, 2 h, 23%.

Alternatively, **1a** was obtained by reductive deamination of **2b** followed by catalytic reduction of the resulting crude benzo[*e*][1,2,4]triazine-1-oxide (**2a**). The latter method is more efficient (overall yield 48%) than the literature one using H_2/Pd reduction of chloride **2c**.[10] The parent heterocycle **1a**

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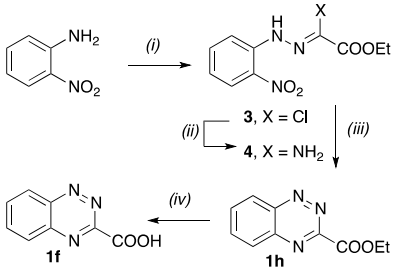
turned out to be sensitive to silica gel, and the crude product was best purified by vacuum sublimation.

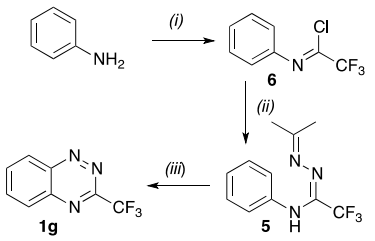
Two other reference compounds were prepared according to literature protocols for similar derivatives: benzo[*e*][1,2,4]-triazine-3-carboxylic acid[35,61] (**1f**, Scheme 3) and 3-(trifluoromethyl)benzo[*e*][1,2,4]triazine[32] (**1g**, Scheme 4) in yields similar to those reported for their analogues. Thus, 2-nitroaniline was diazotized and reacted with ethyl 2-chloroacetoacetate to yield derivative **3** (Scheme 3). Subsequent treatment of **3** with NH_3 gave the amidrazone **4**, which under reductive conditions provided the ethyl ester **1h** in 29% overall yield. Hydrolysis of the ester under basic conditions gave the desired carboxylic acid **1f**.

Scheme 3. Synthesis of Benzo[*e*][1,2,4]triazine-3-carboxylic Acid (1f)[a]



[a]Reagents and conditions: (i) (1) $NaNO_2$, HCl, MeOH/H_2O, 15 min; (2) MeCOCHClCOOEt, 0 °C to rt, 1.5 h, 73% yield; (ii) NH_3, THF, rt, overnight, quant.; (iii) Fe, conc. HCl, AcOH, H_2O, rt, overnight, 29% yield; (iv) (1) 0.1 N KOH/EtOH, THF/H_2O, rt, 10 min; (2) 10% HCl, quant. yield.

Scheme 4. Synthesis of 3-(Trifluoromethyl)-benzo[*e*][1,2,4]triazine (1g)[a]



[a]Reagents and conditions: (i) CF_3COOH, PPh_3, Et_3N, CCl_4, 0 °C → rt → 100 °C, 5 h, 61% yield, ref 62; (ii) $Me_2C{=}NN{=}CMe_2$, $NH_2NH_2{\cdot}H_2O$, DMF, rt, 5 h, 87% yield; (iii) *t*-BuOCl, CH_2Cl_2, −70 °C to rt, 4 h, 37% yield, ref 32.

Nucleophilic Substitution Reactions of 3-Chloro-benzo[*e*][1,2,4]triazine (1c). Chloride **1c** was reacted with a selection of C, N, O, P, and S nucleophiles under typical conditions leading to products **1i–o**, as shown in Table 1. Thus, a reaction of **1c** with $[Et_4N]^+CN^-$ in MeCN gave benzo[*e*][1,2,4]triazine-3-carbonitrile (**1i**) in a nearly quantitative yield. Reactions of **1c** with NaCN or KCN in the presence of 1,4-diazabicyclo[2.2.2]octane, in aqueous (aq) dimethyl sulfoxide (DMSO)[63] or with CuCN in DMF at 100 °C[64] gave only the unreacted chloride **1c**.

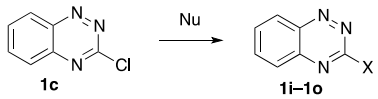
A reaction of **1c** with sodium diethyl malonate in DMF, conditions used for an analogous reaction of 2-chloropyrimidine,[65] gave diethyl 2-(benzo[*e*][1,2,4]triazin-3-yl)malonate (**1j**) in a nearly quantitative yield. Similarly, chloride **1c** reacted with aniline and morpholine in EtOH affording the desired amines **1k** and **1l** in 85 and 89% yields, respectively. Also, a reaction of **1c** with sodium *tert*-butylthiolate in DMF gave sulfide **1o** in 95% yield (Table 1).

In contrast, the formation of the phosphonate ester **1n** was significantly less efficient. Thus, a reaction of **1c** with neat $P(OEt)_3$ gave a mixture of products, of which the desired ester **1n** was isolated in 20% yield. Higher yields of **1n** were obtained using iodide **1d** (vide infra).

Metal-Catalyzed Substitution Reactions of 3-Iodo-benzo[*e*][1,2,4]triazine (1d) and 3-Iodobenzo[*e*][1,2,4]-triazine-1-oxide (2d). Several types of standard Pd-catalyzed C−C coupling reactions, such as Suzuki−Miyaura, Sonogashira, Negishi, and carbonylation, were tested with 3-iodobenzo[*e*][1,2,4]triazine (**1d**). Access to those products, which could not be obtained in satisfactory yields, was attempted in a two-step process using 3-iodobenzo[*e*][1,2,4]-triazine-1-oxide (**2d**) and subsequent catalytic deoxygenation (Scheme 5).

Reactions of 3-iodobenzo[*e*][1,2,4]triazine (**1d**) with phenylboronic and 2-thiopheneboronic acids under standard Suzuki−Miyaura conditions gave the corresponding coupling products **1p** and **1r** in good yields (Table 2). A similar reaction of **1d** with ferrocenylboronic was problematic and much less efficient: the desired 3-ferrocenyl derivative **1s** was obtained only in 27% yield after resubmission of the inseparable mixture of the unreacted **1d** and **1s** to the reaction conditions. A reaction of iodide **1d** with phenylacetylene cleanly afforded

Table 1. Nucleophilic Substitution in 3-Chloro-benzo[*e*][1,2,4]triazine (1c)



	X	conditions	isolated yield (%)
1i	CN	$[Et_4N]^+CN^-$, MeCN, 20 min, rt	98
1j	$CH(COOEt)_2$	NaH, diethyl malonate, DMF, 2 h, 0 °C to rt	99
1k	NHPh	aniline, EtOH, overnight, rt	85
1l	$N(CH_2CH_2)_2O$	morpholine, EtOH, 2 h, rt	89
1m	OEt	EtONa, EtOH, 0.5 h, rt	95
1n	$PO(OEt)_2$	$P(OEt)_3$, 6 h, 100 °C	20
1o	SBu-*t*	NaH, *t*-BuSH, DMF, 2 h, rt	95

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Scheme 5. 3-Iodo Derivatives 1d and 2d as Precursors to C−C Coupling Products

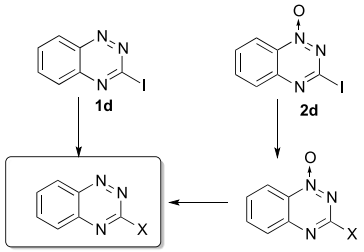
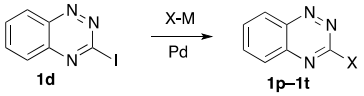


Table 2. Pd-Catalyzed C−C Coupling Reactions of 3-Iodobenzo[*e*][1,2,4]triazine (1d)

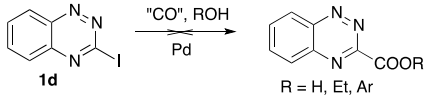


	X	conditions	isolated yield (%)
1p	Ph	$PhB(OH)_2$, $Pd(OAc)_2$, K_2CO_3, toluene/H_2O	82
1r	2-thienyl	thiophene-2-$B(OH)_2$, $Pd(OAc)_2$, K_2CO_3, toluene/H_2O	69
1s	ferrocenyl	ferrocene-$B(OH)_2$, $PdCl_2$(dppf), K_3PO_4, toluene	27
1t	CCPh	PhCCH, $Pd(PPh_3)_4$, CuI, Et_3N, THF, 10 min	79

derivative **1t** in 79% yield under standard Sonogashira conditions.

In contrast, carbonylation and Negishi coupling reactions of **1d** were much less successful (Schemes 6 and 7).[66] In particular, attempts at the preparation of carboxylic acid **1f** or its esters via palladium-catalyzed hydroxycarbonylation, ethoxycarbonylation, or aryloxycarbonylation of 3-iodobenzo[*e*][1,2,4]triazine (**1d**) using several literature protocols and carbon monoxide sources, such as HCOONa in DMF,[67] HCOOH in DMF,[68] HCOOH in toluene,[69] and 2,4,6-trichlorophenyl formate in toluene,[70] gave no reaction or complex mixtures of products, which included **1a**. An attempt at CuI-catalyzed carbonylation of iodide **1d** with CO_2 in the presence of Et_2Zn and tetramethylethylenediamine in DMSO[71] gave no reaction. Similar results were obtained for ethoxycarbonylation[69] of 3-chlorobenzo[*e*][1,2,4]triazine (**1c**) and aryloxycarbonylation[70] of 3-iodobenzo[*e*][1,2,4]triazin-1-oxide (**2d**).

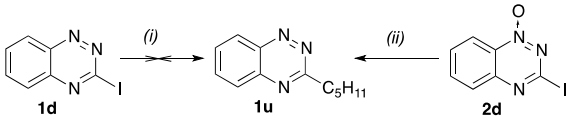
Scheme 6. Attempted Preparation of Carboxylic Acid 1f and Its Esters[a]



[a]For reaction conditions, see the text and the Supporting Information (SI).

The Negishi cross-coupling reaction of 3-iodo-benzo[*e*][1,2,4]triazine (**1d**) with pentylzinc in THF in the presence of PEPPSI-IPr, $Pd(PPh_3)_2Cl_2$, $Pd(OAc)_2$/Xantphos, $Pd_2(dba)_3$/PPh_3, $Pd_2(dba)_3$/P(2-$OMeC_6H_4$), $Pd_2(dba)_3$/Xantphos, or $Pd_2(dba)_3$/P(*c*-Hex)$_2$(Ph-C_6H_4) in the temperature range of rt to 50 °C surprisingly gave no reaction (Scheme 7) and the formation of the desired 3-pentylbenzo[*e*][1,2,4]triazine (**1u**) was not observed.

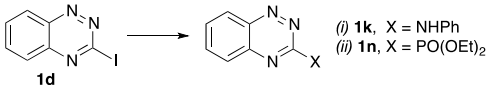
Scheme 7. Preparation of 3-Pentylbenzo[*e*][1,2,4]triazine (1u)[a]



[a]Reagents and conditions: (i) $ZnCl_2$, *n*-$C_5H_{11}MgBr$, PEPPSI-IPr, THF, 0 °C, 15 min → rt, 20 min; (ii) (1) $ZnCl_2$, *n*-$C_5H_{11}MgBr$, PEPPSI-IPr, THF, 0 °C, 15 min → rt, 20 min; (2) H_2, 10% Pd/C, EtOH/AcOEt, rt, overnight (55−58% yield).

In contrast to **1d**, the reactivity of *N*-oxide analogue **2d** in these catalytic systems was much higher even at ambient temperature. Thus, reactions of **2d** with $C_5H_{11}ZnBr$ in the presence of $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, or $Pd_2(dba)_3$/PPh_3 gave a complex mixture of products with small amounts of the expected 3-pentylbenzo[*e*][1,2,4]triazine-1-oxide (**2u**, Scheme 8). Changing the catalyst to PEPPSI-IPr greatly improved the process conducted at ambient temperature, and the desired product **2u** was isolated in 40% yield. The reaction run with 2 or 4 equiv of $C_5H_{11}ZnBr$ at 0 °C gave a mixture of the expected product **2u** and its deoxygenated analogue **1u** in a 3:2 ratio, which after catalytic reduction provided **1u** in 55−58% overall yield.

Scheme 8. CuI-Mediated Substitution Reactions of 3-Iodobenzo[*e*][1,2,4]triazine (1d)[a]



[a]Reagents and conditions: (i) $PhNH_2$, CsF, CuI, DMSO, 60 °C, overnight, 65% yield; (ii) $HP(O)(OEt)_2$, CuI, Et_3N, toluene, 60 °C, 2 h, 75% yield.

Three copper(I)-mediated C−N, C−P, and C−C coupling reactions of **1d** were investigated. Thus, a ligand-free Ullmann-type C−N coupling reaction[72] of **1d** with aniline in the presence of CuI and CsF in DMSO afforded the desired 3-aminophenyl derivative **1k** in 65% yield (Scheme 8), which is comparable to that obtained in nucleophilic substitution of **1c**. Similarly, a reaction of **1d** with $HPO(OEt)_2$ in the presence CuI and Et_3N gave the phosphonate ester **1n** in 75% yield.

The Cu(I)-catalyzed trifluoromethylation[73] of 3-iodobenzo[*e*][1,2,4]triazine (**1d**) with the Ruppert reagent (Me_3SiCF_3) and the preparation of 3-(trifluoromethyl)benzo[*e*][1,2,4]triazine (**1g**) proved to be challenging. All attempts at the direct transformation of the iodo derivative **1d** to **1g** were unsuccessful (Scheme 9).

