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High yielding microwave-assisted synthesis of tri-substituted 1,3,5-triazines using Pd-catalyzed aryl and heteroarylamination

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ABSTRACT

A rapid and efficient Pd-catalyzed aryl and heteroarylamination under microwave irradiation has been developed for various tri-substituted triazines that can serve as versatile building blocks for both supramolecular and medicinal chemistry research. Particularly valuable features of this method included the short reaction time, good yield, and convenient operation.

1. Introduction

Tri-substituted 1,3,5-triazines are one of the oldest classes of organic compounds that continue to be used as important core structure in many chemotherapeutic agents due to their interesting pharmacological properties, including anticancer,[1] anti-angiogenesis,[2] anti-HIV,[3] antimalarial,[4] antibacterial,[5] and antimicrobial activity.[6] These compounds have also been used as subunits in the formation of supramolecular structure because they possess good optical and electronic properties and are able to form multiple hydrogen bonds.[7,8] Despite numerous implications of these compounds, synthetic methods for the preparation of analogues containing different substituents at each carbon are limited. Development of valuable methods for the preparation of many new substituted compounds is still a challenge.

Previous synthetic methods for such compounds mainly relied on two approaches. One involves the formation of triazinic ring by the reaction of substituted biguanides with carboxylates,[9] acid chlorides,[10] anhydrides[11] or by cyclization of acylamidines with amidines or guanidines.[12] A recently published procedure involves the treatment of isothiocyanates with *N*,*N*-diethylamidines through the formation of intermediate amidinothioureas, which react with carbamidines in the presence of mercury (II) chloride.[13] The most used alternative route to these compounds starts with cyanuric chloride, that is, 2,4,6-trichloro-1,3,5-triazine. Each chloride atom of cyanuric chloride can be substituted by various nucleophiles in the presence of a base and controlled by temperature to run in a stepwise manner. An empirical rule, based upon observation, is that mono-substitution of chlorine occurs below or at 0 °C, di-substitution at room temperature and tri-substitution above 60 °C. Although widely used, this route has some deficiencies: most notably, harsh conditions, and low reaction yields resulting from the poor reactivity of its third chlorine atom toward nucleophiles.

We have previously reported an efficient and practical procedure to prepare novel 2-(arylmethyl)amino-4-arylamino-6-alkyl-1,3,5-triazines under microwave (MW) irradiation.[9] MW-assisted organic synthesis is a high-speed methodology with clear benefits: the higher degree of purity achieved due to short residence time at high temperature and the significant rate-enhancements that result in short reaction time, energy saving, and better product yields. Thus, in recent years, MW irradiation has been described for a wide spectrum of organic reactions including, for instance, heterocyclic, organometallic, radio, photo, and combinatorial chemistries.[14,15]

As part of our ongoing research toward the design of new imidazotriazine containing compounds, we wanted to synthesize tri-substituted 1,3,5-triazines **2** (Scheme 1). Herein, we report our optimized conditions, scope, and applications of microwave-assisted Pd-catalyzed aryl and heteroarylamination of compounds **1** and **4**, which provide facile access to these compounds and their derivatives.

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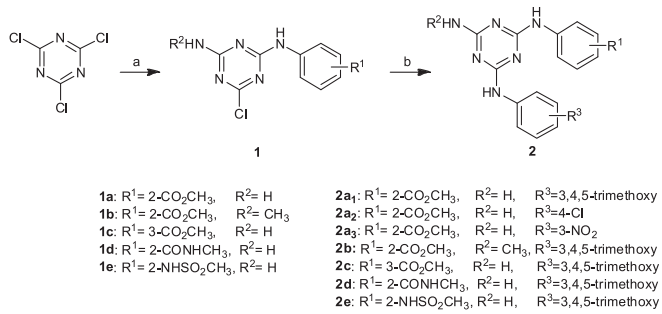


Scheme 1. Reagents and conditions: (a) arylamine/THF/DIEA, −20 °C; NH_3/THF, rt; (b) arylamine/dioxane/$Pd(OAc)_2$/*rac*-BINAP/Cs_2CO_3/MW, 100 °C, 10 min.

