

Palladium-Catalyzed *ortho*-Monoacylation of Arenes with Aldehydes via 1,2,4-Benzotriazine-Directed C–H Bond Activation

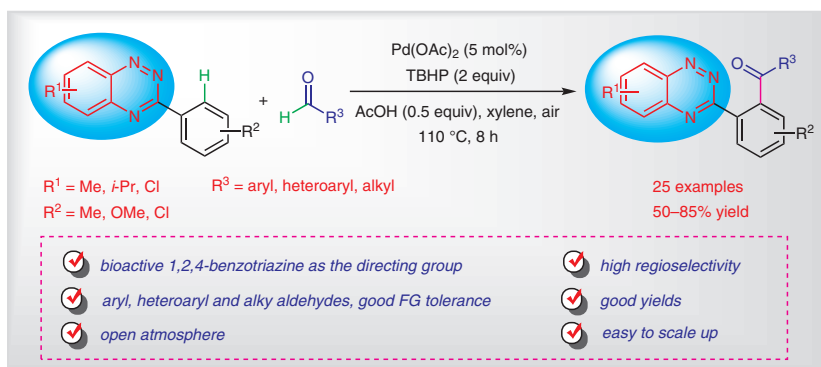
Jin Liu^{a,d}Shaofen Jin^cYingxing Zhou^aDongmei Ni^aTingting Liu^aBingcun Cui^{*a}Gang Hu^aXin Yu^aGuosheng Huang^{*b}

^a Hubei Key Laboratory of Kidney Disease Pathogenesis and Intervention, School of Medicine, Hubei Polytechnic University, Huangshi 435003, P. R. of China
cbc_hbpu@163.com

^b State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P. R. of China
hgs2368@163.com

^c Graduate School, Hubei Normal University, Huangshi 435003, P. R. of China

^d Huangshi Shi Xing Pharmaceutical Co., Ltd., Huangshi 435003, P. R. of China



Received: 30.11.2019

Accepted after revision: 17.12.2019

Published online: 10.02.2020

DOI: 10.1055/s-0039-1691564; Art ID: ss-2019-h0453-op

Abstract An efficient palladium-catalyzed C–H bond functionalization/*ortho*-monoacylation reaction of 3-aryl-1,2,4-benzotriazines with (hetero)aryl or alkyl aldehydes has been developed, which offers a facile and alternative strategy for direct modification and further diversification of 3-aryl-1,2,4-benzotriazines. Bioactive 1,2,4-benzotriazine has been employed as a novel directing group for the palladium-catalyzed regioselective monoacylation of sp^2 C–H bond protocol with broad substrate scope and good functional group tolerance.

Key words palladium-catalyzed, acylation, aldehydes, 1,2,4-benzotriazine, C–H activation

The 1,2,4-benzotriazine and its derivatives are an important class of heterocyclic compounds that display a wide range of biological activities, such as antimalarial,¹ antitumor,² protein kinase modulatory,³ antimicrobial,⁴ antiviral,⁵ and herbicidal.⁶ For instance, 1,2,4-benzotriazine 1,4-dioxides (BTOs) are influential antitumor drug candidates.⁷ In addition, 3-amino-1,2,4-benzotriazine 1,4-dioxide (tirapazamine, TPZ) can act as an excellent bioactive hypoxia-selective anticancer drug.⁸ Because of such broad bioactivities of 1,2,4-benzotriazine derivatives, the synthesis, modification, and development of promising drug leads based on this kind of templates have been a topic of interest to medicinal chemists and organic synthetic chemists in recent years.^{2,9}

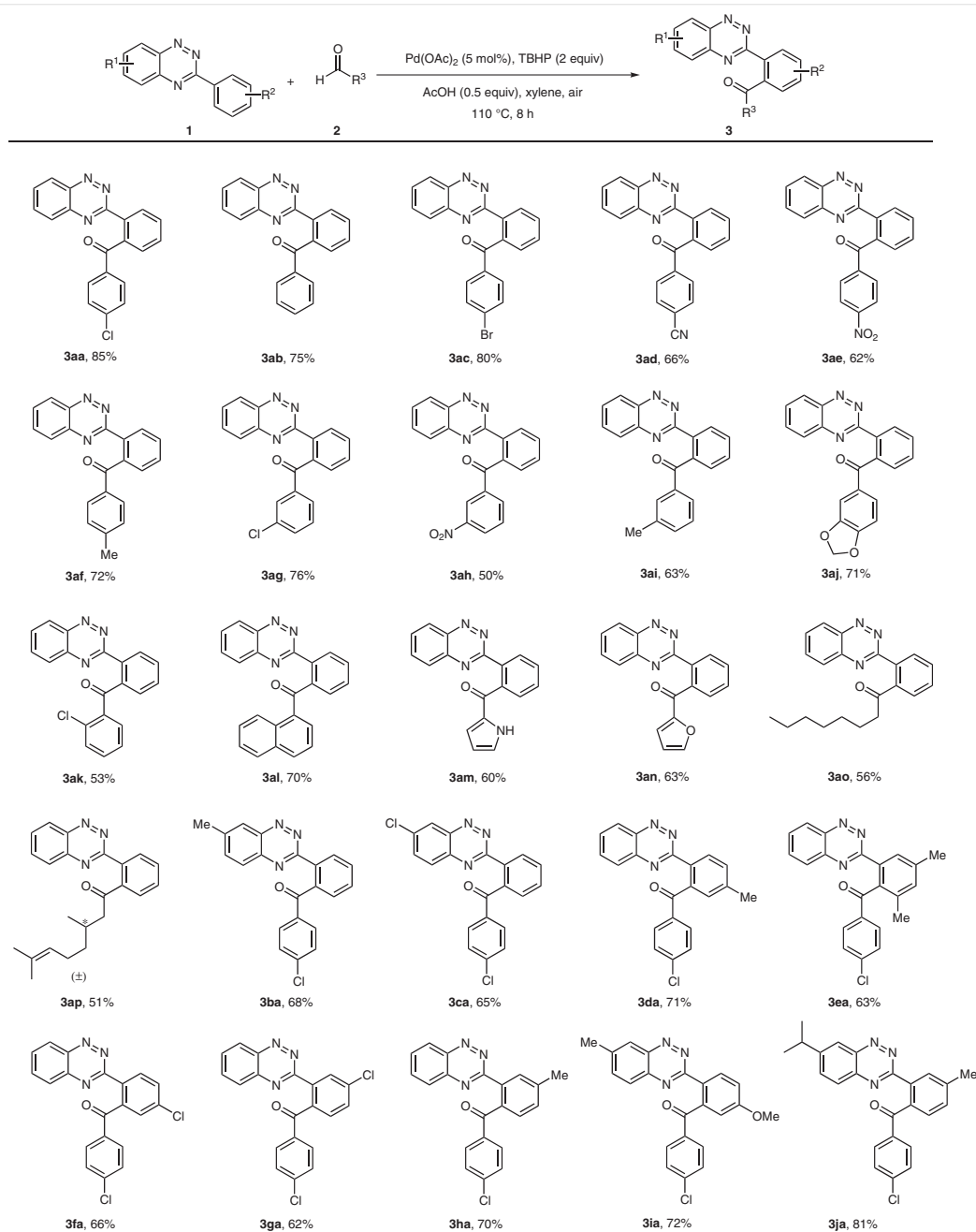
Direct functionalization of C–H bonds has undeniably become a prominent field in contemporary organic chemistry, and has emerged as an increasingly powerful and reli-