A reaction of **1d** with 2 equiv of Me_3SiCF_3 in the presence of CsF and CuI gave unreacted **1d** and a new, less polar product in a 1:2 ratio (NMR). A similar result was obtained when chloride **1c** was used in place of the iodide **1d** and no CuI catalysis was used (dimethoxyethane solvent). The new product was different from the expected **1g**. Its detailed analysis revealed the presence of a broad singlet at 4.70 ppm, characteristic for NH, and 2 equiv CF_3 groups, which suggested structure **7** (Scheme 9). It could be formed by a formal addition of HCF_3 to the C═N bond[73] of the expected product **1g**. The lack of

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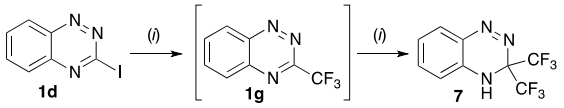
Scheme 9. Attempted Preparation of 3-(Trifluoromethyl)-benzo[*e*][1,2,4]triazine (1g)[a]

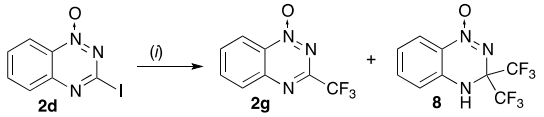


[a]Reagents and conditions: $TMSCF_3$, CsF, CuI, 1,10-phenanthroline, DMF, 60 °C, 1 h. For other reaction conditions, see the text and the SI.

detection of **1g** in the reaction mixture even with 1.3 equiv of Me_3SiCF_3 is related to the high susceptibility of **1g** to the addition reaction.

A similar result was obtained in a reaction of 3-iodo derivative **1d** with 2 equiv of the Ruppert reagent[73] in the presence of CuI, 1,10-phenanthroline, and CsF in a mixture of DMF and *N*-methyl-2-pyrrolidone (1:1).[74] In this case, compound **7** was formed in about 65% yield based on ^1H NMR, after 3 h at 60 °C. On the other hand, reaction of iodide **1d** with Me_3SiCF_3 under similar conditions using KF[75] instead of CsF led to recovery of the starting iodide. Attempts at synthesis of **1g** using $CF_3B(OMe)_3K$ as the trifluoromethylating reagent in DMSO at 60 °C in the presence of CuI and 1,10-phenanthroline[76] gave only 3-methoxybenzo[*e*][1,2,4]triazine (**1v**), which was isolated in 51% yield. Reactions of 3-iodo *N*-oxide **2d** with the Ruppert reagent under conditions described by Oishi were more successful.[74] Thus, a reaction of **2d** with 2 equiv of Me_3SiCF_3 in the presence of CsF and CuI gave full conversion of the iodide in 1 h, resulting in a mixture of products, from which two compounds were isolated. The desired product **2g** was isolated in 7% yield, while the main product of this reaction was less polar derivative **8**, an analogue of **7**, isolated in 24% yield (Scheme 10). Its structure was confirmed by single-crystal XRD analysis (vide infra).

Scheme 10. Trifluoromethylation of 3-Iodo-benzo[*e*][1,2,4]triazine-1-oxide (2d)[a]



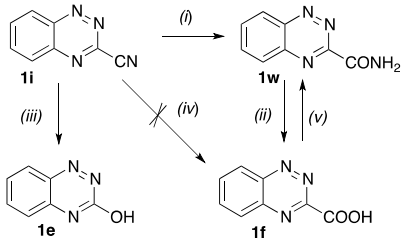
[a]Reagents and conditions: $TMSCF_3$, CsF, CuI, 1,10-phenanthroline, DMF, 60 °C, 1 h; **2g**, 7% yield; **8**, 24% yield.

A test reaction of **2d** with 1 equiv of Me_3SiCF_3 demonstrated that the reaction is completed in less than 10 min and the ratio of the main components **2d**/**2g**/**8** is 4:1:2. This suggests that the rate of formal addition of HCF_3 to the desired product **2g** is comparable to its formation.

Attempted deoxygenation of **2g** under catalytic conditions (H_2/Pd/C) gave a complex mixture of products with the desired **1g** being a minor component.

Functional Group Transformations. In light of a failure of carbonylation of **1d**, an alternative access to the carboxylic acid **1f** was investigated through hydrolysis of the nitrile **1i**. Thus, acidic hydrolysis with conc. HCl at ambient temperature gave amide **1w** after 72 h (Scheme 11). Its structure was confirmed by independent synthesis from acid **1f**. Conversion of the amide to the acid **1f** was accomplished in 98% yield using $NaNO_2$ in aqueous HCl/AcOH. When hydrolysis of nitrile **1i** with conc. HCl was conducted at 70 °C, only the parent

Scheme 11. Hydrolysis of Benzo[*e*][1,2,4]triazine-3-carbonitrile (1i)[a]

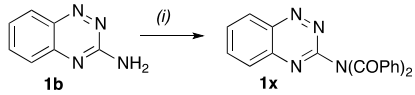


[a]Reagents and conditions: (i) conc. HCl, rt, 72 h, quant.; (ii) $NaNO_2$, 20% HCl, AcOH; rt overnight, 98% yield; (iii) (1) 30% NaOH, 60 °C, 2 h; (2) 20% HCl, rt; (iv) conc. HCl, 70 °C; (v) (1) $(COCl)_2$, CH_2Cl_2, cat DMF; (2) CH_2Cl_2/25% NH_4OH, quant.

benzo[*e*][1,2,4]triazine (**1a**) was isolated in 55% yield. A possibility of formation of **1a** by decarboxylation of **1f** was demonstrated by heating of acid **1f** in conc. HCl. Interestingly, treatment of nitrile **1i** with aqueous NaOH gave a mixture of the expected amide **1w** and apparently the substitution product, the 3-hydroxy derivative **1e**, in about 1:7 ratio on the basis of ^1H NMR spectroscopy (Scheme 11).

Acylation of amine **1b** with 1 equiv of PhCOCl in the presence of Et_3N gave only the dibenzoylated product **1x** and the starting amine **1b** (Scheme 12). No monobenzoylated product was observed. No reaction was observed when $NaHCO_3$ was used as the base.

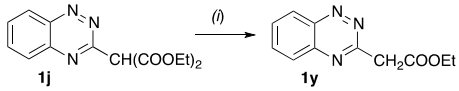
Scheme 12. Acylation of 3-Aminobenzo[*e*][1,2,4]triazine (1b)[a]



[a]Reagents and conditions: (i) 1.5 equiv BzCl, Et_3N, CH_2Cl_2, rt, overnight, 75% yield.

The malonate ester **1j** was converted to the acetate ester **1y** in 89% yield upon heating with sodium chloride in DMSO (Scheme 13), following a procedure described for a pyrimidine analogue.[65]

Scheme 13. Preparation of Ethyl Benzo[*e*][1,2,4]triazine-3-acetate (1y)[a]



[a]Reagents and conditions: (i) NaCl, H_2O, DMSO, 180 °C, 20 min, 89% yield.

Molecular and Crystal Structures. Yellow crystals of 3-morpholinyl (**1l**) and 3-phenyl (**1p**) derivatives suitable for X-ray diffraction studies were obtained by slow evaporation of *n*-heptane solutions, while crystals of 3-iodo (**1d**) and 3-dibenzoylamino (**1x**) derivatives were grown from MeCN solutions. Crystals of 3-trifluoromethyl derivative **1g** were obtained from a petroleum ether/EtOAc (8:1) solution on cooling, and crystals of 3,3-bis(trifluoromethyl) derivative **8** were grown by slow evaporation of an EtOH/MeCN solution. Single-crystal X-ray diffraction experiments were performed at

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Table 3. Selected Interatomic Distances and Angles for Five Benzo[*e*][1,2,4]triazine Derivatives[a]

	1d[b]	1g[c]	1l[d]	1p[e]	1x[f]
N(1)−N(2)	1.323(4)	1.318(1)	1.305(2)	1.308(1)	1.312(2)
N(2)−C(3)	1.366(4)	1.357(2)	1.385(2)	1.357(1)	1.368(2)
C(3)−N(4)	1.310(5)	1.308(2)	1.331(2)	1.323(1)	1.305(2)
N(4)−C(4a)	1.357(5)	1.361(2)	1.358(2)	1.355(1)	1.366(2)
C(4a)−C(5)	1.407(6)	1.410(2)	1.421(3)	1.416(1)	1.413(2)
C(5)−C(6)	1.366(7)	1.367(2)	1.369(3)	1.367(1)	1.372(2)
C(6)−C(7)	1.426(7)	1.424(2)	1.419(3)	1.420(1)	1.422(2)
C(7)−C(8)	1.364(6)	1.360(2)	1.361(3)	1.363(1)	1.361(2)
C(8)−C(8a)	1.417(6)	1.418(2)	1.419(3)	1.416(1)	1.419(2)
C(8a)−N(1)	1.365(6)	1.357(2)	1.364(3)	1.357(1)	1.365(2)
C(8a)−C(4a)	1.421(6)	1.424(2)	1.409(3)	1.418(1)	1.413(2)
N(1)−N(2)−C(3)	117.3(3)	117.4(1)	118.3(2)	119.05(8)	117.3(1)
N(2)−C(3)−N(4)	128.1(3)	129.0(1)	125.9(2)	125.76(8)	128.6(1)

[a]The numbering system according to the chemical nomenclature. For details, see the SI. [b]The C(3)−I distance is 2.105(3) Å. [c]The C(3)−CF_3 distance is 1.519(2) Å. [d]The C(3)−N distance is 1.366(2) Å. [e]The C(3)−Ph distance is 1.481(1) Å; BT−Ph interplanar angle 5.1°. [f]The C(3)−N distance is 1.425(2) Å.

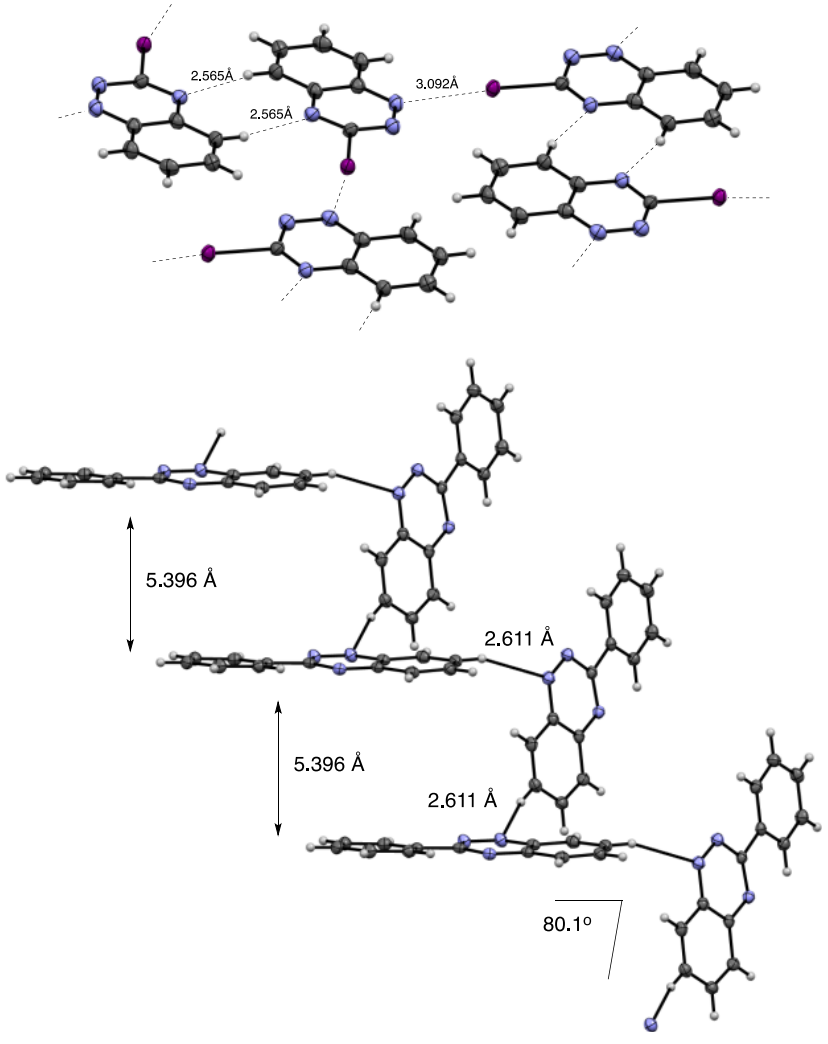

Figure 3. Partial packing diagrams for **1d** (top) showing molecular arrangements in a single sheet and for **1p** (bottom).

100 K. Crystal data, data collection, and structure refinement details are presented in the SI. Selected interatomic distances and angles for investigated derivatives are summarized in Table 3. Respective crystal structures of **1d**, **1l**, **1p**, **1x**, and **8** are shown in Figures 3−5.