2. Results and discussion

For this study, we chose 2,4,6-trichloro-1,3,5-triazine as starting material. Substituted 1,3,5-triazine-2,4-diamines **1a**–**d** can be prepared from corresponding amines in good to excellent yields in a one-pot procedure. Then we first examined the reaction of di-substituted triazine **1a** with 3,4,5-trimethoxyaniline in the presence of DIEA in dioxane to furnish $\mathbf{2a_1}$. As anticipated, reaction times as long as 24 h were necessary under conventional thermal heating conditions and the yield of the desired product was 21%.

In order to optimize the reaction yield, we began our investigation with a microwave-assisted procedure. We were delighted to find a better yield under the MW conditions. The same conversion of this reaction was achieved within 30 min, to give the corresponding $\mathbf{2a_1}$ in 42% yield (Table 1, entry 1). Next, the effect of the solvent was examined and the results are summarized in Table 1. Optimal conditions for the preparation of $\mathbf{2a_1}$ in 59% yield were identified (entry 5), but this reaction is accompanied by a trans esterification.

Table 1
Solvent influence under MW conditions on reaction rate and yield of $\mathbf{2a_1}$

Entry	Solvent	Time (min)	T (°C)	Conversion (%)	Yields (%)
1	Dioxane	30	100	65	42
2	THF	30	100	40	13
3	Toluene	30	110	75	36
4	CH_3CN	30	90	36	12
5	*n*-BuOH	30	120	90	59
6	DMF	30	150	90	32

Considering the remarkable progress made in the development of palladium-catalyzed arylamination of aryl halides,[16,17] we turned our attention to a MW-assisted Buchwald-type coupling. To the best of our knowledge, few approaches using palladium cross-coupling are known for preparing tri-substituted 1,3,5-triazines. For these reactions, the key to success was the optimum combined choice of the solvent, base, and catalyst/ligand. We first tested standard Buchwald amination conditions ($Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3) using dioxane as solvent, under MW conditions. As shown in Table 2 (entry 1), the reaction proceeded rapidly to completion within a few minutes. Thus, treatment of **1a** under MW conditions for 10 min gave $\mathbf{2a_1}$ in 76% yield.

Attempts to increase the yield of $\mathbf{2a_1}$ by varying the base failed. Replacement of cesium carbonate with sodium *tert*-butoxylate or DIEA as the base led to a decrease in the yields to 50% or 53% (entries 2 and 3). Then, we focused our attention on the study of the influence of the palladium catalyst or the ligand on the cross-coupling arylamination. The replacement of $Pd(OAc)_2$ by $Pd_2(dba)_3$ (entry 4) afforded $\mathbf{2a_1}$ in 69%. Similar results were observed using $Pd(dppf)Cl_2$ (entry 6). In contrast, $Pd(Ph_3P)_2Cl_2$ afforded $\mathbf{2a_1}$ in poor yield (entry 5). The use of palladium (II) acetate/(tolyl)$_3$P (entry 7) or palladium (II) acetate/(*t*-Bu)$_3$P (entry 8) as catalyst led to a significant decrease in turnover and yield (32% and 24%, respectively).

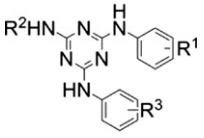
Table 2
Optimization of the arylamination reaction on $\mathbf{2a_1}$ in dioxane under MW irradiation

Entry	Catalyst	Ligand	Base	Time (min)	T (°C)	Conversion (%)	Yield (%)
1	$Pd(OAc)_2$	BINAP[c]	Cs_2CO_3	10	100	100	76
2	$Pd(OAc)_2$	BINAP[c]	*t*-BuONa	10	100	80	50
3	$Pd_2(dba)_3$[a]	BINAP[c]	DIEA	10	100	75	53
4	$Pd(OAc)_2$	BINAP[c]	Cs_2CO_3	10	100	91	69
5	$Pd(Ph_3P)_2Cl_2$	BINAP[c]	Cs_2CO_3	10	100	54	19
6	$Pd(dppf)Cl_2$[b]	BINAP[c]	Cs_2CO_3	10	100	87	62
7	$Pd(OAc)_2$	(tolyl)$_3$P	Cs_2CO_3	10	100	62	32
8	$Pd(OAc)_2$	(*t*-Bu)$_3$P	Cs_2CO_3	10	100	34	24

[a] Tris(dibenzylideneacetone)dipalladium(0).
[b] [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II).
[c] racemic-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl.