able tool in organic synthesis over the past two decades.¹⁰ In this area of research, transition-metal-catalyzed directing groups-assisted strategy is one of the most efficient methods to facilitate the regioselective cleavage of C–H bond and its further transformation.¹¹ In view of the efficiency of C–H bond activation/functionalization and the importance of diaryl ketones in organic synthesis and biological activity,¹² an attracted extensive attention has been observed in *ortho*-acylation of the aromatic C–H bonds catalyzed by several transition metals and assisted by various heteroatom directing groups.¹³ Since Cheng's group pioneered in developing a Pd-catalyzed oxidative coupling of 2-arylpiperidines with benzaldehydes to give aryl ketones in the presence of dioxygen as oxidant in 2009,¹⁴ much progress on the direct sp^2 C–H bond oxidative acylation has been achieved over the past few years.^{13,15} A wide range of structures that contain heteroatoms, such as pyridine,¹⁶ azo group,¹⁷ acyloxy/acyl,¹⁸ oxazolyl,¹⁹ acetamino,²⁰ oxime,²¹ cyano,²² and others,²³ have been extensively employed as directing groups for *ortho*-C–H bond activation/acylation. However, to the best of our knowledge, there is still no report of the transition-metal-catalyzed C–H bond functionalizations directed by 1,2,4-benzotriazine except the only one example about palladium-catalyzed C–O bond formation reaction demonstrated by us in 2013.²⁴ Compared with simple pyridine and quinoline rings, 1,2,4-benzotriazine is considered to be more challenging as a directing group in transition-metal-catalyzed C–H functionalizations. 1,2,4-Benzotriazine possesses two additional nitrogen atoms, which both have a lone pair electrons that can coordinate to

the transition-metal catalyst via a five or six-membered metallacycle.²⁵ Most importantly, this directing group is a useful building block for the potentially bioactive 1,2,4-benzotriazine derivatives and it offers a facile and promising strategy for direct functionalization of 3-aryl-1,2,4-benzotriazines as well as their further diversification.

In the light of the above and as a part of our ongoing interest in developing synthetic methods of bioactive heterocycles,^{24,26} we disclose herein the palladium-catalyzed regio-

selective *ortho*-monoacylation of 3-aryl-1,2,4-benzotriazines via the direct sp^2 C–H bond oxidative coupling reactions with aryl and alkyl aldehydes in the presence of *tert*-butyl hydroperoxide (TBHP) and air, affording various 1,2,4-benzotriazine derivatives bearing aryl ketones in moderate to good yields (Scheme 1).

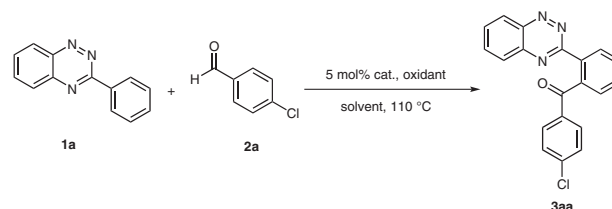


Scheme 1 Substrate scope of 3-aryl-1,2,4-benzotriazines **1** and aldehydes **2**. Reagents and conditions: **1** (0.15 mmol), **2** (0.45 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol%), TBHP (2 equiv), AcOH (0.5 equiv), and anhyd xylene (1 mL) with stirring at 110 °C under air atmosphere for 8 h. Isolated yields are given.

Initially, 3-phenyl-1,2,4-benzotriazine (**1a**) and 4-chlorobenzaldehyde (**2a**) were chosen as model substrates for surveying the reaction conditions (Table 1). The impact of the catalyst, oxidant, and solvent was investigated in detail for the reaction (Table 1). When we performed the oxidative coupling reaction of **1a** and **2a** with PdCl₂ and TBHP at 110 °C in xylene, **3aa** was isolated with 46% yield after 16 hours (Table 1, entry 1). In order to improve the yield, other Pd^{II} catalysts such as PdCl₂(PPh₃)₂ and Pd(OAc)₂ instead of PdCl₂ were applied to the reaction, and Pd(OAc)₂ promoted the reaction in 68% yield of the desired product (entries 2 and 8). However, other screened metal catalysts such as Pd⁰ [Pd(dba)₂, Pd₂(dba)₃ and Pd/C], FeCl₃, and NiCl₂(PPh₃)₂ all gave unsatisfactory results (entries 3–7). Furthermore, a better yield of the desired product **3aa** (77%) was obtained with the use of 0.5 equivalent of AcOH as additive (entry 9).^{15a} And to our delight, the yield of **3aa** could be further improved from 77% to 86% when the reaction was carried out exposed to air under the previous conditions (entries 9, 10). Additionally, when we shortened the reaction time from 16 hours to 8 hours under the same reaction conditions, the yield was almost unchanged (entries 10, 11). As far as we know, aldehydes are usually sensitive to some oxidants, so the choice of oxidants is also crucial for this oxidative coupling reaction. Accordingly, several other oxidants such as dioxygen, air, Oxone, Cu(OAc)₂, and BQ (benzoquinone) were screened, respectively, for the desired product **3aa**, but disappointingly, no better results were obtained compared with TBHP (entries 12–16). Then, different solvents such as toluene, DCE, DMF, acetonitrile, and 1,4-dioxane were also evaluated for the reaction, and those solvents had a profound negative impact on the reaction (entries 17–21). The phenomenon suggested that xylene was the best solvent of choice for the reaction. Finally, it should be pointed out that when 3 equivalents of **2a** were used, diacylated product was not detected. It is perhaps because of the electron-withdrawing effect and the steric hindrance of the benzoyl on the monoacylation product, which both reduce the reactivity of the secondary oxidative coupling. The steric effect of the benzoyl may hinder the arene from rotating for the second cyclopalladation with the N4 atom. In addition, in the investigation of 1 mmol scale-up of this model reaction, we found the main by-product of the reaction was 4-chlorobenzoic acid, which precipitated from the reaction mixture after the reaction was cooled to room temperature and 1.4 mmol of 4-chlorobenzoic acid was isolated by direct filtration (Scheme 2). In other words, there was only a little excessive amount of 4-chlorobenzaldehyde for the oxidative acylation and this may also give an explanation for the absence of the diacylated product in the reaction. Based on these investigating experiments, we established the optimized reaction conditions as 3-phenyl-1,2,4-benzotriazine (**1a**; 0.15 mmol), 4-chlorobenzaldehyde (**2a**; 0.45 mmol),

Pd(OAc)₂ (5 mol%), TBHP (2 equiv), AcOH (0.5 equiv), and xylene (1 mL), with stirring at 110 °C under air atmosphere for 8 hours (entry 11).