All five 3-substituted benzo[*e*][1,2,4]triazines crystallize with one unique molecule, while derivative **8** with two unique molecules in the asymmetric unit of the crystal lattice. Derivatives **1d**, **1g**, and **8** crystallize in the monoclinic $P2_1/c$ space group, while **1l** and **1p** are in $P2_1/n$ and $C2/c$ settings,

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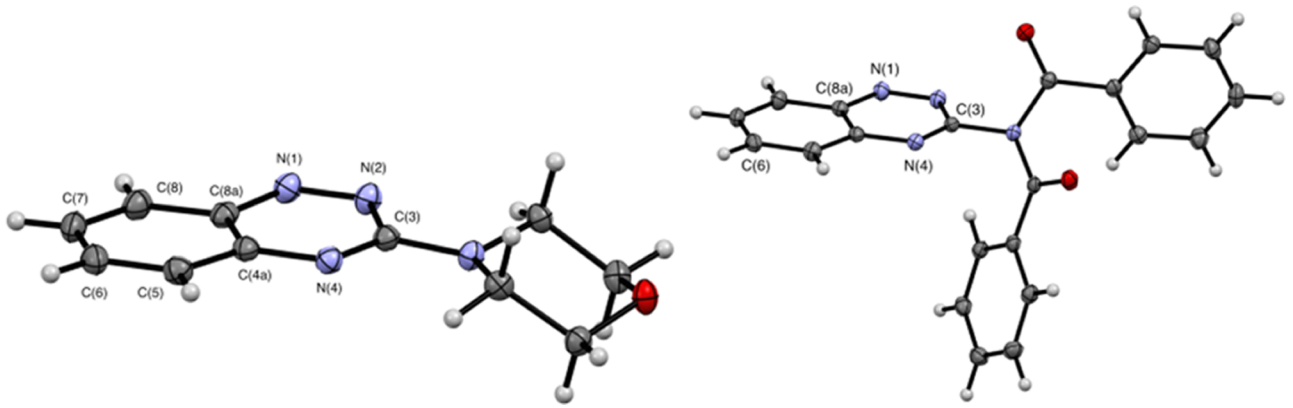

Figure 4. Thermal ellipsoid diagram for **1l** (left) and **1x** (right). For selected geometrical parameters, see Table 3. Ellipsoids are drawn at 50% probability, and the numbering system according to the chemical nomenclature.

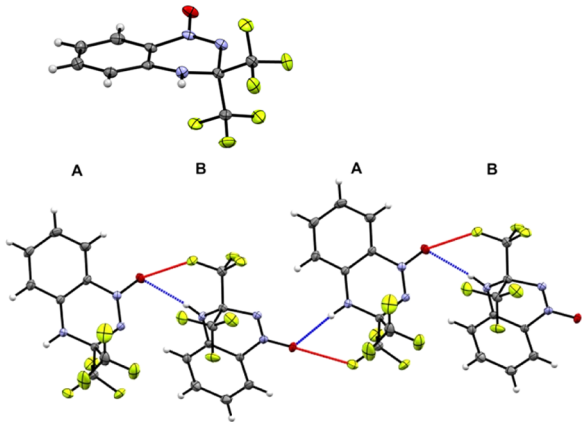

Figure 5. Top: thermal ellipsoid diagram for molecule A of compound **8**. Pertinent geometrical parameters: N(1)−O 1.260(2) Å, N(1)−N(2) 1.283(2) Å, N(2)−C(3) 1.465(2) Å, C(3)−N(4) 1.427(2) Å, C(3)−CF_3 1.547(3) and 1.558(3) Å. Bottom: partial packing diagrams for **8** showing an alternating chain of molecules with close contacts O···F 0.112 and 0.186 Å and O···H 0.487 and 0.592 Å inside the van der Waals (VDW) separation. Ellipsoids are drawn at 50% probability, and the numbering system according to the chemical nomenclature.

respectively. Compound **1x** crystallizes in the orthorhombic $Pca2_1$ space group. Analysis of crystal packing indicates some specific features for each investigated derivative. Most interesting is the 3-iodo derivative **1d**, which forms a dimeric structure with two mutual C(5)−H···N(4) nonbonding interactions (0.185 Å inside the VDW separation, Figure 3). The dimers are then interconnected through strong I···N(1) interactions (0.438 Å inside the VDW separation), which result in parallel sheets separated by 3.312 Å (Figure 3). In the 3-phenyl derivative **1p**, there are two interacting slipped stacks oriented at 80.1° relative to each other with a distance between the heterocycle planes of 5.396 Å (Figure 3). Molecules of 3,4-dihydrobenzo[*e*][1,2,4]triazine derivative **8** form an infinite chain of type ···ABABA··· through two types of close contacts: N(4)−H···O and F···O, which are 0.487/0.592 and 0.112/0.186 Å inside the VDW separation, respectively (Figure 5).

The benzo[*e*][1,2,4]triazine ring is planar in all five derivatives (Figures 3 and 4), and interatomic distances shown in Table 3 are consistent with those found in the five derivatives **9**,[17,18] **10**,[16] **11**,[15] and **12**[19] with known structures (Figure 6).

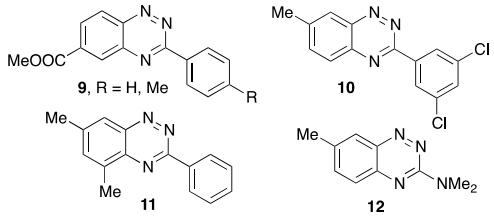

Figure 6. Structures of previously structurally characterized benzo-[*e*][1,2,4]triazine derivatives.

Analysis of data in Table 3 demonstrates that the dimensions of the [1,2,4]triazine ring respond to electronic effects of the substituent at the C(3) position. Thus, the increase of the electron-withdrawing ability of the substituent results in lengthening of the N(1)−N(2) bond and shortening of the N(2)−C(3), C(3)−N(4), and C(4a)−C(5) distances. These observations are consistent with DFT results (M06-2x/6-31G(2d,p) level) for a set of 11 derivatives.[66] They demonstrate that the C(3) substituent exerts the strongest effect on the N(2)−C(3) distance, which contracts upon increasing the electron-withdrawing character of the substituent. About a half as strong effect is observed on the C(3)−N(4) bond, which also contracts, and on the N(1)−N(2) bond, which expands when the value of the σ_p parameter increases. The calculated changes in all three bonds show reasonable correlation with the σ_p parameter.[66] Effect on other bonds in the benzo[*e*][1,2,4]-triazine skeleton is much weaker or negligible.[66]

Orientation of the C(3) substituents in the five experimentally investigated derivatives of the benzo[*e*][1,2,4]triazine is noteworthy. Thus, the phenyl group in **1p** is nearly coplanar with the heterocycle ring (interplanar angle, 5.6°), which is consistent with the predicted fully planar geometry at the conformational minimum. The morpholine ring in **1l** is oriented parallel to the heterocycle plane (Figure 4) allowing for full interactions of the nitrogen's lone pair with the heterocycle π system. The morpholine nitrogen atom is nearly planar with a distance of 0.156 Å from the plane defined by its three substituents. In the dibenzoyl derivative **1x**, all three π substituents of the imide nitrogen atom, the heterocycle and the two benzoyl groups, are arranged in a propeller-like mode (Figure 4). The nitrogen is slightly pyramidalized, and the distance from the plane defined by its three sp^2-hybridized substituents is 0.184 Å. All of these molecular features are fully consistent with the DFT computational results obtained at the M06-2x/6-31G(2d,p) level of theory.[66]

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Table 4. Selected Experimental[a] and Calculated[b] Electronic Transition Energies and Oscillator Strength Values

compound	experimental[a]		theoretical[b]		
X	λ_{max} (n → π*)/nm (log ε)	λ_{max} (π → π*)/nm (log ε)	n → π* (A″)/nm (f)	π → π* (A′)/nm (f)	π → π* (A′)/nm (f)
1a, H	443 (2.52)	333 (2.89),[c] 303 (3.57)	415.8 (0.005)	293.7 (0.054)	264.9 (0.110)
1c, Cl	427 (2.44)	339 (3.41), 305 (3.55)	404.2 (0.004)	305.6 (0.049)	271.9 (0.131)
1g, CF_3	433 (2.52)	309 (3.50)	409.0 (0.004)	299.8 (0.039)	269.2 (0.080)
1i, CN	431 (2.27)	320 (3.17)	409.1 (0.004)	308.4 (0.039)	278.0 (0.056)
1l, $N(C_2H_4)_2O$	[d]	416 (3.28), 304 (3.22)[c]	419.8 (0.004)	360.0 (0.103)	270.8 (0.066)
1m, OEt	429 (2.55)	354 (3.47), 295 (3.62)	405.9 (0.004)	309.8 (0.082)	265.9 (0.166)
1p, Ph	454 (2.52)	352 (3.65), 272 (4.44)	429.5 (0.003)	318.1 (0.179)	261.8 (0.864)
1r, thienyl	453 (2.56)[c]	378 (3.73), 301 (4.33)	419.0 (0.004)	335.2 (0.249)	277.0 (0.489)
1t, CCPh	439 (2.66)[c]	355 (3.86), 301 (4.38)	415.6 (0.004)	326.3 (0.499)	281.6 (0.784)

[a]Recorded in CH_2Cl_2. [b]Obtained with the TD-CAM-B3LYP/6-31++G(2d,p)//M06-2x/6-31G(2d,p) method in CH_2Cl_2 dielectric medium. [c]After deconvolution; see the SI. [d]Overlap with the π → π* transition.

Analysis of the molecular structure of derivative **8** demonstrated a puckered [1,2,4]triazine ring with the tetrasubstituted C(3) atom displaced from the 3,4-dihydrobenzo[*e*][1,2,4]triazine plane by 0.25 and 0.43 Å in the two unique molecules. The two CF_3 groups are orthogonal to the heterocycle plane, as indicated by the angle between the heterocycle and the CF_3−C(3)−CF_3 planes in both molecules.

Electronic Absorption Spectroscopy. For a better understanding of the C(3) substituent effect on the electronic structure of the benzo[*e*][1,2,4]triazine system, UV−vis absorption spectra were obtained for series **1** in CH_2Cl_2 solutions with the focus on low-energy absorption bands above 250 nm. Results are shown in Table 4 and Figure 7.

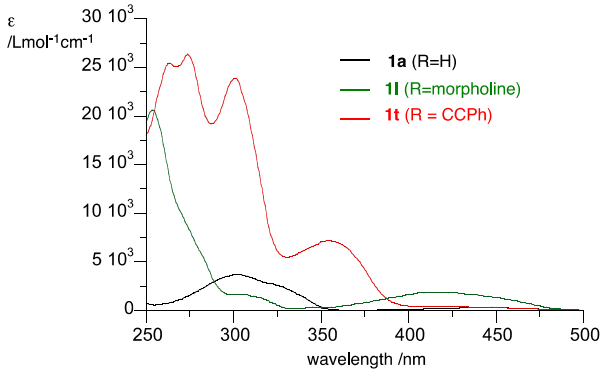

Figure 7. Electronic absorption spectra for **1a** (black), **1l** (green), and **1t** (red) in CH_2Cl_2.

The spectrum of the parent heterocycle **1a** exhibits two medium-intensity absorptions bands at 303 and 333 nm (after deconvolution; see the SI) corresponding to π → π* transitions and a low-intensity n → π* band at 443 nm (Figure 7). This is consistent with spectra recorded for **1a** in EtOH (304.5, 321sh, and 434 nm).[21] Substitution of the C(3) position affects the energy of all three absorption bands, with the position of the n−π* band being least affected by the nature of the C(3) substituent. It is around 430 nm and oscillates in a range of 427−454 nm. In contrast, the π → π* transition is shifted to higher energies for electron-accepting substituents (CN and CF_3), while for substituents with a lone pair (morpholine and EtO), the π → π* absorption bands are at lower energies. A particularly large bathochromic shift is observed for the amino derivative **1l** (Table 4 and Figure 7), for which the first π → π* band is shifted by −0.74 eV to 416 nm. Extended π substituents at the C(3), such as phenyl (**1p**), thienyl (**1r**), and phenylethynyl (**1t**), also cause bathochromic shift of the first π → π* band with a simultaneous hyperchromic shift. For instance, the first π → π* band in **1p** is shifted by −0.20 eV and in thienyl **1r** by −0.44 eV to lower energies and have over 5 times higher molar extinction than **1a**. This hyperchromic effect is even larger, over 9 times, for acetylene derivative **1t** (Table 4 and Figure 7).

Time-dependent (TD) DFT computational analysis of all members of series **1** in CH_2Cl_2 dielectric medium reproduced trends in excitation energies and also the relative intensities (Table 4). The calculated transition energies are systematically overestimated for all three bands (0.17 eV for n−π*, 0.5 eV for π−π*1). In the parent benzo[*e*][1,2,4]triazine (**1a**), the lowest-energy absorption band at 443 nm (calculated at 416 nm) is related to n−π* excitation from the highest occupied molecular orbital (HOMO), involving the lone pairs of the nitrogen atoms, to the lowest unoccupied molecular orbital (LUMO), delocalized over the heterocycle (Figure 8). The two lowest-energy π−π* excitations involve mainly the HOMO−1 → LUMO and HOMO−2 → LUMO transitions, respectively, which also include the extended π systems (Figure 9). This simple description cannot be applied to derivative **1s**, due to the

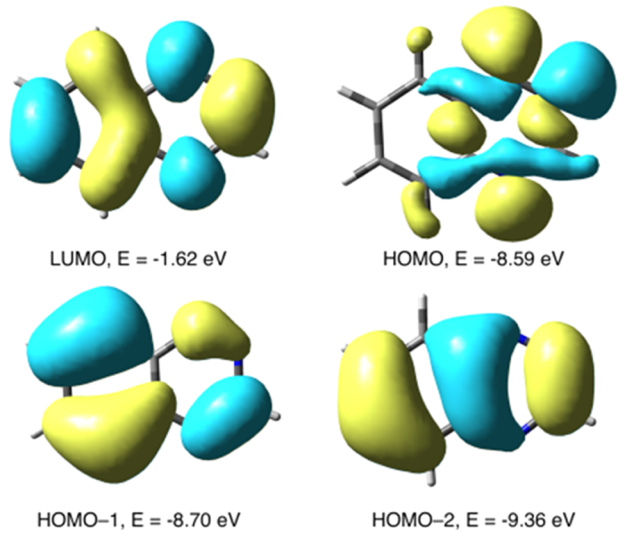

Figure 8. TD-CAM-B3LYP/6-31++G(2d,p)//M06-2x/6-31G(2d,p)-derived contours and energies of molecular orbitals for **1a** in CH_2Cl_2 dielectric medium relevant to the lowest-energy transitions.