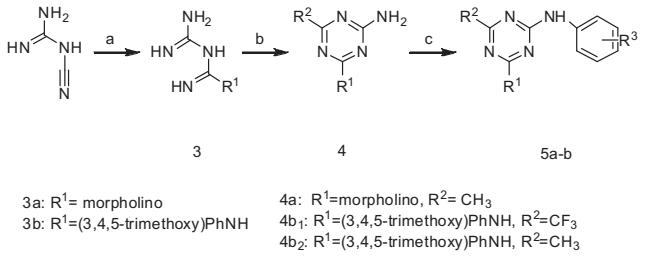
The scope of Pd-catalyzed arylamination method was explored by applying the optimized reaction conditions to **1a** and other less nucleophilic anilines (Table 3, entries 1, 2). The results showed that the reaction could be efficiently generalized. Under these conditions, excellent conversion and good isolated yields were obtained. We also applied the same conditions to various di-substituted triazines **1b** to **1e** and 3,4,5-trimethoxyaniline (Table 3, entries 3–6). The corresponding products **2b**–**e** were generated in good yields of 61–78%.

Table 3
Preparation of tri-substituted triazines **2**



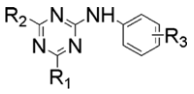
Entry	**2**	R^1	R^2	R^3	Time (m n)	T (°C)	Conversion (%)	Yield (%)
1	$\mathbf{2a_2}$	2-CO_2Me	H	4-Cl	10	100	100	67
2	$\mathbf{2a_3}$	2-CO_2Me	H	3-NO_2	10	100	100	67
3	**2b**	2-CO_2Me	CH_3	3,4,5-(OMe)$_3$	10	100	93	75
4	**2c**	3-CO_2Me	H	3,4,5-(OMe)$_3$	10	100	95	78
5	**2d**	2-CONHMe	H	3,4,5-(OMe)$_3$	10	100	92	61
6	**2e**	2-$NHSO_2$Me	H	3,4,5-(OMe)$_3$	10	100	92	62

Encouraged by these results, we decided to apply this procedure to the arylation of *N*-4-substituted 1,3,5-triazine-2,4-diamine **4**, which were prepared by reaction of substituted biguanides with esters under MW irradiation[9] (Scheme 2), because this reaction does not work under classical reaction conditions. Initially, attempts to condense 6-methyl-*N*-morpholino-1,3,5-triazine-2,4-diamine **4a** with 1-bromo-2-nitrobenzene using the same microwave-assisted palladium cross-coupling procedure ($Pd(OAc)_2$, BINAP, Cs_2CO_3) were unsuccessful. Therefore, we focused on investigating this procedure with different combinations of catalyst/ligand. When the reaction was performed with $Pd(OAc)_2$ (4%), xantphos (4%), and Cs_2CO_3 (1.5 equiv) in dioxane at 150 °C using irradiation power of 150 W (entry 1, Table 4), we were very pleased to find that the arylation of **4a** proceeded efficiently and we observed completion of reaction within 15 min with 82% isolated yield. Similarly, **4a** reacts with 4-iodotoluene to give the corresponding compound $\mathbf{5a_2}$ in 60% yield (entry 2, Table 4). Moreover, high yields were also obtained in the reaction of 1-bromo-2-nitrobenzene with compounds $\mathbf{4b_1}$–$\mathbf{b_2}$ (entries 3, 4, Table 4).



Scheme 2. (a) RNH_2/dioxane/MW, 90 °C, 15 min; (b) R_2CO_2Et/MeONa/THF/MW, 70 °C, 20 min; (c) 4-iodotoluene or 1-bromo-2-nitrobenzene/dioxane/$Pd(OAc)_2$/xantphos/Cs_2CO_3/MW, 150 °C, 15–30 min.

Table 4
Preparation of tri-substituted triazines **5**



Entry	5	R^1	R^2	R^3	Time (min)	T (°C)	Conversion (%)	Yield (%)
1	$\mathbf{5a_1}$	*N*-morpholino	CH_3	2-NO_2	15	150	100	82
2	$\mathbf{5a_2}$	*N*-morpholino	CH_3	4-CH_3	30	150	85	60
3	$\mathbf{5b_1}$	[3,4,5-$(OMe)_3$]PhNH	CF_3	2-NO_2	15	150	100	74
4	$\mathbf{5b_2}$	[3,4,5-$(OMe)_3$]PhNH	CH_3	2-NO_2	15	150	100	80