Table 1 Optimization of the Reaction Conditions^a



Entry	Catalyst	Oxidant	Solvent	Yield (%) ^b
1	PdCl ₂	TBHP	xylene	46
2	PdCl ₂ (PPh ₃) ₂	TBHP	xylene	43
3	Pd(dba) ₂	TBHP	xylene	<10
4	Pd ₂ (dba) ₃	TBHP	xylene	<10
5	Pd/C	TBHP	xylene	n.d.
6	FeCl ₃	TBHP	xylene	n.d.
7	NiCl ₂ (PPh ₃) ₂	TBHP	xylene	n.d.
8	Pd(OAc) ₂	TBHP	xylene	68
9 ^c	Pd(OAc) ₂	TBHP	xylene	77
10 ^d	Pd(OAc) ₂	TBHP	xylene	86
11 ^e	Pd(OAc)₂	TBHP	xylene	85
12	Pd(OAc) ₂	O ₂	xylene	56
13	Pd(OAc) ₂	air	xylene	38
14	Pd(OAc) ₂	Oxone	xylene	<10
15	Pd(OAc) ₂	Cu(OAc) ₂	xylene	<10
16	Pd(OAc) ₂	BQ	xylene	<10
17 ^e	Pd(OAc) ₂	TBHP	toluene	73
18 ^e	Pd(OAc) ₂	TBHP	DCE	55
19 ^e	Pd(OAc) ₂	TBHP	DMF	46
20 ^e	Pd(OAc) ₂	TBHP	MeCN	52
21 ^e	Pd(OAc) ₂	TBHP	1,4-dioxane	58

^a Reaction conditions: **1a** (0.15 mmol), **2a** (0.45 mmol), catalyst (5 mol%), oxidant (2 equiv), anhyd solvent (1 mL), 110 °C, 16 h, sealed reaction tube. BQ: Benzoquinone.

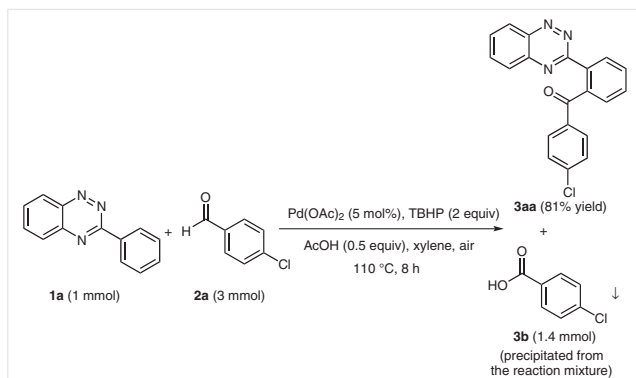
^b Isolated yield. n.d.: Not detected.

^c With the additive of 0.5 equiv AcOH to the solvent.

^d With the additive of 0.5 equiv AcOH to the solvent and the reaction was performed exposed to air.

^e With the additive of 0.5 equiv AcOH to the solvent; the reaction was performed exposed to air and ran for 8 h.

Encouraged by the optimization results, we then set out to explore the scope and generality of the reaction (Scheme 1). First, we tested a variety of aldehydes **2**, and the detailed results are summarized in Scheme 1. As can be seen from Scheme 1, a variety of benzaldehydes **2a–k** bearing either electron-withdrawing or electron-donating groups could react smoothly with 3-phenyl-1,2,4-benzotriazine (**1a**) under the optimized conditions, affording the corresponding



Scheme 2 Scale-up synthesis (1 mmol) of [2-(benzo[e][1,2,4]triazin-3-yl)phenyl](4-chlorophenyl)methanone (**3aa**) under the optimized conditions

desired products **3aa–ak** in moderate to good yields (50–85%). Subsequently, the target product **3al** was obtained in 70% yield when 1-naphthaldehyde (**2l**) was employed as a substrate for the reaction. In addition, the heteroaryl aldehydes such as pyrrole-2-aldehyde (**2m**) and furan-2-aldehyde (**2n**) could also be applied to afford the desired products. Notably, when the aliphatic aldehydes, for instance, *n*-caprylic aldehyde **2o** and citronellal (**2p**) were employed for this transformation, the corresponding products **3ao** and **3ap** were also formed in 56% and 51% yield, respectively.

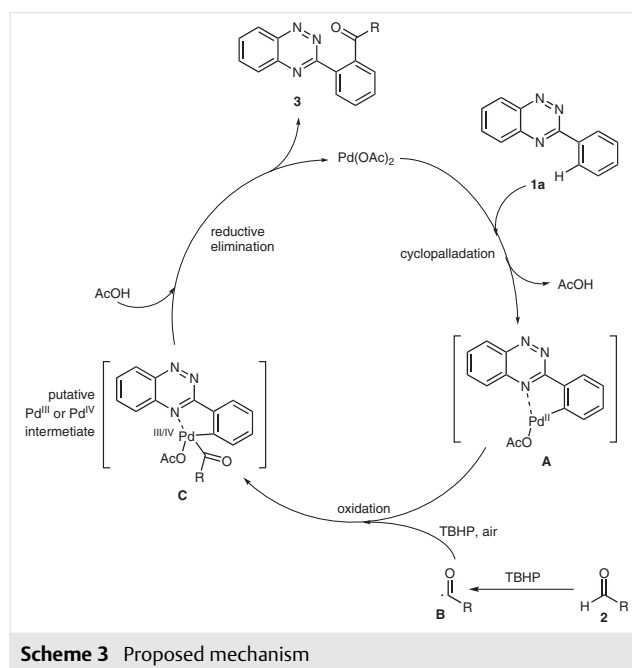
Aromatic aldehydes have been shown to be much more reactive than aliphatic aldehydes in the reaction. And it could be found that a majority of benzaldehydes with electron-withdrawing groups were superior to those with electron-donating groups. Particularly, the benzaldehydes, which have an electron-deficient substituent such as *para*-chloro and *para*-bromo are more reactive in the reaction (**3aa**, **3ac**). However, lower yield of the product **3** was obtained when these electron-deficient substituents were changed into the stronger ones such as nitro and cyano (**3ad**, **3ae**, **3ah**). Especially, the *meta*-nitro-substituted benzaldehyde **2h** gave the corresponding product **3ah** in only 50% yield. It should be emphasized that the chloro, bromo, cyano, and nitro groups could all be well tolerated in the reaction, which were favorable for further transformation.