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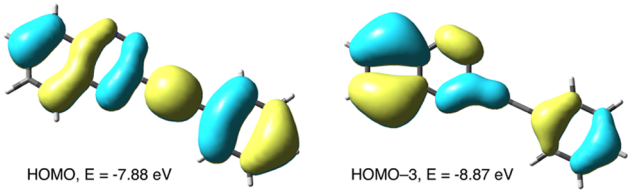

Figure 9. TD-CAM-B3LYP/6-31++G(2d,p)// M06-2x/6-31G(2d,p)-derived contours and energies of selected molecular orbitals for **1t** in CH_2Cl_2 dielectric medium.

extensive involvement of the ferrocene electron manifold in low-energy transitions. Calculations demonstrate that the C(3) substituent affects the energy of the π orbitals involved in these three lowest-energy transitions. Thus, energy of these orbitals decreases with an increasing electron-withdrawing character of the substituent σ_m,[77] with the strongest effect observed for the highest π-symmetry occupied molecular orbital (MO) (π1).[66] While correlation factor r^2 between energy of the MOs and σ_m is modest (r^2 = 0.66) and good (r^2 = 0.915), essentially no reasonable correlation was found for the calculated three lowest-energy excitation energies and the substituent constant σ.

NMR Spectroscopy. The availability of benzo[*e*][1,2,4]-triazines with a relatively broad range of substituents at the C(3) position allowed for another glimpse into the distribution of electronic effects in the heterocyclic ring through a correlation analysis of ^{1}H NMR shifts in the fused benzene ring. For this purpose, the ^{1}H NMR signals observed in the aromatic region were assigned to positions C(5)−H through C(8)−H of benzo[*e*][1,2,4]triazine on the basis of multiplicity, coupling constants, correlation spectroscopy, and trends in DFT computational results.[66]

A comparison of calculated and experimental chemical shifts (δ) for a series of 17 derivatives **1** in $CDCl_3$ demonstrates high correlation factors for all aromatic hydrogen atoms ($r^2 \geq 0.96$) with the slope being essentially a unity.[66] In contrast, the same correlation of ^{13}C NMR shifts for the C(3) atom shows a significant discrepancy for **1d**, due to heavy atom effect of the iodine atom, **1b** and **1k**. In the latter two cases, the calculated and experimental values differ by over 10 ppm, which suggests that the imino tautomeric forms **1b**′ and **1k**′ might be dominant (Figure 10). For instance, the calculated C(3) NMR chemical

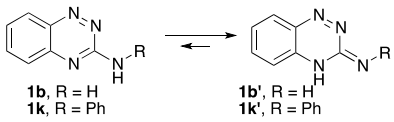

Figure 10. Tautomeric equilibrium for amines **1b** and **1k**.

shifts for **1k** and **1k**′ are 158.3 and 144.0 ppm, respectively, while the observed signal is found at 141.2 ppm. The dominance of tautomer **1k**′ in the sample is consistent with significant deshielding of the N−H proton (8.46 ppm) and the presence of an intense band at 1557 cm^{-1} in the IR spectrum (DFT calculated at $\nu_{C=N}$ = 1641 cm^{-1}). Therefore, further correlation analysis excluded data also for **1b** and **1k**.

A correlation of experimental ^{1}H NMR chemical shifts for each position of the fused benzene ring in 15 derivatives with available substituent parameters σ_p revealed a linear relationship with the correlation parameter r^2 in a range of 0.88−0.92. Excluding data for the parent **1a** improved the correlation (r^2 = 0.89−0.94) shown in Figure 11. Analysis of the best-fit lines shows that the slopes are nearly twice larger for correlations of

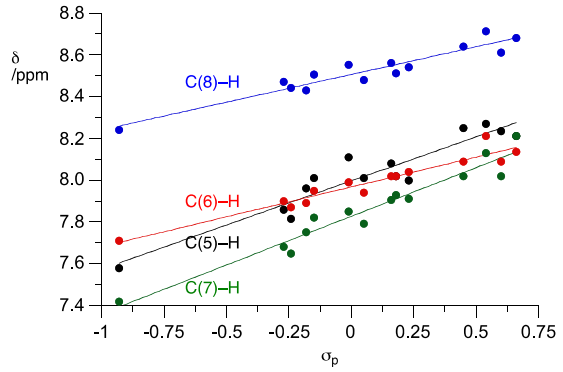

Figure 11. Correlation of ^{1}H NMR chemical shifts (δ) obtained in $CDCl_3$ for 14 derivatives of benzo[*e*][1,2,4]triazines **1** and the substituent parameter σ_p. Best-fit lines: δ_{H5} = 8.00 + 0.42 × σ_p, r^2 = 0.89; δ_{H6} = 7.97 + 0.29 × σ_p, r^2 = 0.93; δ_{H7} = 7.83 + 0.47 × σ_p, r^2 = 0.94; δ_{H8} = 8.50 + 0.27 × σ_p, r^2 = 0.91.

C(5)−H and C(7)−H chemical shifts (0.42 and 0.47, respectively) than for those of the other two positions (0.29 and 0.27). The results indicate that all four protons of the benzene ring undergo deshielding upon increase of the electron-withdrawing character of the C(3) substituent, and its impact on the electron density is approximately twice larger for positions C(5)−H and C(7)−H than for those in positions C(6)−H and C(8)−H. This effect is about 80% of that observed for the C(4) position in monosubstituted benzene derivatives (slope 0.55 ± 0.03 for 12 derivatives).[66]

The observed good-quality correlation of the chemical shifts with the parameter σ_p permitted the estimate of the substituent parameter σ_p for the CH_2COOEt group: 0.11 ± 0.01 as an average value obtained from correlation for all four H atoms.

SUMMARY AND CONCLUSIONS

We have demonstrated that benzo[*e*][1,2,4]triazines with a wide range of substituents at the C(3) position are readily available directly from the corresponding 3-halo derivatives **1c** and **1d**, which are obtained in three simple steps from 2-nitroaniline. The chloride **1c** is a convenient substrate for direct and efficient introduction of substituents such as OR, NHAr, NR_2, SR, and soft C-nucleophiles (CN and malonate) via S_N2Ar nucleophilic substitution reactions, while the iodo derivative **1d** provided access to C(3) (het)aryl (Suzuki), acetylene (Sonogashira), and phosphonate through Pd- or Cu-catalyzed substitution reactions. These methods failed to obtain 3-CF_3 (**1g**), 3-carboxyl (**1f**), and 3-alkyl (**1u**) derivatives from **1d** using the Ruppert, Pd-catalyzed carbonylation, and Negishi reactions, respectively. The use of iodide *N*-oxide **2d** instead of **1d** allowed to obtain 3-pentyl derivative **1u** in good yields, but failed again to provide access to **1g** and **1f**. Analysis of reaction products suggested that the 3-CF_3 derivatives **1g** and **2g** are highly electrophilic and their formation under the Ruppert conditions competes with addition of a second equivalent of the "CF_3" anion to the C═N bond in the [1,2,4]triazine ring. The carboxylic acid **1f** is susceptible to decarboxylation under acidic conditions, and this tendency may be at the root of failure to carbonylate iodides **1d** and **2d**. The carboxylic acid **1f** was prepared in high yield by a two-step hydrolysis of nitrile **1i**.

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Table 5. Comparison of Methods for Preparation of Functional Derivatives 1 in This Work and Previously Used[a]

functionality	this work (from 2-nitroaniline)	previous methods
3-COOH (**1f**)	six steps, 38 avrg% yield	four steps from 2-nitroaniline, 21% yield (method D)[b]
3-alkyl (**1u**)	four steps, 28 avrg% yield	three steps from 2-iodoaniline, 65% yield (method E)[c]
3-(het)aryl (**1p** and 1r)	four steps, 39 avrg% yield	three steps from 2-iodoaniline, 36% yield (method E)[c]
3-CH_2COOEt (**1y**)	five steps, 36 avrg% yield	three steps from 2-nitrophenylhydrazine and ethyl 3-amino-3-ethoxyacry-late, 43% yield (method D)[d]
3-amino (**1k** and **1l**)	four steps, 35 avrg% yield	multistep processes[e]

[a]See Figure 2 for methods. [b]Refs 35, 61. [c]Ref 36. [d]Ref 33. [e]Refs 24, 48.

Table 5 compares efficiencies of preparation of functional derivatives in this work with those previously reported.

Among the prepared compounds, there are several new functional derivatives of benzo[*e*][1,2,4]triazine. They include malonate **1j**, phosphonate ester **1n**, ferrocene **1s**, acetylene **1t**, and amides **1w** and **1x**. It should be added that two other important functional groups, $NHNH_2$, which was obtained from chloride **1c**, and N_3 prepared from the C(3)−$NHNH_2$ derivative, have been useful for the preparation of other heterocyclic systems.[28,45] Also the cyano group in **1i** offers access to other functionalities and heterocyclic systems through standard transformations.[78] Thus, a variety of derivatives of **1a** are available from common easily accessible intermediates.

Spectroscopic analysis augmented with DFT calculations revealed three low-intensity principal absorption bands above 250 nm corresponding to n → π^* and $\pi \rightarrow \pi^*$ transitions. The C(3) substituent has a significant impact on the position of the lower-energy $\pi \rightarrow \pi^*$ transition through considerable interactions with the π-symmetry highest-energy-occupied MO (π1).

NMR and IR analyses demonstrate that the tautomeric imino form is dominant in derivatives containing the NHR group at the C(3) position (compounds **1b** and **1k**). Analogously, the keto form is expected to be the main tautomer in C(3)−OH derivatives (**1e**). Analysis of ^{1}H NMR chemical shifts indicates that the C(3) substituent affects primarily positions C(5) and C(7). The magnitude of this effect in series **1** is comparable to that in monosubstituted benzene at the C(4) position.

Simplified availability of a variety of derivatives **1** offers a broader and simpler access to C(3)-functionalized 1,4-dihydrobenzo[*e*][1,2,4]triazin-4-yl radicals by addition of ArLi reagents. These results will be reported elsewhere.

COMPUTATIONAL DETAILS

Quantum-mechanical calculations were carried out using Gaussian 09 suite of programs.[79] Geometry optimizations were undertaken at the M06-2x/6-31G(2d,p) level of theory using tight convergence limits and appropriate symmetry constraints. Calculations involving iodine and iron used the LANL2DZdp effective core potential basis set (available from http://www.emsl.pnl.gov/forms/-basisform.html) and 6-31G-(2d,p) for the remaining elements implemented with the GEN keyword. The nature of stationary points was confirmed with vibrational frequency calculations.

Zero-point energy corrections were scaled by 0.9806.[80] Electronic excitation energies in CH_2Cl_2 dielectric medium were obtained at the CAM-B3LYP/6-31++G(2d,p)//M06-2x/6-31G(2d,p) level using the time-dependent DFT method[81] supplied in the Gaussian package. The same method was used to obtain isotropic shielding constants requested with the NMR = GIAO keyword and performed in $CHCl_3$ dielectric medium. Solvation models in both types of calculations were implemented with the polarizable continuum model[82] using SCRF(solvent = CH_2Cl_2) and SCRF(solvent = chloroform) keywords, respectively.

EXPERIMENTAL SECTION

Reagents and solvents were obtained commercially. Heat in reactions involving elevated temperatures was supplied using oil baths, and reported temperature refers to that of the bath.

NMR spectra were obtained at 500 or 600 MHz (^{1}H) and 125 or 150 MHz (^{13}C) in $CDCl_3$ or DMSO-d_6. Chemical shifts were referenced to the solvent (^{1}H and ^{13}C: 7.26 and 77.16 ppm for $CDCl_3$, and 2.50 and 39.52 ppm for DMSO-d_6, respectively).[83] Mass spectra were typically recorded in a positive-ion mode on a G2-Si Waters Synapt HDMS instrument fitted with an atmospheric pressure ionization electrospray source. Melting points are uncorrected. UV−vis spectra were recorded in spectroscopic grade CH_2Cl_2 at concentrations in the range of (2−20) × 10^{-5} M. Molar extinction coefficients ε were obtained by fitting the maximum absorbance against concentration in agreement with Beer's law. More details are provided in the SI.