The structures of tri-substituted triazines were determined in solution using NMR spectroscopy. Conformers resulting from the restricted rotation about the amine-triazine bond for compounds **1b**, **2b**, and $\mathbf{5b_1}$ were detected and identified in solution and at room temperature (300 K). This effect of internal rotation can be also observed for melamine derivatives in solution as well as in the solid state.[18] Theoretically, compounds **I** and **II** can exist in four and sixteen possible rotamers arising from two possible conformations about the triazine C–N bonds and the two orientations possible for the aromatic rings, while compounds **1b** and **2b** present eight and thirty-two possible rotamers. All the rotamers, which would interconvert by α, β, γ, δ, and ω rotations are equivalent for compounds **1**–**5**, so that there is a single distinguishable form, as shown in Fig. 1. Each of the α, β, γ, δ, and ω rotations would, if fast on the NMR time-scale, result in averaging of some of the ^1H and ^{13}C resonances for their structure.

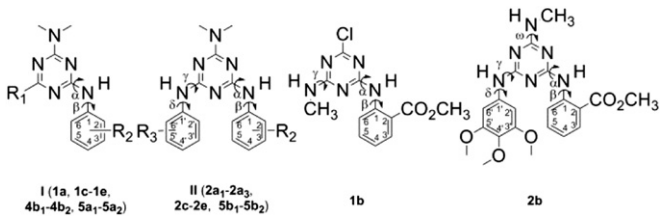


Fig. 1. Compounds **1**–**5** rotamer (except **3**, **4a**).

The NMR spectrum of **1b** (Fig. 2, Table S1) at 363 K in DMF-d_7 solution showed a single compound, consistent with fast rotation about all the bonds. At 300 K in DMF-d_7 solution, α rotation has slowed and all of signals except the OCH_3 peak have split in two. A similar behavior was observed in the DMSO-d_6 solution. On lowering the temperature in DMF-d_7 solution, the resonances broaden, by 213 K the signals were split, and in particular, four signals were observed for each of two NH groups (PhNH, CH_3NH), suggesting that γ rotation is now slow. One signal of high intensity, one signal of medium intensity and two signals of low intensity were observed.

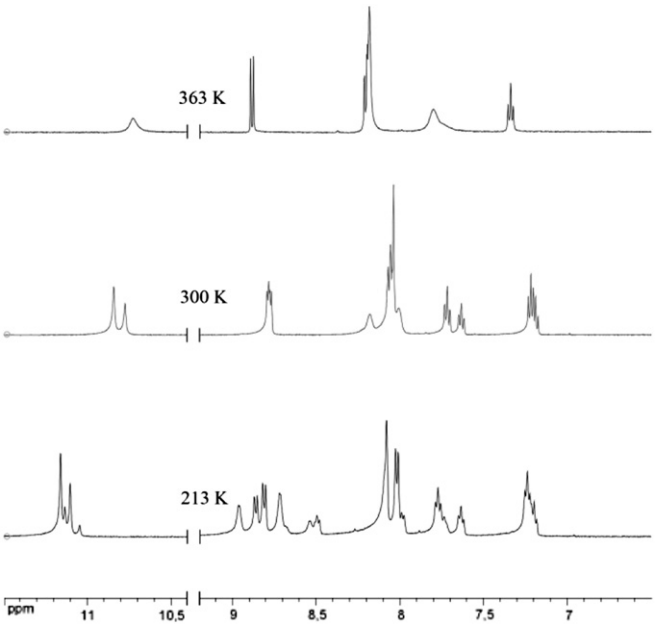


Fig. 2. . Aromatic and NH regions of the solution-state ^1H NMR spectrum of **1b**.

Finally, the NMR spectra of **1a**, $\mathbf{2a_1}$, and **2b** (Table S3–S5) at 213 K (DMF-d_7) showed the presence of two, four, and eight distinguishable rotamers, in an analogous way to the effects observed for **1b**. As the temperature is increased, $\mathbf{2a_1}$ and **2b** present two and four rotamers along the range of temperatures used (240–280 K for $\mathbf{2a_1}$ and 240–260 K for **2b**). At 280 K, the signals for **2b** coalesced again to show the presence of two rotamers. On heating further temperature to 363 K for **2b** and 300 K for **1a** and $\mathbf{2a_1}$, a rapid rotation of all bonds was observed, giving signals for a unique compound.