Subsequently, the scope with respect to 3-aryl-1,2,4-benzotriazines **1** was surveyed under the optimized reaction conditions. Satisfactorily, a series of 3-aryl-1,2,4-benzotriazines **1** with either electron-donating or electron-withdrawing substituents could be transformed smoothly into the corresponding desired products **3ba–ja** in good yields (62–81%). We could observe obviously that electron-donating groups on the 3-aryl-1,2,4-benzotriazines considerably increased the yields of the corresponding products. However, the product **3ea**, which has two electron-donating groups on the benzene ring was obtained in a lower yield (63%), possibly because of the steric effect in this transfor-

mation process. It is also worth noting that the chloro group on the 3-aryl-1,2,4-benzotriazines was found to be well compatible under the reaction conditions (**3ca**, **3ga**).

The 1 mmol scale-up synthesis of [2-(benzo[e][1,2,4]triazin-3-yl)phenyl](4-chlorophenyl)methanone (**3aa**) demonstrated the robustness of the method (Scheme 2). A mixture of 3-phenyl-1,2,4-benzotriazine (**1a**; 1.0 mmol), 4-chlorobenzaldehyde (**2a**; 3.0 mmol), $\text{Pd}(\text{OAc})_2$ (0.05 mmol), and anhyd xylene (4 mL) was heated to 110°C , then a solution of TBHP (2 mmol) in xylene (6 mL) was added dropwise into the mixture. The reaction mixture was kept under stirring for 8 hours exposed to air. The corresponding product **3aa** was isolated in 81% yield (0.81 mmol, 0.28 g). The method proved to be efficient in obtaining the product of interest **3aa**, with nearly no decrease in yield on a 1 mmol scale. It should be pointed out that the main by-product 4-chlorobenzoic acid (**3b**) precipitated from the reaction mixture after the reaction was cooled to room temperature and a small amount of the common decarbonylation by-product was also observed from LC-MS in the 1 mmol scale-up of the acylation experiment.

On the basis of the experimental results and previous reports,^{14,15a,b,24,27} a plausible mechanism is proposed in Scheme 3. First, the active palladium catalyst could react with 1,2,4-benzotriazine (**1a**) to form a five-membered cyclopalladated intermediate **A** by chelation-directed C–H bond activation on the arene. The intermediate palladacycle **A** (Pd^{II}) could then react with the acyl radical **B**, generated in situ by hydrogen atom abstraction from the aldehyde **2**, to afford the key Pd^{IV} or dimeric Pd^{III} intermediate **C** through oxidation in the presence of TBHP and air.^{15b,27g} In the process, TBHP plays the roles of both radical initiator



Scheme 3 Proposed mechanism

and oxidant,^{15b,27c} while air assists the oxidation. Finally, the resulting Pd^{III} or Pd^{IV} intermediate **C** could undergo a subsequent reductive elimination to convert into the desired *ortho*-acylation product **3** along with the regeneration of the active palladium species to complete the catalytic cycle.

In summary, we have developed an efficient palladium-catalyzed *ortho*-acylation reaction of 3-aryl-1,2,4-benzotriazines via direct C–H bond activation with (hetero)aryl and alkyl aldehydes in the presence of TBHP and air. Multiple-nitrogen-containing 1,2,4-benzotriazine, which is a useful moiety for various potentially bioactive compounds, has been explored as a directing group for this C–H functionalization protocol. Additionally, it offers a facile and alternative access to various 1,2,4-benzotriazine derivatives bearing aryl ketones, which may be of importance in medicinal chemistry for drug discovery processes. The applications of 1,2,4-benzotriazine as a directing group for more fields of C–H activation and potential bioactivities screening of these diversified 1,2,4-benzotriazine derivatives are underway in our laboratory.

Melting points were determined using an XT-4 melting point apparatus and are uncorrected. ¹H NMR and ¹³C NMR spectra were determined in CDCl₃ on a Varian-Inova 400 MHz with TMS as an internal standard. IR spectra were obtained on Nicolet NEXUS 670 FT-IR instrument and only major peaks were reported in cm⁻¹. HRMS data were performed on Bruker Apex II mass instrument (ESI). Copies of their ¹H NMR and ¹³C NMR spectra are provided in the Supporting Information. Column chromatography was performed with 200–300 mesh silica gel using flash column techniques. Xylene was distilled over sodium. 3-Aryl-1,2,4-benzotriazines were prepared according to our reported literature methods^{26d} (see Supporting Information for details). Other materials were purchased from common commercial sources and used without additional purification.

Palladium-Catalyzed *ortho*-Monoacylation of 3-Aryl-1,2,4-Benzotriazines **1** with Aldehydes **2**; General Procedure

A 10 mL oven-dried reaction tube was charged with 3-aryl-1,2,4-benzotriazine **1** (0.15 mmol), aldehyde **2** (0.45 mmol), Pd(OAc)₂ (1.7 mg, 0.0075 mmol) and anhyd xylene (1 mL). Then the reaction tube was immersed in an oil bath at 110 °C. TBHP (60 µL, 0.3 mmol) was added dropwise with a syringe and the reaction was kept under stirring for 8 h exposed to the air. After the completion of the reaction monitored by TLC analysis, the solvent was evaporated under reduced pressure and the residue was directly purified by flash column chromatography on a silica gel, eluting with PE/EtOAc (v/v, 10:1) to afford the desired product **3** in moderate to good yield (50–85%).

[2-(Benzo[e][1,2,4]triazin-3-yl)phenyl](4-chlorophenyl)methanone (**3aa**)

Yellow solid; yield: 44.1 mg (85%); mp 105–107 °C.

IR (KBr): 3396, 2924, 1670, 1508, 1278, 1090, 929, 770 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.72 (d, *J* = 8.0 Hz, 1 H), 8.44 (d, *J* = 8.0 Hz, 1 H), 7.90 (t, *J* = 8.0 Hz, 1 H), 7.81 (d, *J* = 8.0 Hz, 2 H), 7.78–7.75 (m, 3 H), 7.69 (t, *J* = 8.0 Hz, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 7.26 (d, *J* = 8.0 Hz, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 196.3, 159.1, 145.7, 140.7, 140.1, 138.8, 136.4, 135.7, 134.7, 130.9, 130.7, 130.5, 130.4, 129.5, 128.8, 128.6, 128.5.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₀H₁₃ClN₃O: 346.0742; found: 346.0740.