Benzo[*e*][1,2,4]triazine (1a).[10] *Method A.* Following the general procedure,[60] *t*-BuONO (0.32 mL, 2.68 mmol) was added to a stirred solution of 3-aminobenzo[*e*][1,2,4]triazine (**1b**, 0.195 g, 1.34 mmol) in DMF (7 mL) and the resulting mixture was stirred at 60 °C (oil bath) for 2 h. The mixture was diluted with water (20 mL) and extracted with AcOEt. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (SiO_2; hexane/AcOEt, 4:1) giving 0.041 g (23% yield; 19−23% in several runs) of benzo[*e*][1,2,4]triazine (**1a**) as a yellow solid.

Method B. *t*-BuONO (0.66 mL, 5.56 mmol) was added to a stirred solution of 3-aminobenzo[*e*][1,2,4]triazine-1-oxide (**2b**, 0.448 g, 2.77 mmol) in DMF (10 mL) and the resulting mixture was stirred at 60 °C (oil bath) for 2 h. The mixture was diluted with water (20 mL) and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was dissolved in EtOH/EtOAc (1:1, 50 mL) and the mixture was stirred overnight with 10% Pd/C (0.040 g) under H_2 (balloon). The mixture was filtered through Celite, which was washed with EtOH, and the filtrate was evaporated. The residue was passed through a SiO_2 plug (AcOEt) giving 0.186 g (51% yield) of benzo[*e*][1,2,4]triazine (**1a**), which was further purified by vacuum sublimation (60 °C, 2.25 Tr): mp (*n*-heptane) 70−71 °C (lit.[10] mp (petroleum ether/AcOEt) 75−76 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.94 (ddd, J_1 = 1.2 Hz, J_2 = 6.9 Hz, J_3 = 8.3 Hz, 1H), 8.04 (ddd, J_1 = 1.4 Hz, J_2 = 6.9 Hz, J_3 = 8.4 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.57 (d, J = 8.6 Hz, 1H), 9.97 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 129.1, 129.9, 131.3, 135.8, 141.2, 148.5, 153.9; UV−vis (CH_2Cl_2), λ_{max}(log ε) 303 (3.57), 333 (2.89), 443 (2.54) nm; mass spectrometry (MS) (atmospheric pressure chemical ionization (CI)-time-of-flight (TOF)) *m*/*z* 132 (100, $[M]^+$); high-resolution mass spectrometry (HRMS) (electrospray ionization (ESI)-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_7H_6N_3$ 132.0562, found 132.0565. Anal. Calcd for $C_7H_5N_3$: C, 64.11; H, 3.84; N, 32.04. Found: C, 63.95; H, 3.92; N, 32.05.

3-Aminobenzo[*e*][1,2,4]triazine (1b).[10] *Method A.* A mixture of 3-aminobenzo[*e*][1,2,4]triazine-1-oxide (**2b**, 1.00 g, 6.17 mmol) and 10% Pd/C (0.130 g, 1.23 mmol) in EtOH/AcOEt (1:1, 100 mL) was stirred overnight at rt in the atmosphere of H_2 (balloon). When the thin-layer chromatography (TLC) showed absence of the starting

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material, the mixture was filtered through Celite and the solvent was evaporated giving 0.892 g (99% yield; 95−99% in several runs) of amine **1b** as a yellow solid.

Method B. Following a literature procedure,[10] a solution of 3-aminobenzo[*e*][1,2,4]triazine-1-oxide (**2b**, 2.00 g, 12.3 mmol) and sodium dithionite (3.21 g, 18.5 mmol) in 70% aqueous ethanol was heated at reflux (oil bath) for 10 min. The hot suspension was filtered, the filtrate was concentrated, then diluted with water (15 mL), and extracted with chloroform (4 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated giving 1.13 g (63% yield; 33−63% in several runs) of amine **1b** as a yellow solid: mp ($CHCl_3$) 204−206 °C (lit.[10] mp (MeOH/$CHCl_3$) 200−203 °C); ^{1}H NMR (DMSO-d_6, 600 MHz) δ 7.45 (ddd, J_1 = 0.8 Hz, J_2 = 6.8 Hz, J_3 = 8.0 Hz, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.58 (bs, 2H), 7.78 (ddd, J_1 = 1.1 Hz, J_2 = 6.9 Hz, J_3 = 8.2 Hz, 1H), 8.19 (d, J = 8.3 Hz, 1H); ^{13}C{^{1}H} NMR (DMSO-d_6, 150 MHz) δ 124.7, 125.8, 129.2, 135.6, 141.9, 142.1, 160.5; UV−vis (CH_2Cl_2), λ_{max}(log ε) 298 (3.55), 384 (3.58) nm; electron ionization (EI)-MS, m/z 146 (56 [M]$^+$), 118 (100 [M]$^+$ − N_2). Anal. Calcd for $C_7H_6N_4$: C, 57.53; H, 4.14; N, 38.33. Found: C, 57.39; H, 4.23; N, 38.14.

3-Chlorobenzo[*e*][1,2,4]triazine (1c).[26] *Method A.* Following a general procedure,[59] 3-aminobenzo[*e*][1,2,4]-triazine (**1b**, 0.699 g, 4.79 mmol) was added to a mixture of $CuCl_2$·$2H_2O$ (0.980 g, 5.75 mmol) and *t*-BuONO (0.68 mL, 5.75 mmol) in MeCN (100 mL). The reaction mixture was stirred at 60 °C (oil bath) for 30 min, then poured into 10% aqueous HCl (10 mL), and extracted with AcOEt (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (SiO_2; hexane/AcOEt, 3:1) giving 0.401 g (51% yield; 48−52% in several runs) of chloride **1c**.

Method B. Following a literature procedure,[26] Zn powder (1.12 g) and NH_4Cl (0.84 g) were added to a suspension of 3-chlorobenzo-[*e*][1,2,4]triazine-1-oxide (**2c**, 2.80 g, 0.015 mol) in H_2O (70 mL). The reaction mixture was stirred at rt for 48 h, and then glacial acetic acid (70 mL) was added. The mixture was placed in a beaker and Na_2CO_3 was added in small portions until the evolution of CO_2 was ceased. The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated giving 1.00 g (39% yield) of chloride **1c** as a yellow solid: mp (hexane) 99−100 °C (lit.[26] mp (pentane) 96−98 °C); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.92 (ddd, J_1 = 1.0 Hz, J_2 = 6.8 Hz, J_3 = 8.2 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 8.05 (ddd, J_1 = 0.8 Hz, J_2 = 6.8 Hz, J_3 = 8.3 Hz, 1H), 8.55 (d, J = 8.4 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 128.1, 129.8, 131.4, 137.2, 142.1, 146.4, 159.6; IR ν 1560, 1495, 1039, 769 cm^{-1}; UV−vis (CH_2Cl_2), λ_{max}(log ε) 305 (3.55), 339 (3.41), 427 (2.44) nm; EI-MS, m/z 167 and 165 (15 [M]$^+$), 139 and 137 (100 [M]$^+$ − N_2). Anal. Calcd for $C_7H_4N_3Cl$: C, 50.78; H, 2.43; N, 25.38. Found: C, 50.68; H, 2.46; N, 25.46.

3-Iodobenzo[*e*][1,2,4]triazine (1d). Following a literature procedure for the preparation of **2d**,[51] *t*-BuONO (2.1 mL, 17.6 mmol) was added to a stirred solution of 3-aminobenzo[*e*][1,2,4]-triazine (**1b**, 0.859 g, 5.88 mmol), I_2 (1.49 g, 5.88 mmol), and CuI (1.12 g, 5.88 mmol) in THF (100 mL). The resulting mixture was stirred at reflux (oil bath) for 2 h. The mixture was cooled, filtered through a short plug of alumina, and washed with THF (100 mL). The filtrate was evaporated. The residue was dissolved in CH_2Cl_2; washed with Na_2SO_3 solution, water, and brine; dried (Na_2SO_4); and the solvent was evaporated. The residue was purified by column chromatography (SiO_2; hexane/AcOEt, 20:1) giving 0.931 g (62% yield; 59−65% in several runs) of iodide **1d** as a yellow solid: mp (MeCN) 184−185 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.93 (ddd, J = 1.7, 6.3, 8.3 Hz, 1H), 8.00−8.03 (m, 2H), 8.51 (d, J = 8.9 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 128.2, 130.0, 130.1, 131.6, 136.8, 142.6, 146.5; CI-MS (isobutane) m/z 258 (100 [M]$^+$), 229 (20 [M]$^+$ − N_2). Anal. Calcd for $C_7H_4N_3I$: C, 32.71; H, 1.57; N, 16.35. Found: C, 32.65; H, 1.63; N, 16.22.

Benzo[*e*][1,2,4]triazine-3-carboxylic Acid (1f).[61,84] *Method A.* A solution of ethyl ester **1h** (0.90 g, 4.43 mmol) in THF/H_2O (9:1, 50 mL) was treated with 0.1 N KOH in EtOH (1.5 equiv, 66.4 mmol). The reaction mixture was stirred for 10 min at rt and poured into 10% HCl (20 mL). The resulting mixture was extracted with AcOEt, and the organic layer was washed with H_2O and dried (Na_2SO_4). The solvent was removed giving 0.773 g (99% yield) of carboxylic acid **1f** as an orange solid.

Method B. A mixture of benzo[*e*][1,2,4]triazine-3-carboxamide (**1v**, 0.055 g, 0.31 mmol), 20% HCl (1 mL), CH_3COOH (1 mL), and $NaNO_2$ (0.043 mg, 0.62 mmol) was stirred at rt overnight. The resulting mixture was poured into water, and the product was extracted with AcOEt (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated giving 54.7 mg (98% yield) of acid **1f** as an orange solid: mp (MeCN) 192−194 °C (lit.[84] mp 215−216 °C); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.14 (ddd, J_1 = 2.2 Hz, J_2 = 5.9 Hz, J_3 = 8.4 Hz, 1H), 8.22−8.26 (m, 1H), 8.68 (d, J = 8.4 Hz, 1H); ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz) δ 129.1, 129.3, 133.5, 137.2, 139.9, 147.2, 152.9, 164.2; IR ν 3443 (OH) and 1731 (CO) cm^{-1}; EI-MS m/z 175 (10 [M]$^+$), 147 (50 [M]$^+$ − N_2). Anal. Calcd for $C_8H_5N_3O_2$: C, 54.86; H, 2.88; N, 23.99. Found: C, 54.82; H, 3.01; N, 23.73.

3-(Trifluoromethyl)benzo[*e*][1,2,4]triazine (1g). Following a general procedure,[32] to a solution of amidrazone **5**[32] (4.35 g, 17.9 mmol) in CH_2Cl_2 (45 mL) was added dropwise a solution of *t*-BuOCl (4.25 g, 39.2 mmol) in CH_2Cl_2 (24 mL) at −70 °C. The resulting orange mixture was stirred at rt for 4 h. Then, aq solution of $Na_2S_2O_4$ (100 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 30 mL). Combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash chromatography (SiO_2; petroleum ether/AcOEt, 8:2) giving 1.30 g (37% yield) of the trifluoromethyl derivative **1g** as an orange solid: mp (petroleum ether/AcOEt) 82−84 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.10 (t, J = 7.9 Hz, 1H), 8.18 (t, J = 8.0 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.68 (d, J = 8.5 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 120.2 (q, J_{HF}^1 = 276 Hz), 129.5, 129.9, 133.5, 137.4, 140.1, 148.5, 152.7 (q, J_{HF}^2 = 37 Hz); UV−vis (CH_2Cl_2), λ_{max}(log ε) 309 (3.50), 433 (2.52) nm. Anal. Calcd for $C_8H_4N_3O_2$: C, 48.25; H, 2.02; N, 21.10. Found: C, 48.31; H, 2.13; N, 21.21.

Attempted Preparation of 3-(Trifluoromethyl)-benzo[*e*]-[1,2,4]triazine (1g). *3-Methoxy-benzo[e][1,2,4]triazine (1v).* Following a general procedure,[76] to a dried flask charged with CuI (0.024 g, 0.128 mmol), 1,10-phenanthroline (0.023 g, 0,128 mmol), and $CF_3B(OMe)_3$ (1.69 g, 9.57 mmol) was added anhydrous, deoxygenated DMSO (4 mL). Then, 3-iodobenzo[*e*][1,2,4]triazine (**1d**, 0.164 g, 0.638 mmol) was added directly to the flask and the resulting mixture was stirred at 60 °C (oil bath) for 48 h until TLC showed absence of the starting **1d**. After cooling, the solution was diluted with AcOEt (20 mL) and washed with 1 N HCl (10 mL) and water (10 mL). The washing was reextracted with AcOEt (2 × 10 mL), combined organic layers were dried (Na_2SO_4), and solvent was evaporated. The residue was separated by column chromatography (SiO_2; petroleum ether/AcOEt, 9:1) giving 0.052 g (51% yield) of 3-methoxybenzo[*e*][1,2,4]-triazine (**1v**) as a yellow solid: mp (MeCN) 102−104 °C (lit.[49] mp (hexane) 104−105 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.24 (s, 1H), 7.68 (ddd, J_1 = 1.4 Hz, J_2 = 6.7 Hz, J_3 = 8.3 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.90 (ddd, J_1 = 1.3 Hz, J_2 = 6.7 Hz, J_3 = 8.1 Hz, 1H), 8.47 (d, J = 8.4 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 55.5, 127.4, 127.9, 129.9, 136.2, 141.9, 144.9, 162.9. Anal. Calcd for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.64; H, 4.42; N, 26.14.