3. Conclusion

In conclusion, we have developed a two-step or three-step approach to tri-substituted triazines that can serve as versatile building blocks for both supramolecular and medicinal chemistry research. The advantageous features of this method, including simple operation, good yielding, and short reaction times provide an excellent opportunity for parallel synthesis. We have also shown different rotamers resulting from the restricted rotation about the amino triazine bond. Determining the molecular structure in solution could allow insight into possible supramolecular interactions and prediction of the crystal structure of a system.

4. Experimental section

4.1. General information

All reagents were purchased from Sigma–Aldrich, Acros Organics and Alfa Aesar and used without further purification. Microwave irradiation was carried out with a BenchMate monomode reactor (IR detector for temperature) from CEM corporation. Melting points were determined on a Kofler apparatus as uncorrected values. TLC was carried out on a Merck Kieselgel 60 PF_{254} and visualized with UV light. Column chromatography was performed using Silica gel 60 (40–63 μm) purchased from Carlo Erba-SDS. ^1H NMR and ^{13}C NMR spectra were measured on a Bruker WMFT-250 MHz or AMX-500 MHz spectrometer in DMSO-d_6 or $CDCl_3$ or DMF-d_7 with chemical shift (δ) given in parts per million (ppm) relative to TMS as internal standard and recorded at the temperature indicated (300±0.1 K except **1a**, **1b**, **2b**, and $\mathbf{2a_1}$) with

a probe calibrate with methanol. MS (ESI) was determined by using a Q-Tof1 spectrometer with Z-spray source. High-resolution mass spectra (HRSM) were performed on Q-TOF Micro micromass positive ESI (CV=30 V).

4.2. General procedure for the synthesis of di-substituted triazines 1

The solution of cyanuryl chloride (3 mmol, 1 equiv) in THF (20 ml) was stirred, cooled to −15 °C, and aniline (3 mmol, 1 equiv) in THF (6 ml) and DIEA (3.6 mmol, 1.2 equiv) was added dropwise. The mixture was stirred at this temperature for 0.5–1 h. Upon completion, monitored by TLC, NH_3 (13 ml, 28% in water) was added. The mixture was stirred under room temperature for 1 h. After the solvent was removed under reduced pressure the resulting solid was collected by filtration, dried, and crystallized or purified by silica gel column chromatography to get the desired product.

*4.2.1. Methyl 2-(4-amino-6-chloro-1,3,5-triazin-2-ylamino)benzoate (**1a**).* Yield 79%, white solid, mp 234 °C; ^{1}H NMR (250 MHz, DMSO): δ 3.85 (s, 3H, CH_3), 7.19 (t, 1H, ArH), 7.63 (t, 1H, ArH), 7.70 (s, 2H, NH_2), 7.95 (d, 1H, ArH), 8.42 (d, 1H, ArH), 10.51 (s, 1H, NH). ^{13}C NMR (500 MHz, DMSO): δ 170.5, 169.6, 168.8, 165.9, 141.9, 135.7, 132.5, 124.5, 123.4, 119.3, 54.3. MS (ESI) *m/z* 280.0 $[M+1]^+$. ESI-HRMS *m/z* calcd for $C_{11}H_{11}ClN_5O_2^+$ $[M+H]^+$ 280.0601, found 280.0612.

*4.2.2. Methyl 2-(4-methylamino-6-chloro-1,3,5-triazin-2-ylamino) benzoate (**1b**).* Yield 83%, white solid, mp 248 °C; ^{1}H NMR (250 MHz, DMF, 363 K): δ 3.17 (d, 3H, NCH_3), 4.14 (s, 3H, OCH_3), 7.33 (t, 1H, ArH), 7.79 (s, br, 2H, ArH, NH), 8.19 (d, 1H, ArH), 8.88 (d, 1H, ArH), 10.71 (s, 1H, NH). ^{13}C NMR (500 MHz, DMF, 363 K): δ 169.8, 168.7, 166.0, 142.9, 135.4, 132.7, 124.0, 122.9, 118.3, 53.6, 28.9. MS (ESI) *m/z* 294.0 $[M+1]^+$. ESI-HRMS *m/z* calcd for $C_{12}H_{13}ClN_5O_2^+$ $[M+H]^+$ 294.0758, found 294.0743.