[2-(Benzo[e][1,2,4]triazin-3-yl)phenyl](phenyl)methanone (**3ab**)

Yellow solid; yield: 35.0 mg (75%); mp 117–119 °C.

IR (KBr): 3320, 3063, 2247, 1668, 1509, 1278, 1016, 931, 770, 709 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.70 (d, *J* = 8.0 Hz, 1 H), 8.40 (d, *J* = 8.0 Hz, 1 H), 7.86 (t, *J* = 8.0 Hz, 1 H), 7.81–7.73 (m, 5 H), 7.69 (t, *J* = 8.0 Hz, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.35 (t, *J* = 8.0 Hz, 1 H), 7.28 (d, *J* = 8.0 Hz, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 197.5, 159.3, 145.6, 141.1, 140.0, 137.9, 135.5, 134.9, 132.4, 130.8, 130.6, 130.3, 130.2, 129.4, 129.2, 129.0, 128.6, 128.2.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₀H₁₄N₃O: 312.1132; found: 312.1129.

[2-(Benzo[e][1,2,4]triazin-3-yl)phenyl](4-bromophenyl)methanone (**3ac**)

Yellow solid; yield: 46.8 mg (80%); mp 56–58 °C.

IR (KBr): 3325, 3064, 2247, 1671, 1509, 1279, 1014, 928, 771 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.71 (d, *J* = 8.0 Hz, 1 H), 8.41 (d, *J* = 8.0 Hz, 1 H), 7.88 (t, *J* = 8.0 Hz, 1 H), 7.80–7.73 (m, 3 H), 7.70–7.66 (m, 3 H), 7.57 (d, *J* = 8.0 Hz, 1 H), 7.42 (d, *J* = 8.0 Hz, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 196.3, 159.0, 145.7, 140.5, 140.0, 136.8, 135.7, 134.6, 131.5, 130.9, 130.7, 130.6, 130.4, 129.4, 128.7, 128.4, 127.5.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₀H₁₃BrN₃O: 390.0237; found: 390.0235.

4-[2-(Benzo[e][1,2,4]triazin-3-yl)benzoyl]benzonitrile (**3ad**)

Yellow solid; yield: 33.3 mg (66%); mp 188–190 °C.

IR (KBr): 3336, 3066, 2230, 1676, 1509, 1273, 1018, 932, 772 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.76 (dd, *J* = 8.0, 0.8 Hz, 1 H), 8.43 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.94–7.89 (m, 3 H), 7.84–7.78 (m, 3 H), 7.73 (tt, *J* = 8.0, 1.2 Hz, 1 H), 7.61–7.57 (m, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 195.7, 158.6, 145.8, 141.4, 140.0, 139.9, 136.0, 134.6, 132.2, 131.2, 131.0, 130.9, 130.4, 129.5, 129.3, 128.8, 128.3, 118.0, 115.5.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₁H₁₃N₄O: 337.1084; found: 337.1081.

[2-(Benzo[e][1,2,4]triazin-3-yl)phenyl](4-nitrophenyl)methanone (**3ae**)

Yellow solid; yield: 33.1 mg (62%); mp 180–182 °C.

IR (KBr): 3362, 2923, 1678, 1523, 1344, 1274, 1017, 932, 770, 712 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.80 (d, *J* = 8.0 Hz, 1 H), 8.43 (d, *J* = 8.0 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 2 H), 7.98 (d, *J* = 8.0 Hz, 2 H), 7.93 (t, *J* = 8.0 Hz, 1 H), 7.84–7.80 (m, 3 H), 7.75 (t, *J* = 8.0 Hz, 1 H), 7.62 (d, *J* = 8.0 Hz, 1 H).

¹³C NMR (100 MHz, CDCl₃): δ = 195.5, 158.5, 149.7, 145.8, 142.9, 140.0, 139.8, 136.0, 134.5, 131.3, 131.0, 130.5, 129.8, 129.6, 128.8, 128.3, 123.6.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₀H₁₃N₄O₃: 357.0982; found: 357.0977.

[2-(Benzo[e][1,2,4]triazin-3-yl)phenyl](p-tolyl)methanone (3af)

Yellow solid; yield: 35.1 mg (72%); mp 56–58 °C.

IR (KBr): 3312, 2923, 1666, 1510, 1278, 1016, 931, 771 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.70 (dd, J = 8.0, 0.8 Hz, 1 H), 8.43 (d, J = 8.0 Hz, 1 H), 7.88 (tt, J = 8.0, 1.2 Hz, 1 H), 7.83–7.76 (m, 3 H), 7.75–7.66 (m, 3 H), 7.60 (dd, J = 8.0, 0.8 Hz, 1 H), 7.09 (d, J = 8.0 Hz, 2 H), 2.28 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 197.3, 159.4, 145.7, 143.2, 141.4, 140.1, 135.5, 135.4, 134.8, 130.7, 130.5, 130.4, 130.1, 129.4, 129.4, 129.0, 128.9, 128.7, 21.5.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₁H₁₆N₃O: 326.1288; found: 326.1294.

[2-(Benzo[e][1,2,4]triazin-3-yl)phenyl](3-chlorophenyl)methanone (3ag)

Yellow solid; yield: 39.4 mg (76%); mp 138–140 °C.

IR (KBr): 3328, 3066, 2925, 2248, 1673, 1509, 1290, 1016, 910, 770, 734 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.75 (d, J = 8.0 Hz, 1 H), 8.44 (d, J = 8.0 Hz, 1 H), 7.93–7.89 (m, 1 H), 7.85–7.76 (m, 4 H), 7.71 (tt, J = 8.0, 1.2 Hz, 1 H), 7.64 (dt, J = 8.0, 1.2 Hz, 1 H), 7.59 (dd, J = 8.0, 0.8 Hz, 1 H), 7.35 (dq, J = 8.0, 1.2 Hz, 1 H), 7.22 (t, J = 8.0 Hz, 1 H).

¹³C NMR (100 MHz, CDCl₃): δ = 196.1, 159.0, 145.7, 140.4, 140.0, 139.7, 135.7, 134.7, 134.6, 132.4, 131.0, 130.7, 130.5, 130.4, 129.6, 129.5, 129.0, 128.8, 128.5, 127.3.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₀H₁₃ClN₃O: 346.0742; found: 346.0740.

[2-(Benzo[e][1,2,4]triazin-3-yl)phenyl](3-nitrophenyl)methanone (3ah)

Yellow solid; yield: 26.7 mg (50%); mp 149–151 °C.