Attempted Preparation of 3-(Trifluoromethyl)-benzo[*e*]-[1,2,4]triazine (1g). *3,3-Bis(trifluoromethyl)-3,4-dihydrobenzo[e]-[1,2,4]triazine (7).* Following a general literature procedure,[74] to a mixture of CsF (0.083 g, 0.545 mmol), CuI (5.2 mg, 0.027 mmol), 1,10-phenanthroline (4.9 mg, 0.028 mmol), and iodide **1d** (0.071 g, 0.272 mmol) in dry DMF at 60 °C (oil bath) was added $TMSCF_3$ (0.08 mL, 0.545 mmol). The reaction mixture was stirred at 60 °C for 1 h, then quenched with H_2O, and extracted with AcOEt (3 × 20 mL). Combined organic layers were dried (Na_2SO_4) and solvent was evaporated. The residue was separated by column chromatography (SiO_2; petroleum ether/AcOEt, 10:1) giving 0.021 g (29% yield) of **7** as a yellow solid: mp (MeOH) 80−82 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.70 (s, 1H), 6.67 (dd, J_1 = 0.7 Hz, J_2 = 8.1 Hz, 1H), 6.99 (td,

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J_1 = 1.1 Hz, J_2 = 7.8 Hz, 1H), 7.38 (td, J_1 = 1.5 Hz, J_2 = 8.0 Hz, 1H), 7.92 (d, J = 7.9 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 75.7 (sept, J_{HF}^2 = 32 Hz), 114.0, 121.1 (q, J_{HF}^1 = 289 Hz), 121.2, 127.1, 131.9, 132.7, 136.5; ^{19}F NMR ($CDCl_3$, 188 MHz) δ −77.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_9H_6N_3F_6$ 270.0466, found 270.0474.

Ethyl Benzo[*e*][1,2,4]triazine-3-carboxylate (1h).[61] Following a general literature procedure,[35] to a stirred mixture of iron (7.80 g, 139.4 mmol), H_2O (43 mL), and conc. HCl (36.8 mL) was added dropwise a solution of amidrazone **4** (8.84 g, 36.9 mmol) in a mixture of CH_3COOH (178 mL) and conc. HCl (18.5 mL). The resulting mixture was stirred overnight at rt. The reaction mixture was portioned between ethyl acetate (100 mL) and H_2O (100 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic extract was washed with brine and dried ($MgSO_4$). After evaporation of solvent, the residue was purified by flash chromatography (SiO_2; petroleum ether/ethyl acetate, 1:1) giving 2.06 g (29% yield) of ester **1h** as a yellow solid: mp 77−79 °C (ref[61] mp (EtOH) 93 °C); ^1H NMR ($CDCl_3$, 600 MHz) δ 1.52 (t, J = 7.1 Hz, 3H), 4.66 (q, J = 7.1 Hz, 2H), 8.02 (t, J = 8.2 Hz, 1H), 8.09 (ddd, J_1 = 1.2 Hz, J_2 = 7.0 Hz, J_3 = 8.2 Hz, 1H), 8.26 (d, J = 8.5 Hz, 1H), 8.64 (d, J = 8.5 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ 14.4, 63.4, 129.8, 129.9, 133.0, 136.6, 140.5, 148.0, 152.6, 163.1; IR ν 1737 (CO), 1252, 1066, 785 cm^{-1}. Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.31; H, 4.45; N, 20.82.

Benzo[*e*][1,2,4]triazine-3-carbonitrile (1i). To a solution of 3-chlorobenzo[*e*][1,2,4]triazine (**1c**, 0.050 g, 0.321 mmol) in dry MeCN (2 mL) was added $[Et_4N]^+CN^-$ (0.052 g, 0.333 mmol). The resulting mixture was stirred at rt for 20 min and solvent was evaporated. The residue was purified by column chromatography (SiO_2; hexane/AcOEt, 20:1) giving 0.049 g (98% yield; 95−98% in several runs) of nitrile **1i** as a yellow solid: mp (*n*-heptane) 96−97 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.12−8.15 (m, 1H), 8.20−8.21 (m, 2H), 8.68 (d, J = 8.5 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 115.2, 129.2, 130.1, 134.3, 137.8, 140.1, 142.4, 147.3; UV−vis (CH_2Cl_2), λ_{max}(log ε) 249 (4.26), 320 (3.17), 431 (2.27) nm. Anal. Calcd for $C_8H_4N_4$: C, 61.54; H, 2.58; N, 35.88. Found: C, 61.52; H, 2.51; N, 35.69.

Diethyl 2-(Benzo[*e*][1,2,4]triazin-3-yl)malonate (1j). Following a similar procedure,[65] to the stirred solution of NaH (0.045 g, 1.2 mmol) in dry DMF (0.5 mL) under nitrogen atmosphere at 0 °C was added dropwise a solution of diethyl malonate (0.17 mL, 1.2 mmol) in dry DMF (1 mL). The resulting mixture was stirred at rt for 2 h, followed by addition of 3-chlorobenzo[*e*][1,2,4]triazine (**1c**, 0.093 g, 0.56 mmol) in DMF (1 mL). The reaction mixture was stirred at 100 °C (oil bath) for 1 h until TLC showed absence of the starting **1c**. The reaction mixture was cooled, quenched with sat. ammonium chloride solution, and then extracted with AcOEt (3 × 5 mL). The combined organic layers were washed with water and brine and dried (Na_2SO_4). After evaporation of the solvent, the crude product was purified by column chromatography (SiO_2; petroleum ether/AcOEt, 6:1) giving 0.160 g (99% yield) of malonate **1j** as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.30 (t, J = 7.2 Hz, 3H), 4.33 (q, J = 7.2 Hz, 2H), 5.59 (s, 1H), 7.91 (ddd, J_1 = 1.2 Hz, J_2 = 6.8 Hz, J_3 = 8.3 Hz, 1H), 8.01 (ddd, J_1 = 1.3 Hz, J_2 = 6.8 Hz, J_3 = 8.3 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H), 8.56 (d, J = 8.5 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 14.1, 60.5, 62.5, 129.1, 129.7, 131.4, 136.1, 140.9, 146.6, 159.3, 166.3; IR ν 1737 (CO), 1216, 757 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{16}N_3O_4$ 290.1141, found 290.1152.

3-Phenylaminobenzo[*e*][1,2,4]triazine (1k).[24] *Method A.* To a solution of 3-chlorobenzo[*e*][1,2,4]triazine (**1c**, 0.050 g, 0.303 mmol) in absolute ethanol (1.5 mL), aniline (0.056 mL, 0.606 mmol) was added dropwise. The resulting mixture was stirred overnight at rt, then concentrated in vacuo. The residue was treated with water and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by recrystallization from *n*-heptane giving 0.057 g (85% yield) of amine **1k** as an orange solid.

Method B. According to a general method,[72] to a solution of 3-iodobenzo[*e*][1,2,4]triazine (**1d**, 0.200 g, 0.778 mmol), aniline (0.14 mL, 1.56 mmol), and CsF (0.237 g, 1.56 mmol) in DMSO (5 mL), CuI (0.015 g, 0.078 mmol) was added. The resulting mixture was stirred overnight at 60 °C (oil bath), diluted with AcOEt (20 mL), and washed with water. The organic layer was dried (Na_2SO_4), solvent was evaporated, and the crude product was purified by column chromatography (SiO_2; hexane/AcOEt, 9:1) giving 0.112 g (65% yield) of amine **1k** as an orange solid: mp (*n*-heptane) 198−200 °C (lit.[24] mp (EtOH) 197 °C); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.14 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.54 (ddd, J_1 = 1.5 Hz, J_2 = 6.6 Hz, J_3 = 8.2 Hz, 1H) 7.78 (d, J = 7.7 Hz, 1H), 7.82 (ddd, J_1 = 1.2 Hz, J_2 = 6.7 Hz, J_3 = 8.5 Hz, 1H), 7.92 (d, J = 8.7 Hz, 2H), 8.34 (d, J = 8.4 Hz, 1H), 8.47 (bs, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 119.2, 123.5, 126.3, 127.2 129.2, 130.0, 136.0, 138.8, 141.3; IR ν 3442, 3256 (NH), 1557 (C═N) cm^{-1}; EI-MS m/z 222 (40 $[M]^+$), 194 (100 $[M]^+-N_2$). Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.26; H, 4.54; N, 25.21. Found: C, 70.03; H, 4.81; N, 25.10.

3-(Morpholin-4-yl)benzo[*e*][1,2,4]triazine (1l).[48] To a solution of 3-chlorobenzo[*e*][1,2,4]triazine (**1c**, 0.100 g, 0.61 mmol) in absolute ethanol (3 mL), morpholine (0.1 mL, 1.2 mmol) was added dropwise. The resulting mixture was stirred for 2 h at rt, then concentrated in vacuo. The residue was treated with water and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by recrystallization from *n*-heptane giving 0.117 g (89% yield) of amine **1l** as a yellow solid: mp (*n*-heptane) 123−125 °C (lit.[48] mp 125 °C, cyclohexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.86 (t, J = 5.1 Hz, 4H), 4.09 (t, J = 4.4 Hz, 4H), 7.42 (ddd, J_1 = 1.1 Hz, J_2 = 6.8 Hz, J_3 = 8.1 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.71 (ddd, J_1 = 1.4 Hz, J_2 = 6.8 Hz, J_3 = 8.4 Hz, 1H), 8.24 (dd, J_1 = 0.8 Hz, J_2 = 8.4 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz,) δ 44.3 (2C), 67.0 (2C), 125.4, 126.7, 129.9, 135.7, 142.4, 142.8, 158.7; UV−vis (CH_2Cl_2), λ_{max}(log ε) 254 (4.31), 278 (3.72), 304 (3.22), 416 (3.28) nm; EI-MS m/z 216 (45 $[M]^+$), 188 (50 $[M]^+ - N_2$), 131 (100 $[M]^+ - C_4H_8NO$). Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 61.12; H, 5.67; N, 25.85.

3-Ethoxybenzo[*e*][1,2,4]triazine (1m).[45] A solution of NaOEt [prepared by dissolving Na (8.3 mg) in absolute ethanol (3.6 mL)] was added to a solution of 3-chlorobenzo[*e*][1,2,4]triazine (**1c**, 0.060 g, 0.4 mmol) in absolute ethanol (1.2 mL). The resulting mixture was refluxed (oil bath) for 0.5 h. The precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was neutralized with 3 N HCl and extracted with CH_2Cl_2. Combined organic layers were dried (Na_2SO_4), solvent was evaporated, and the resulting crude product was recrystallized (*n*-heptane) giving 0.060 g (95% yield) of ether **1m** as a yellow solid: mp (*n*-heptane) 83−85 °C (lit.[45] mp (benzene) 74−75 °C); ^1H NMR ($CDCl_3$, 500 MHz,) δ 1.55 (t, J = 7.1 Hz, 3H), 4.65 (q, J = 7.1 Hz, 2H), 7.65 (ddd, J_1 = 1.4 Hz, J_2 = 6.8 Hz, J_3 = 8.3 Hz, 1H), 7.82 (dd, J_1 = 1.1 Hz, J_2 = 8.5 Hz, 1H), 7.87 (ddd, J_1 = 1.4 Hz, J_2 = 6.7 Hz, J_3 = 8.5 Hz, 1H), 8.44 (d, J = 8.5 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 14.5, 64.4, 127.3, 127.7, 129.9, 136.1, 142.0, 144.8, 162.4; UV−vis (CH_2Cl_2), λ_{max}(log ε) 295 (3.62), 354 (3.47), 429 (2.55) nm; EI-MS m/z 175 (30 $[M]^+$), 147 (40 $[M]^+ - N_2$), 119 (110). Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.73; H, 5.22; N, 23.95.

Diethyl Benzo[*e*][1,2,4]triazin-3-ylphosphonate (1n). *Method A.* Following a general procedure,[47] a mixture of 3-chlorobenzo-[*e*][1,2,4]triazine (**1c**, 0.02 g, 0.121 mmol) and triethyl phosphite (0.07 mL, 0.42 mmol) was heated at 100 °C (oil bath) for 6 h until **1c** was no longer detected by TLC. The reaction mixture was separated by column chromatography (SiO_2; petroleum ether/AcOEt, 1:10) giving 6.4 mg (20% yield) of phosphonate **1n** as a yellow oil.

Method B. To a mixture of 3-iodobenzo[*e*][1,2,4]triazine (**1d**, 0.05 g, 0.195 mmol), CuI (3.8 mg, 0.0195 mmol), and Et_3N (0.001 mL, 0.0195 mmol) in toluene (1 mL) was added diethyl phosphite (0.031 mL, 0.234 mmol). The resulting mixture was stirred at 60 °C (oil bath) for 20 h. The solvent was evaporated, and the crude product was purified by column chromatography (SiO_2; petroleum ether/AcOEt, 1:10) giving 0.041 mg (79% yield) of phosphonate **1n** as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.44 (t, J = 7.1 Hz, 6H), 4.46−4.50 (m, 4H), 8.01 (ddd, J_1 = 0.9 Hz, J_2 = 7.0 Hz, J_3 = 8.1 Hz, 1H), 8.08 (ddd, J_1 = 1.4 Hz, J_2 = 6.9 Hz, J_3 = 8.3 Hz, 1H), 8.22 (d, J = 8.5 Hz, 1H), 8.59

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(d, J = 8.5 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 16.6 (d, J = 6.2 Hz, 2C), 64,5 (d, J = 5.8 Hz, 2C), 129.6, 129.8, 132.9, 136.5, 140.1 (d, J = 17.2 Hz), 147.5, 159.3 (d, J = 262 Hz); ^{31}P NMR ($CDCl_3$, 81 MHz) δ 4.79; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{11}H_{15}N_3O_3P$ 268.0851, found 268.0856.