*4.2.3. Methyl 3-(4-amino-6-chloro-1,3,5-triazin-2-ylamino)benzoate (**1c**).* Yield 82.3%, white solid, mp 256 °C; ^{1}H NMR (250 MHz, DMSO): δ 3.87 (3H, s, CH_3) 7.47 (1H, t, ArH), 7.65 (3H, m, ArH, NH_2), 8.19 (2H, m, ArH), 10.17 (1H, s, NH). ^{13}C NMR (500 MHz, DMSO): δ 170.4, 168.8, 168.0, 166.0, 141.3, 132.0, 130.8, 126.8, 125.4, 122.8, 54.0. MS (ESI) *m/z* 280.1 $[M+1]^+$. ESI-HRMS *m/z* calcd for $C_{11}H_{11}ClN_5O_2^+$ $[M+H]^+$ 280.0601, found 280.0615.

*4.2.4. 2-(4-Amino-6-chloro-1,3,5-triazin-2-ylam-ino)-N-methylbenzamide (**1d**).* Yield 87%, white solid, mp 230 °C; ^{1}H NMR (250 MHz, DMSO): δ 2.80 (3H, d, CH_3), 7.13 (1H, t, ArH), 7.51 (1H, t, ArH), 7.70 (3H, m, ArH, NH_2), 8.58 (1H, d, ArH), 8.77 (1H, s, NH), 11.18 (1H, s, NH). ^{13}C NMR (500 MHz, DMSO): δ 170.7, 170.5, 168.8, 165.6, 140.6, 133.4, 129.9, 124.0, 123.1, 122.9, 28.1. MS (ESI) *m/z* 278.9 $[M+1]^+$. ESI-HRMS *m/z* calcd for $C_{11}H_{12}ClN_6O^+$ $[M+H]^+$ 279.0761, found 279.0752.

*4.2.5. N-(2-(4-Amino-6-chloro-1,3,5-triazin-2-ylamino)phenyl) methanesulfonamide (**1e**).* Yield 85%, white solid, mp 254 °C; ^{1}H NMR (250 MHz, DMSO): δ 2.92 (3H, s, CH_3), 7.14 (2H, m, ArH), 7.39 (1H, t, ArH), 7.54 (2H, s, NH_2), 7.74 (1H, t, ArH), 8.56 (1H, s, NH), 9.0 (1H, s, NH). ^{13}C NMR (500 MHz, DMSO): δ 168.6, 166.9, 164.1, 139.7, 138.5, 129.1, 116.3, 114.5, 112.2. MS (ESI) *m/z* 315.1 $[M+1]^+$. ESI-HRMS *m/z* calcd for $C_{10}H_{12}ClN_6O_2S^+$ $[M+H]^+$ 315.0431, found 315.0426.

4.3. General procedure for the synthesis of tri-substituted triazines 2

To a 10 ml microwave vessel were added the corresponding compounds **1** (0.18 mmol, 1 equiv), arylamine (0.18 mmol, 1 equiv), $Pd(OAc)_2$ (7.2 μmol), BINAP (7.2 μmol) and Cs_2CO_3 (0.27 mmol, 1.5 equiv) and anhydrous dioxane (2 ml). The vessel was sealed and purged with argon. The mixture was subjected to microwave irradiation for 10 min at 100 °C using irradiation power of 100 W. On cooling to room temperature, the mixture was concentrated, and filtered. The crude product was purified by flash chromatography (silica gel, 5% methanol/CH_2Cl_2) to afford the desired product.

*4.3.1. Methyl 2-(4-amino-6-(3,4,5-trimethoxyphe-nylamino)-1,3,5-triazin-2-ylamino)benzoate (**2a$_1$**).* 76%, white solid, mp 224 °C; ^{1}H NMR (250 MHz, DMSO): δ 3.65 (s, 3H, OMe), 3,79 (s, 6H, OMe), 3.91 (s, 3H, CH_3); 6.95 (s, 2H, NH_2), 7.06 (t, 1H, ArH), 7.22 (s, 2H, ArH), 7.60 (t, 1H, ArH), 8.0 (d, 1H, ArH), 8.98 (d, 1H, ArH), 9.20 (s, 1H, NH), 10.43 (s, 1H, NH). ^{13}C NMR (500 MHz, DMSO): δ 167.0, 168.7, 166.2, 165.9, 154.5, 144.3, 138.0, 136.0, 134.5, 132.6, 122.5, 122.0, 116.0, 99.9, 62.0, 57.6, 54.2. MS (ESI) *m/z* 427.1 $[M+1]^+$. ESI-HRMS *m/z* calcd for $C_{20}H_{23}N_6O_5^+$ $[M+H]^+$ 427.1730, found 427.1729.