IR (KBr): 3491, 3082, 2925, 1673, 1530, 1348, 1286, 1083, 1015, 771, 707 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.79 (d, J = 8.0 Hz, 1 H), 8.69–8.68 (m, 1 H), 8.44–8.42 (m, 1 H), 8.26–8.23 (m, 1 H), 8.12 (d, J = 8.0 Hz, 1 H), 7.94–7.90 (m, 1 H), 7.84–7.79 (m, 3 H), 7.74 (tt, J = 8.0, 1.2 Hz, 1 H), 7.60 (dd, J = 8.0, 0.8 Hz, 1 H), 7.51 (t, J = 8.0 Hz, 1 H).

¹³C NMR (100 MHz, CDCl₃): δ = 195.1, 158.6, 148.3, 145.8, 140.1, 139.7, 139.7, 136.0, 134.5, 134.5, 131.2, 130.9, 130.6, 129.5, 129.5, 128.6, 128.4, 126.7, 123.8.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₀H₁₃N₄O₃: 357.0982; found: 357.0977.

[2-(Benzo[e][1,2,4]triazin-3-yl)phenyl](m-tolyl)methanone (3ai)

Yellow solid; yield: 30.7 mg (63%); mp 111–113 °C.

IR (KBr): 3377, 3063, 2923, 1667, 1510, 1283, 1015, 770, 725 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.69 (dd, J = 8.0, 0.8 Hz, 1 H), 8.43 (d, J = 8.0 Hz, 1 H), 7.91–7.88 (m, 1 H), 7.87–7.74 (m, 3 H), 7.71–7.65 (m, 1 H), 7.65–7.62 (m, 2 H), 7.57 (d, J = 8.0 Hz, 1 H), 7.15 (d, J = 8.0 Hz, 2 H), 2.27 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 197.7, 159.5, 145.6, 141.3, 140.1, 137.8, 135.5, 135.0, 133.2, 130.7, 130.5, 130.4, 130.2, 129.7, 129.4, 129.0, 128.6, 128.1, 126.7, 21.2.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₁H₁₆N₃O: 326.1288; found: 326.1294.

Benzo[d][1,3]dioxol-5-yl[2-(benzo[e][1,2,4]triazin-3-yl)phenyl]methanone (3aj)

Yellow solid; yield: 37.8 mg (71%); mp 86–88 °C.

IR (KBr): 3348, 2921, 1660, 1505, 1442, 1259, 1037, 771 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.68 (d, J = 8.0 Hz, 1 H), 8.46 (d, J = 8.0 Hz, 1 H), 7.94–7.86 (m, 2 H), 7.83–7.79 (m, 1 H), 7.76–7.72 (m, 1 H), 7.68 (tt, J = 8.0, 1.2 Hz, 1 H), 7.56 (dd, J = 8.0, 0.8 Hz, 1 H), 7.44 (d, J = 1.6 Hz, 1 H), 7.29 (d, J = 1.6 Hz, 1 H), 6.65 (d, J = 8.0 Hz, 1 H), 5.96 (s, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 195.9, 159.4, 151.4, 148.0, 145.7, 141.3, 140.2, 135.6, 134.7, 132.9, 130.7, 130.6, 130.4, 130.1, 129.5, 128.8, 128.7, 126.1, 108.7, 107.6, 101.7.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₁H₁₄N₃O₃: 356.1031; found: 356.1036.

[2-(Benzo[e][1,2,4]triazin-3-yl)phenyl](2-chlorophenyl)methanone (3ak)

Yellow solid; yield: 27.5 mg (53%); mp 144–146 °C.

IR (KBr): 3345, 3065, 2923, 1676, 1508, 1294, 1015, 930, 769 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.46–8.43 (m, 2 H), 8.03 (d, J = 8.0 Hz, 1 H), 7.93 (tt, J = 8.0, 1.2 Hz, 1 H), 7.83–7.66 (m, 4 H), 7.51 (dd, J = 8.0, 1.6 Hz, 1 H), 7.23 (d, J = 8.0 Hz, 1 H), 7.15 (tt, J = 8.0, 1.6 Hz, 1 H), 7.07–7.03 (m, 1 H).

¹³C NMR (100 MHz, CDCl₃): δ = 195.3, 160.2, 145.6, 140.8, 140.2, 137.0, 136.0, 135.5, 133.3, 132.0, 131.6, 131.2, 131.0, 130.9, 130.7, 130.6, 130.0, 129.4, 129.0, 126.2.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₀H₁₃ClN₃O: 346.0742; found: 346.0740.

[2-(Benzo[e][1,2,4]triazin-3-yl)phenyl](naphthalen-1-yl)methanone (3al)

Yellow solid; yield: 38.0 mg (70%); mp 168–170 °C.

IR (KBr): 3308, 3059, 2924, 1662, 1509, 1284, 1016, 914, 775 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 9.17 (d, J = 8.0 Hz, 1 H), 8.57 (d, J = 8.0 Hz, 1 H), 8.27 (dd, J = 8.0, 1.6 Hz, 1 H), 7.80–7.75 (m, 3 H), 7.71–7.63 (m, 5 H), 7.57–7.55 (m, 1 H), 7.52–7.48 (m, 2 H), 7.13 (t, J = 8.0 Hz, 1 H).

¹³C NMR (100 MHz, CDCl₃): δ = 198.7, 160.0, 145.4, 142.3, 139.9, 135.9, 135.3, 135.2, 133.6, 132.7, 131.0, 130.8, 130.7, 130.6, 130.3, 130.2, 129.2, 128.7, 128.1, 127.9, 126.6, 126.3, 123.9.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₄H₁₆N₃O: 362.1288; found: 362.1291.

[2-(Benzo[e][1,2,4]triazin-3-yl)phenyl](1H-pyrrol-2-yl)methanone (3am)

Dark-brown solid; yield: 27.0 mg (60%); mp 204–206 °C.

IR (KBr): 3275, 2924, 1621, 1399, 1328, 1016, 894, 765 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 9.67 (br, 1 H), 8.48 (q, J = 8.0 Hz, 2 H), 7.92 (q, J = 8.0 Hz, 2 H), 7.83–7.79 (m, 1 H), 7.77–7.72 (m, 2 H), 7.67 (t, J = 8.0 Hz, 1 H), 6.95 (s, 1 H), 6.46 (s, 1 H), 6.07–6.05 (m, 1 H).

¹³C NMR (100 MHz, CDCl₃): δ = 186.2, 160.7, 145.6, 140.5, 140.5, 135.5, 135.4, 132.4, 130.9, 130.5, 130.4, 130.3, 129.4, 129.2, 128.9, 124.7, 118.8, 110.8.

HRMS (ESI): m/z [M + H]⁺ calcd for C₁₈H₁₃N₄O: 301.1084; found: 301.1081.