3-(*tert*-Butylthio)benzo[*e*][1,2,4]triazine (1o). Following a general procedure,[85] to a suspension of NaH (0.029 g, 1.2 mmol) in dry DMF (2 mL), 2-methylpropane-2-thiol (0.054 g, 0.6 mmol) was added dropwise. The mixture was stirred for 30 min at rt, then 3-chlorobenzo[*e*][1,2,4]triazine (**1c**, 0.100 g, 0.6 mmol) was added, and the resulting mixture was stirred for 2 h at rt. The mixture was treated with water, and the residue was extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by recrystallization from *n*-heptane giving 0.126 mg (95% yield) of sulfide **1o** as a yellow solid: mp (*n*-heptane) 67−68 °C; ^1H NMR ($CDCl_3$, 500 MHz,) δ 1.73 (s, 9H), 7.70 (ddd, J_1 = 1.9 Hz, J_2 = 6.2 Hz, J_3 = 8.3 Hz, 1H), 7.84−7.90 (m, 2H), 8.39 (d, J = 8.3 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 30.1 (3C), 48.5, 127.7, 129.0, 129.9, 135.8, 140.9, 144.8, 170.8; EI-MS m/z 191 (25 $[M]^+ - N_2$), 135 (68), 57 (100). Anal. Calcd for $C_{11}H_{13}N_3S$: C, 60.25; H, 5.98; N, 19.16. Found: C, 60.31; H, 6.02; N, 19.19.

3-Phenylbenzo[*e*][1,2,4]triazine (1p).[34] To a solution of 3-iodobenzo[*e*][1,2,4]triazine (**1d**, 0.08 g, 0.31 mmol) in degassed toluene (2 mL) were added successively phenylboronic acid (0.091 g, 0.75 mmol), $Pd(OAc)_2$ (0.004 g, 0.016 mmol), K_2CO_3 (0.066 g, 0.62 mmol), and water (0.01 mL). The reaction mixture was refluxed (oil bath) overnight, and the progress of the reaction was controlled by TLC. When **1d** was no longer detected by TLC, the mixture was filtered through Celite and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2; hexane/AcOEt, 20:1) giving 0.053 g (82% yield) of 3-phenylbenzo[*e*][1,2,4]-triazine (**1p**) as a yellow solid: 122−123 °C (lit.[34] mp 120−124 °C); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.58−7.61 (m, 3H), 7.85 (ddd, J_1 = 1.3 Hz, J_2 = 6.9 Hz, J_3 = 8.3 Hz, 1H), 7.99 (ddd, J_1 = 1.4 Hz, J_2 = 6.8 Hz, J_3 = 8.3 Hz, 1H), 8.11 (dd, J_1 = 0.5 Hz, J_2 = 8.5 Hz, 1H), 8.55 (dd, J_1 = 0.7 Hz, J_2 = 8.5 Hz, 1H), 8.76−8.78 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 128.9, 129.1, 129.3, 129.7, 130.4, 131.6, 135.7, 135.8, 141.3, 146.6, 160.0; UV−vis (CH_2Cl_2), $\lambda_{max}(\log \varepsilon)$ 2.59 (4.47), 272 (4.44), 3.52 (3.65), 454 (2.52). Anal. Calcd for $C_{13}H_9N_3$: C, 75.35; H, 4.38; N, 20.28. Found: C, 75.14, H, 4.42; N, 20.25.

3-(Thiophen-2-yl)benzo[*e*][1,2,4]triazine (1r).[36] Following the procedure for preparation of **1p**, the thiophene derivative **1r** was obtained in 69% yield from 0.101 g of 3-iodobenzo[*e*][1,2,4]triazine (**1d**) as a yellow solid: mp (*n*-heptane) 133−135 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.25−7.26 (m, 1H), 7.62 (dd, J_1 = 1.2 Hz, J_2 = 5.0 Hz, 1H), 7.79 (ddd, J_1 = 1.2 Hz, J_2 = 6.8 Hz, J_3 = 8.2 Hz, 1H), 7.94 (ddd, J_1 = 1.4 Hz, J_2 = 6.8 Hz, J_3 = 8.4 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 8.36 (dd, J_1 = 1.1 Hz, J_2 = 3.7 Hz, 1H), 8.48 (dd, J_1 = 0.6 Hz, J_2 = 8.4 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 128.8 (2C), 129.9 (2C), 130.8, 131.5, 135.9, 140.9, 141.1, 146.2, 157.5; UV−vis (CH_2Cl_2), $\lambda_{max}(\log \varepsilon)$ 277 (4.26), 301 (4.33), 378 (3.73), 4.53 (2.56); EI-MS m/z 213 (10 $[M]^+$), 185 (100 $[M]^+ - N_2$). Anal. Calcd for $C_{11}H_7N_3S$: C, 61.95; H, 3.31; N, 19.70. Found: C, 61.74; H, 3.47; N, 19.52.

3-(Ferrocenyl)benzo[*e*][1,2,4]triazine (1s). To a solution of 3-iodobenzo[*e*][1,2,4]triazine (**1d**, 0.110 g, 0.428 mmol) in degassed toluene (3 mL) were added successively ferroceneboronic acid (0.148 g, 0.642 mmol), K_3PO_4 (0.272 g, 1.28 mmol), and $PdCl_2(dppf)$ (0.016 g, 0.0214 mmol). The reaction mixture was refluxed (oil bath) for 8 h, with an additional portion of ferroceneboronic acid (0.148 mmol, 0.642 mmol), and the reaction mixture was refluxed overnight. The mixture was filtered through Celite and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2; petroleum ether) giving 0.065 g of inseparable mixture of starting **1d** and product **1s**. The mixture was dissolved in degassed toluene (2 mL), and ferroceneboronic acid (0.074 g, 0.321 mmol), K_3PO_4 (0.136 g, 0.64 mmol), and $PdCl_2(dppf)$ (0.008 g, 0.0107 mmol) were added successively. The reaction mixture was refluxed (oil bath) overnight, filtered through Celite, and concentrated in vacuo. The residue was separated by column chromatography (SiO_2; petroleum ether) giving 0.036 g (27% yield) of 3-(ferrocenyl)benzo[*e*][1,2,4]triazine (**1s**) as a dark red solid: mp ($CHCl_3$) 177−179 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.10 (s, 5H), 4.64 (t, J = 1.8 Hz, 2H), 5.45 (t, J = 1.8 Hz, 2H), 7.75 (ddd, J_1 = 1.3 Hz, J_2 = 6.8 Hz, J_3 = 8.3 Hz, 1H), 7.89 (ddd, J_1 = 1.3 Hz, J_2 = 6.4 Hz, J_3 = 7.9 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 8.43 (dd, J_1 = 0.7 Hz, J_2 = 8.4 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 69.7 ($2C_{Cp}$), 70.1 ($5C_{Cp}$), 71.9 ($2C_{Cp}$), 79.8, 128.5, 129.1, 129.9, 135.4, 141.5, 145.5, 166.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{14}N_3Fe$ 316.0537, found 316.0543. Anal. Calcd for $C_{17}H_{13}N_3Fe$: C, 64.79; H, 4.16; N, 13.33. Found: C, 64.72; H, 4.11; N, 13.14.

3-(Phenylethynyl)benzo[*e*][1,2,4]triazine (1t). To a stirred solution of 3-iodobenzo[*e*][1,2,4]triazine (**1d**, 0.102 g, 0.4 mmol), in dry THF (3 mL) under a nitrogen atmosphere, $Pd(PPh_3)_4$ (9.2 mg, 2 mol %) was added. After 5 min, Et_3N (0.3 mL) and CuI (3.1 mg, 0.016 mmol) were added and the mixture was stirred for 5 min. Then, phenylacetylene (0.04 mL, 0.4 mmol) was added dropwise and the resulting mixture was stirred for additional 10 min. The solution was filtered through Celite and concentrated in vacuo. The crude product was purified by column chromatography (Al_2O_3; hexane/AcOEt, 20:1) giving 0.071 g (79% yield) of acetylene **1t** as a yellow solid: mp (*n*-heptane) 125−127 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.41−7.48 (m, 3H), 7.78 (dt, J_1 = 2.0 Hz, J_2 = 8.2 Hz, 2H), 7.91 (ddd, J_1 = 1.3 Hz, J_2 = 6.8 Hz, J_3 = 8.2 Hz, 1H), 8.02 (ddd, J_1 = 1.3 Hz, J_2 = 6.8 Hz, J_3 = 8.4 Hz, 1H), 8.08 (d, J = 8.1 Hz, 1H), 8.56 (d, J = 8.4 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 500 MHz) δ 86.9, 92.3, 121.1, 128.7 (2C), 129.9, 130.3, 131.4, 132.9, 136.3, 140.5, 145.5, 150.4; UV−vis (CH_2Cl_2), $\lambda_{max}(\log \varepsilon)$ 263 (4.40), 274 (4.42), 301 (4.38), 353 (3.86), 439 (2.66) nm. Anal. Calcd for $C_{15}H_9N_3$: C, 77.91; H, 3.92; N, 18.17. Found: C, 77.94; H, 4.05; N, 17.92.

3-Pentylbenzo[*e*][1,2,4]triazine (1u). A suspension of dry $ZnCl_2$ (0.092 g, 0.68 mmol) in dry THF (2 mL) at 0 °C was treated with a 2 M solution of pentylmagnesium bromide in diethyl ether (0.34 mL, 0.68 mmol). The reaction mixture was stirred at 0 °C for 15 min and then at rt for 20 min. PEPPSI-IPr (11.6 mg, 0.017 mmol) was added, and the reaction mixture was stirred for 10 min, followed by addition of iodide **2d** (50.0 mg, 0.17 mmol, obtained according to ref 51). The reaction mixture was stirred at 0 °C for 20 min, filtered through Celite, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2; hexane/AcOEt, 10:1) giving a mixture of **2u** and **1u** as a brown oil. The oil was dissolved in EtOH/AcOEt (1:1, 10 mL), Pd/C (11 mg, 10 mol %) was added, and the resulting mixture was stirred overnight at rt in the atmosphere of H_2 (balloon). The resulting yellow solution was filtered through Celite, and the solvent was evaporated giving 20.2 mg (58% yield) of product **1u** as a brown oil, which was short-path-distilled (85 °C/225 Torr): ^1H NMR ($CDCl_3$, 500 MHz,) δ 0.91 (t, J = 7.2 Hz, 3H), 1.38−1.46 (m, 4H), 2.01 (quint, J = 7.7 Hz, 2H), 3.39 (t, J = 7.8 Hz, 2H), 7.82 (ddd, J_1 = 1.3 Hz, J_2 = 6.8 Hz, J_3 = 8.3 Hz, 1H), 7.95 (ddd, J_1 = 1.3 Hz, J_2 = 6.7 Hz, J_3 = 8.1 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 8.50 (d, J = 8.5 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 14.1, 22.6, 28.8, 31.7, 37.9, 128.6, 129.7, 130.0, 135.5, 141.0, 146.3, 166.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{16}N_3$ 202.1344, found 202.1349.

Benzo[*e*][1,2,4]triazine-3-carboxamide (1w). *Method A.* To nitrile **1i** (0.050 g, 0.32 mmol) conc. HCl (1 mL) was added, and resulting mixture was stirred at rt for 72 h. The mixture was evaporated giving 55.8 mg (100% yield) of amide **1w** as a yellow solid.

Method B. To a suspension of acid **1f** (0.150 g, 0.857 mmol) in CH_2Cl_2 (3 mL) was added DMF (cat.) and oxalyl chloride (0.22 mL, 2.57 mmol). The reaction mixture was stirred at rt for 1 h, and the solvent was evaporated to remove volatiles. The solid residue was dissolved in CH_2Cl_2 (3 mL) and poured into conc. aq NH_4OH (10 mL). The precipitate was filtered giving 0.149 g (99% yield) of amide **1w**: mp (MeOH) 248−250 °C; ^1H NMR (DMSO-d_6, 500 MHz) δ 8.13−8.16 (m, 1H), 8.20 (bs, 1H), 8.24−8.26 (m, 2H), 8.65 (dd, J_1 = 1.9 Hz, J_2 = 8.4 Hz, 1H), 8.72 (bs, 1H); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 125 MHz) δ 129.2, 133.1, 137.2, 140.0, 147.2, 153.9, 163.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_8H_7N_4O$ 175.0620, found 175.0619. Anal. Calcd. for $C_8H_6N_4O$: C, 55.17; H, 3.47; N, 32.17. Found: C, 55.24; H, 3.59; N, 32.14.

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Attempted Preparation of Benzo[*e*][1,2,4]triazine-3-carboxamide (1w). *3-Hydroxybenzo[e][1,2,4]triazine (1e).* Nitrile **1i** (50 mg, 0.32 mmol) was stirred with NaOH (0.026 g, 0.65 mmol) in water (0.5 mL) at 55 °C (oil bath) for 2 h. Evaporation of the solvent gave a mixture of the expected amide **1w** and 3-hydroxy derivative **1e** in a ratio of 1:7 (based on ^{1}H NMR) as a yellow solid: ^{1}H NMR (DMSO-d_6, 500 MHz) major signals δ 7.01 (t, J = 7.3 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.42 (t, J = 7.4 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H); ^{13}C{^{1}H} NMR (DMDO-d_6, 125 MHz) major signals δ 119.8, 125.4, 128.8, 132.7, 139.2, 145.6, 165.7; IR ν 3059 (br) and 1577 (br) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_7H_6N_3O$ 148.0511, found 148.0515.

3-(*N*,*N*-Dibenzoylamino)benzo[*e*][1,2,4]triazine (1x). A solution of amine **1b** (0.079 g, 0.541 mmol) and Et_3N (0.11 mL, 0.812 mmol) in dry CH_2Cl_2 (3 mL) was treated with benzoyl chloride (0.10 mL, 0.812 mmol). The reaction mixture was stirred overnight at rt, diluted with CH_2Cl_2, and washed with H_2O. The organic layer was dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (SiO_2; hexane/AcOEt, 4:1) giving 0.090 g (75% yield) of amide **1x** as a yellow solid: mp (MeCN) 202−203 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (t, J = 7.5 Hz, 4H), 7.48 (t, J = 8.6 Hz, 2H), 7.82−7.85 (m, 5H), 7.91 (dd, J_1 = 0.7 Hz, J_2 = 8.5 Hz, 1H), 7.97 (ddd, J_1 = 1.3 Hz, J_2 = 6.6 Hz, J_3 = 8.4 Hz, 1H), 8.50 (d, J = 8.4 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 128.5, 128.9, 129.6, 129.7, 131.2, 133.2, 134.1, 136.6, 141.6, 145.5, 157.9, 172.5; IR ν 1699 (CO) cm^{-1}. Anal. Calcd for $C_{21}H_{14}N_4O_2$: C, 71.18; H, 3.98; N, 15.81. Found: C, 71.07; H, 3.95; N, 15.83.

Ethyl 2-(Benzo[*e*][1,2,4]triazin-3-yl)acetate (1y).[33] Following an analogous procedure,[65] to the stirred solution of malonate **1j** (0.116 g, 0.4 mmol) in DMSO (0.3 mL) was added a solution of NaCl (0.047 g, 0.8 mmol) in water (0.3 mL). The resulting mixture was heated overnight at 180 °C (oil bath). Then, the reaction was cooled to rt, quenched with water, and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with water and brine and dried (Na_2SO_4). After evaporation of solvent, the crude product was purified by column chromatography (SiO_2; petroleum ether/CH_2Cl_2, 7:3) giving 0.070 g (89% yield) of acetate **1y** as a dark yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.30 (t, J = 7.2 Hz, 6H), 4.33 (q, J = 7.2 Hz, 4H), 4.46 (s, 1H), 7.88 (ddd, J_1 = 1.4 Hz, J_2 = 6.8 Hz, J_3 = 8.3 Hz, 1H), 7.99 (ddd, J_1 = 1.4 Hz, J_2 = 6.8 Hz, J_3 = 8.2 Hz, 1H), 8.05 (dd, J_1 = 0.6 Hz, J_2 = 8.5 Hz, 1H), 8.54 (dd, J_1 = 0.5 Hz, J_2 = 8.4 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 14.3, 43.9, 61.7, 128.8, 129.7, 130.9, 135.9, 141.0, 146.5, 160.1, 169.4; IR ν 1737 (CO) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{11}H_{12}N_3O_2$ 218.0930, found 218.0933.

3-Aminobenzo[*e*][1,2,4]triazine-1-oxide (2b).[26] Following a literature procedure,[26] a mixture of 2-nitroaniline (20.0 g, 0.14 mol) and cyanamide (20.0 g, 0.47 mol) was melted at 100 °C (oil bath), cooled to rt, and conc. HCl (50 mL) was slowly added to the reaction (Caution: the reaction is strongly exothermic). The mixture was cooled to rt, and H_2O (50 mL) and NaOH (40 g) were carefully added. The mixture was stirred at 100 °C (oil bath) for 0.5 h, cooled to rt, and diluted with water (100 mL). The resulting yellow solid was filtered, washed with H_2O, and dried under vacuum to give 19.80 g (82% yield; 82−85% in several runs) of oxide **2b**: mp (EtOH) 277−278 °C (lit.[26] mp (EtOH) 284−287 °C); ^{1}H NMR (DMSO-d_6, 600 MHz) δ 7.30−7.33 (m, 3H), 7.52 (d, J = 8.4 Hz, 1H), 7.76 (t, J = 7.5 Hz, 1H), 8.12 (d, J = 8.5 Hz, 1H); ^{13}C{^{1}H} NMR (DMSO-d_6, 150 MHz) δ 119.8, 124.6, 125.8, 129.9, 135.6, 148.7, 160.2. Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.55. Found: C, 51.85; H, 3.79; N, 34.60.

3-Chlorobenzo[*e*][1,2,4]triazine-1-oxide (2c).[26] Following a literature procedure,[26] a solution of 3-hydroxybenzo[*e*][1,2,4]triazine-1-oxide (**2e**, 15.50 g) in $POCl_3$ (120 mL) was stirred at reflux (oil bath) for 2 h. The reaction was concentrated, poured onto ice, diluted with H_2O (150 mL), and then extracted with $CHCl_3$ (3 × 100 mL). The combined organic fraction was dried (Na_2SO_4) and the solvent was evaporated giving 9.80 g (57% yield) of chloride **2c**: mp (hexane/CH_2Cl_2) 116−117 °C (lit.[10] mp (CH_2Cl_2) 119−119.5 °C); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.76 (ddd, J = 2.0, 5.6, 8.4 Hz, 1H), 7.97−8.01 (m, 2H), 8.39 (d, J = 8.6 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 120.4, 128.6, 131.1, 133.9, 136.9, 147.4, 157.1. Anal. Calcd for $C_7H_4N_3OCl$: C, 46.30; H, 2.22; N, 23.14. Found: C, 46.30; H, 2.24; N, 23.38.

3-Hydroxybenzo[*e*][1,2,4]triazine-1-oxide (2e).[26] Following a literature procedure,[26] a solution of $NaNO_2$ (32.9 g) in H_2O (45 mL) was added dropwise for 1 h to a stirred solution of 3-aminobenzo[*e*][1,2,4]triazine-1-oxide (**2b**, 16.9 g, 0.1 mol) in H_2O (180 mL) and conc. H_2SO_4 (66 mL) at 0 °C. The reaction mixture was stirred at this temperature for 2 h and then overnight at rt. The precipitate was filtered, washed with H_2O, and dried under vacuum giving 16.10 (95% yield) of 3-hydroxy derivative **2e**: mp (MeOH) 239−240 °C dec. (lit[26] mp (MeOH) 241−244 °C); ^{1}H NMR (DMSO-d_6, 600 MHz) δ 7.32 (t, J = 7.4 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.80 (ddd, J = 1.0, 7.2, 8.2 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 12.53 (s, 1H); ^{13}C{^{1}H} NMR (DMSO-d_6, 150 MHz) δ 116.3, 120.9, 123.8, 129.3, 136.4, 136.6, 152.8. Anal. Calcd for $C_7H_5N_3O_2$: C, 51.54; H, 3.09; N, 25.76. Found: C, 51.55; H, 3.12; N, 25.76.

3-(Trifluoromethyl)benzo[*e*][1,2,4]triazine-1-oxide (2g). Following a general literature procedure,[74] to a mixture of 3-iodobenzo[*e*][1,2,4]triazine-1-oxide (**2d**, 0.199 g, 0.732 mmol, obtained according to ref 51), CuI (0.014 mg, 0.073 mmol), 1,10-phenanthroline (0.013 g, 0.073 mmol), and CsF (0.222 g, 1.46 mmol) in dry DMF (2 mL) at 60 °C (oil bath) was added the Ruppert reagent (0.22 mL, 1.46 mmol). The reaction mixture was stirred at this temperature for 1 h in the atmosphere of Ar, then cooled to rt, and quenched with H_2O. The mixture was extracted with EtOAc (3 × 20 mL). Combined organic layers were dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (SiO_2; petroleum ether/AcOEt, 10:1) giving 0.050 g (24% yield) of **8** as a yellow solid (first fraction) and 0.011 g (7% yield) of 3-(trifluoromethyl)benzo[*e*][1,2,4]-triazine-1-oxide (**2g**) as a yellow solid (second fraction): mp 63−65 °C (AcOEt); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92 (ddd, J_1 = 1.2 Hz, J_2 = 7.1 Hz, J_3 = 8.5 Hz, 1H), 8.10 (ddd, J_1 = 1.3 Hz, J_2 = 7.1 Hz, J_3 = 8.4 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.53 (dd, J_1 = 0.8 Hz, J_1 = 8.7 Hz 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 117.7 (q, J_{HF}^1 = 276 Hz), 120.5, 130.2, 133.1, 135.5, 137.0, 146.6, 153.2 (q, J_{HF}^2 = 38 Hz); ^{19}F NMR ($CDCl_3$, 188 MHz) δ −69.4; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_8H_5N_3OF_3$ 216.0385, found 216.0389.

3,3-Bis(trifluoromethyl)-3,4-dihydro-benzo[*e*][1,2,4]-triazine-1-oxide (8). mp 132−134 °C (MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.11 (s, 1H), 6.86 (dd, J_1 = 1.0 Hz, J_2 = 8.2 Hz, 1H), 6.96 (ddd, J_1 = 1.2 Hz, J_2 = 7.5 Hz, J_3 = 8.5 Hz, 1H), 7.46 (ddd, J_1 = 1.4 Hz, J_2 = 7.5 Hz, J_3 = 8.8 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 77.5 (sept, J_{HF}^2 = 31 Hz), 114.8, 120.9, 121.3 (q, J_{HF}^1 = 291 Hz), 122.6, 127.7, 136.1, 136.9; ^{19}F NMR ($CDCl_3$, 188 MHz) δ −77.9; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_9H_6N_3OF_6$ 286.0415, found 286.0412.

Ethyl [(2-Nitrophenyl)hydrazono](chloro)acetate (3).[61] Following a similar literature procedure,[35] to a stirred mixture of *ortho*-nitroaniline (8.0 g, 58 mmol) in MeOH (126 mL) was added conc. HCl (34 mL). The mixture was cooled in an ice−water bath and a solution of $NaNO_2$ (4.4 g, 63.6 mmol) in H_2O (24 mL) was added dropwise with stirring over 15 min. The suspension was filtered, and to the clear solution was added ethyl 2-chloroacetoacetate (8.8 mL, 63.7 mmol) at rt. The resulting mixture was stirred at rt for 1.5 h. The suspension was filtered, and the filtered yellow solid was washed with H_2O and dried at 50 °C to give 11.36 g (73% yield) of chloro ester **3** as a yellow solid: mp (MeOH) 121−122 °C: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.42 (t, J = 7.1 Hz, 3H), 4.41 (q, J = 7.1 Hz, 2H), 7.07 (t, J = 8.4 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H), 8.21 (dd, J_1 = 11 Hz, J_2 = 8.5 Hz, 1H), 11.35 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 14.3, 63.4, 117.3, 121.7, 122.0, 126.1, 133.7, 136.4, 139.0, 159.2. Anal. Calcd for $C_{10}H_{10}ClN_3O_4$: C, 44.21; H, 3.71; N, 15.47. Found: C, 44.16; H, 3.67; N, 15.45.

Ethyl[2-(2-nitrophenyl)hydrazine](imino)acetate (4).[61] Following a similar literature procedure,[35] a stirring solution of chloride **3** (10.0 g, 37.2 mmol) in dry THF (200 mL) was saturated with ammonia for 10 min. The mixture was stirred for 4 h and again saturated with ammonia for 20 min. The resulting solution was stirred overnight at rt under argon atmosphere. The reaction mixture was

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poured into H_2O (200 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), and solvent was evaporated giving 9.24 g (100% yield) of **4** as red crystals: mp (MeOH) 119−121 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.41 (t, J = 7.1 Hz, 3H), 4.39 (q, J = 7.1 Hz, 2H), 4.99 (bs, 1H), 6.84 (t, J = 8.2 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H), 8.13 (dd, J_1 = 1.0 Hz, J_2 =8.6 Hz, 1H), 10.07 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 14.3, 62.8, 116.9, 118.9, 125.9, 132.2, 136.4, 138.8, 142.4, 161.9. Anal. Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.79; N, 22.21. Found: C, 47.70; H, 4.79; N, 22.20.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00716.

Additional synthetic details, copies of NMR spectra, UV−vis data analysis, assignment of ^{1}H NMR chemical shifts and correlation analysis with Hammett constants, XRD data collection details, computation details, results and analysis for geometrical parameters, NMR chemical shifts, and electronic absorption spectra for selected derivatives **1**, archive for DFT calculation output files (PDF)

Crystallographic data (CIF)(CIF)(CIF)(CIF)(CIF)-(CIF)

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The manuscript was written through contributions of all authors, and all authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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