[2-(Benzo[e][1,2,4]triazin-3-yl)phenyl](furan-2-yl)methanone (3an)

Dark-green oil; yield: 28.5 mg (63%).

IR (neat): 3377, 3122, 2923, 1657, 1463, 1301, 1017, 767 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.64 (d, J = 8.0 Hz, 1 H), 8.46 (d, J = 8.0 Hz, 1 H), 7.92–7.91 (m, 2 H), 7.84–7.79 (m, 1 H), 7.77–7.73 (m, 1 H), 7.69–7.68 (m, 2 H), 7.38 (s, 1 H), 6.93 (d, J = 4.0 Hz, 1 H), 6.32 (dd, J = 4.0, 1.6 Hz, 1 H).

¹³C NMR (100 MHz, CDCl₃): δ = 184.7, 159.7, 153.1, 146.4, 145.7, 140.2, 139.8, 135.6, 135.2, 130.7, 130.7, 130.6, 130.6, 129.4, 129.0, 128.8, 118.5, 112.0.

HRMS (ESI): m/z [M + H]⁺ calcd for C₁₈H₁₂N₃O₂: 302.0925; found: 302.0929.

1-[2-(Benzo[e][1,2,4]triazin-3-yl)phenyl]octan-1-one (3ao)

Dark-brown oil; yield: 28.0 mg (56%).

IR (neat): 3373, 2926, 1697, 1509, 1457, 1324, 1015, 769 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.57 (d, J = 8.0 Hz, 1 H), 8.47 (dd, J = 8.0, 1.2 Hz, 1 H), 8.06 (d, J = 8.0 Hz, 1 H), 8.00 (tt, J = 8.0, 1.6 Hz, 1 H), 7.88 (tt, J = 8.0, 1.2 Hz, 1 H), 7.69–7.60 (m, 2 H), 7.56 (dd, J = 8.0, 1.2 Hz, 1 H), 2.83 (t, J = 8.0 Hz, 2 H), 1.81–1.74 (m, 2 H), 1.33–1.25 (m, 8 H), 0.86 (t, J = 8.0 Hz, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 206.3, 160.4, 146.0, 143.2, 140.5, 135.7, 134.0, 130.8, 130.6, 130.2, 130.0, 128.8, 127.2, 43.1, 31.7, 29.2, 29.1, 24.3, 22.6, 14.0.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₁H₂₄N₃O: 334.1914; found: 334.1916.

1-[2-(Benzo[e][1,2,4]triazin-3-yl)phenyl]-3,7-dimethyloct-6-en-1-one (3ap)

Dark-brown oil; yield: 27.5 mg (51%).

IR (neat): 3375, 2923, 1693, 1507, 1452, 1324, 1016, 770 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.57 (d, J = 8.0 Hz, 1 H), 8.38 (d, J = 8.0 Hz, 1 H), 8.07 (d, J = 8 Hz, 1 H), 8.03–7.98 (m, 1 H), 7.89 (t, J = 8 Hz, 1 H), 7.69–7.59 (m, 3 H), 5.08 (t, J = 8 Hz, 1 H), 2.93–2.87 (m, 1 H), 2.74–2.65 (m, 2 H), 2.28–2.12 (m, 2 H), 1.67 (s, 3 H), 1.56 (s, 3 H), 1.26 (t, J = 8 Hz, 2 H), 1.06–1.02 (m, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 205.3, 160.9, 146.0, 143.0, 140.5, 135.7, 134.6, 131.1, 130.6, 130.5, 129.7, 128.9, 127.5, 124.4, 49.8, 37.1, 35.3, 31.5, 29.2, 25.7, 25.5, 19.9, 17.6.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₃H₂₆N₃O: 360.2071; found: 360.2068.

(4-Chlorophenyl)[2-(7-methylbenzo[e][1,2,4]triazin-3-yl)phenyl]methanone (3ba)

Yellow solid; yield: 36.7 mg (68%); mp 153–155 °C.

IR (KBr): 3396, 2923, 1670, 1586, 1504, 1415, 1277, 1090, 1014, 929, 833, 739 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.70 (d, J = 8.0 Hz, 1 H), 8.18 (s, 1 H), 7.77–7.66 (m, 6 H), 7.57 (d, J = 8.0 Hz, 1 H), 7.24 (d, J = 8.0 Hz, 2 H), 2.61 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 196.3, 158.7, 145.8, 141.8, 140.5, 138.8, 138.7, 138.4, 136.5, 134.9, 130.8, 130.5, 130.4, 130.2, 128.8, 128.6, 128.0, 127.7, 22.0.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₁H₁₅ClN₃O: 360.0899; found: 360.0902.

[2-(7-Chlorobenzo[e][1,2,4]triazin-3-yl)phenyl](4-chlorophenyl)methanone (3ca)

Yellow solid; yield: 37.2 mg (65%); mp 152–154 °C.

IR (KBr): 3328, 3068, 2924, 1672, 1589, 1503, 1409, 1279, 1090, 1013, 929, 840, 732 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.71 (d, J = 8.0 Hz, 1 H), 8.43 (s, 1 H), 7.83 (dd, J = 8.0, 2.0 Hz, 1 H), 7.79–7.74 (m, 4 H), 7.71 (tt, J = 8.0, 0.8 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.28 (d, J = 8.0 Hz, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 196.1, 159.3, 145.6, 140.7, 139.0, 138.7, 137.0, 136.6, 136.3, 134.3, 131.2, 130.5, 130.5, 130.0, 128.9, 128.7, 128.1.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₀H₁₂Cl₂N₃O: 380.0352; found: 380.0359.

[2-(Benzo[e][1,2,4]triazin-3-yl)-5-methylphenyl](4-chlorophenyl)methanone (3da)

Yellow solid; yield: 38.3 mg (71%); mp 156–158 °C.

IR (KBr): 3332, 3064, 2923, 1670, 1589, 1507, 1293, 1091, 1017, 837, 765 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.65 (d, J = 8.0 Hz, 1 H), 8.41 (d, J = 8.0 Hz, 1 H), 7.87 (tt, J = 8.0, 1.2 Hz, 1 H), 7.79–7.75 (m, 4 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.37 (s, 1 H), 7.25 (d, J = 8.0 Hz, 2 H), 2.52 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 196.5, 159.0, 145.7, 141.8, 140.7, 140.1, 138.7, 136.6, 135.6, 131.8, 131.1, 130.5, 130.3, 129.5, 129.3, 128.6, 128.4, 21.5.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₁H₁₅ClN₃O: 360.0899; found: 360.0902.

[2-(Benzo[e][1,2,4]triazin-3-yl)-4,6-dimethylphenyl](4-chlorophenyl)methanone (3ea)

Yellow solid; yield: 35.3 mg (63%); mp 200–202 °C.

IR (KBr): 3336, 3063, 2924, 1672, 1587, 1509, 1264, 1090, 918, 758 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.54 (s, 1 H), 8.43 (d, J = 8.0 Hz, 1 H), 7.87 (tt, J = 8.0, 1.2 Hz, 1 H), 7.81 (d, J = 8.0 Hz, 2 H), 7.76 (dd, J = 8.0, 1.2 Hz, 1 H), 7.69 (d, J = 8.0 Hz, 1 H), 7.33–7.31 (m, 3 H), 2.55 (s, 3 H), 2.25 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 197.4, 159.0, 145.8, 139.9, 139.5, 138.7, 137.3, 137.2, 136.1, 135.6, 134.4, 133.7, 130.5, 130.0, 129.4, 128.8, 128.5, 128.4, 21.3, 19.6.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₂H₁₇ClN₃O: 374.1055; found: 374.1059.

[2-(Benzo[e][1,2,4]triazin-3-yl)-5-chlorophenyl](4-chlorophenyl)methanone (3fa)

Yellow solid; yield: 37.6 mg (66%); mp 150–152 °C.

IR (KBr): 3333, 3066, 2922, 1673, 1590, 1507, 1262, 1088, 1016, 763 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.73 (d, J = 8.0 Hz, 1 H), 8.45 (dd, J = 8.0, 0.4 Hz, 1 H), 7.92 (tt, J = 8.0, 1.6 Hz, 1 H), 7.84–7.72 (m, 5 H), 7.55 (d, J = 2.0 Hz, 1 H), 7.31 (dt, J = 8.0, 2.0 Hz, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 194.6, 158.1, 145.8, 142.1, 140.0, 139.2, 137.7, 135.9, 135.9, 132.9, 131.7, 131.0, 130.5, 129.5, 128.8, 128.8, 128.5.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₀H₁₂Cl₂N₃O: 380.0352; found: 380.0359.

[2-(Benzo[e][1,2,4]triazin-3-yl)-4-chlorophenyl](4-chlorophenyl)methanone (3ga)

Yellow solid; yield: 35.4 mg (62%); mp 122–124 °C.

IR (KBr): 3323, 3068, 2924, 1674, 1588, 1507, 1397, 1280, 1091, 928, 740 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.71 (d, J = 2.0 Hz, 1 H), 8.45 (dd, J = 8.0, 1.6 Hz, 1 H), 7.92 (dd, J = 8.0, 1.6 Hz, 1 H), 7.85–7.82 (m, 2 H), 7.74 (d, J = 8.0 Hz, 2 H), 7.66 (dd, J = 8.0, 2.0 Hz, 1 H), 7.52 (d, J = 8.0 Hz, 1 H), 7.27 (d, J = 8.0 Hz, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 195.2, 158.0, 145.9, 140.1, 139.1, 138.9, 136.7, 136.4, 136.1, 136.0, 131.2, 130.9, 130.5, 130.4, 130.2, 129.5, 128.8, 128.6.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₀H₁₂Cl₂N₃O: 380.0352; found: 380.0359.

[2-(Benzo[e][1,2,4]triazin-3-yl)-4-methylphenyl](4-chlorophenyl)methanone (3ha)

Yellow solid; yield: 37.8 mg (70%); mp 141–143 °C.

IR (KBr): 3319, 3062, 2924, 1668, 1587, 1509, 1396, 1282, 1090, 933, 739 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.49 (s, 1 H), 8.43 (d, J = 8.0 Hz, 1 H), 7.89 (t, J = 8.0 Hz, 1 H), 7.81 (t, J = 8.0 Hz, 2 H), 7.75 (t, J = 8.0 Hz, 2 H), 7.49 (s, 2 H), 7.24 (d, J = 8.0 Hz, 2 H), 2.59 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 196.3, 159.4, 145.7, 140.8, 140.1, 138.6, 137.9, 136.7, 135.7, 134.8, 131.5, 131.0, 130.6, 130.5, 129.5, 129.0, 128.5, 128.5, 21.5.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₁H₁₅ClN₃O: 360.0899; found: 360.0902.

(4-Chlorophenyl)[5-methoxy-2-(7-methylbenzo[e][1,2,4]triazin-3-yl)phenyl]methanone (3ia)

Yellow solid; yield: 42.1 mg (72%); mp 158–160 °C.

IR (KBr): 3329, 3063, 2932, 1673, 1599, 1505, 1412, 1290, 1235, 1092, 1013, 833, 733 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.73 (d, J = 8.0 Hz, 1 H), 8.14 (s, 1 H), 7.76 (d, J = 8.0 Hz, 2 H), 7.68 (dd, J = 8.0, 1.6 Hz, 1 H), 7.62 (d, J = 8.0 Hz, 1 H), 7.24 (dd, J = 8.0, 2.8 Hz, 3 H), 7.06 (d, J = 2.8 Hz, 1 H), 3.94 (s, 3 H), 2.59 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 195.9, 161.8, 158.2, 145.5, 142.2, 141.1, 138.8, 138.7, 138.2, 136.5, 131.8, 130.4, 128.6, 127.8, 127.7, 126.9, 115.9, 114.0, 55.7, 21.9.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₂H₁₇ClN₃O₂: 390.1004; found: 390.1002.

(4-Chlorophenyl)[2-(7-isopropylbenzo[e][1,2,4]triazin-3-yl)-4-methylphenyl]methanone (3ja)

Yellow solid; yield: 48.9 mg (81%); mp 120–122 °C.

IR (KBr): 3324, 3060, 2964, 1671, 1587, 1505, 1428, 1280, 1090, 930, 842, 742 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.48 (s, 1 H), 8.21 (d, J = 1.2 Hz, 1 H), 7.81 (d, J = 8.0 Hz, 2 H), 7.75–7.72 (m, 3 H), 7.49 (s, 1 H), 7.23 (d, J = 8.0 Hz, 2 H), 3.19–3.12 (m, 1 H), 2.59 (s, 3 H), 1.38 (d, J = 2.4 Hz, 3 H), 1.36 (d, J = 2.4 Hz, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 196.4, 159.1, 152.2, 145.9, 140.8, 139.1, 138.5, 137.7, 136.8, 136.2, 135.0, 131.3, 130.8, 130.5, 129.0, 128.5, 128.1, 125.0, 34.3, 23.3, 21.5.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₄H₂₁ClN₃O: 402.1368; found: 402.1372.

Funding Information

We thank the State Key Laboratory of Applied Organic Chemistry, Talent Introduction Project of Hubei Polytechnic University (No.19XJK03R), and Medical School (HBPU) for financial support.

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0039-1691564>.

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