*4.3.2. Methyl 2-(4-amino-6-(4-chlorophenylami-no)-1,3,5-triazin-2-ylamino)benzoate (**2a$_2$**).* Yield 67.2%, white solid, mp 146 °C; ^{1}H NMR (250 MHz, DMSO): δ 3.89 (s, 3H, CH_3), 6.97 (s, 2H, NH_2), 7.08 (t, 1H, ArH), 7.31 (d, 2H, ArH), 7.60 (t, 1H, ArH), 7.82 (d, 2H, ArH), 8.0 (d, 1H, ArH); 8.91 (d, 2H, ArH), 9.47 (s, 1H, NH), 10.38 (s, 1H, NH). ^{13}C NMR (500 MHz, DMSO): δ 168.0, 166.9, 164.3, 164.1, 142.4, 139.2, 134.1, 130.7, 128.1, 125.5, 121.38, 120.8, 120.4, 114.5, 52.2. MS (ESI) *m/z* 371.0 $[M+1]^+$. ESI-HRMS *m/z* calcd for $C_{17}H_{16}ClN_6O_2^+$ $[M+H]^+$ 371.1023, found 371.1015.

*4.3.3. Methyl 2-(4-amino-6-(3-nitrophenylamino)-1,3,5-triazin-2-ylamino)benzoate (**2a$_3$**).* Yield 66.8%, pale yellow solid, mp 172 °C; ^{1}H NMR (250 MHz, DMSO): δ 3.90 (s, 3H, CH_3), 7.08 (m, 3H, NH_2, ArH), 7.60 (m, 2H, ArH), 7.80 (d, 1H, ArH), 7.89 (d, 1H, ArH), 8.19 (d, 1H, ArH), 8.62 (s, 1H, ArH), 8.90 (d, 1H, ArH), 9.82 (s, 1H, NH), 10.44 (s, 1H, NH). ^{13}C NMR (500 MHz, DMSO): δ 169.9, 168.8, 166.3, 166.1, 149.9, 143.9, 143.3, 136.0, 132.6, 131.5, 127.6, 122.8, 122.3, 118.0, 116.5, 115.7, 54.2. MS (ESI) *m/z* 382.1 $[M+1]^+$. ESI-HRMS *m/z* calcd for $C_{17}H_{16}N_7O_4^+$ $[M+H]^+$ 382.1264, found 382.1251.

*4.3.4. Methyl 2-(4-methylamino-6-(3,4,5-trimethoxyphenylamino)-1,3,5-triazin-2-ylamino)benzoate (**2b**).* Yield 74.8%, white solid, mp 209 °C; ^{1}H NMR (250 MHz, DMSO, 300 K): δ 2.92 (s, 3H, NMe), 3.67 (s, 6H, OMe), 3.79 (s, 6H, OMe), 3.9 (s, 3H, CH_3), 7.09 (t, 1H, ArH), 7.16 (s, 2H, ArH), 7.45 (s, 1H, NH), 7.57 (t, 1H, ArH), 7.98 (d, 1H, ArH), 8.78 (d, 1H, ArH), 9.06 (s, 1H, NH), 10.29 (s, 1H, NH). ^{13}C NMR (500 MHz, DMSO, 363 K): δ 169.8, 167.2, 166.4, 165.0, 155.0, 143.5, 137.3, 136.1, 135.6, 132.5, 123.2, 123.0, 117.8, 101.5, 62.1, 58.2, 54.0, 29.2. MS (ESI) *m/z* 441.1 $[M+1]^+$. ESI-HRMS *m/z* calcd for $C_{21}H_{25}N_6O_5^+$ $[M+H]^+$ 441.1886, found 441.1879.

*4.3.5. Methyl 3-(4-amino-6-(3,4,5-trimethoxyphenylamino)-1,3,5-triazin-2-ylamino)benzoate (**2c**).* Yield 78.4%, white solid, mp 152 °C; ^{1}H NMR (250 MHz, DMSO): δ 3.62 (3H, s, OCH_3), 3.73 (6H, s, OCH_3), 3.83 (3H, s, CH_3), 6.68 (2H, s, NH_2), 7.14 (2H, s, ArH), 7.40 (1H, t, ArH), 7.52 (1H, d, ArH), 8.18 (1H, s, ArH), 8.27 (1H, d, ArH), 8.94 (1H, s, NH), 9.22 (1H, s, NH). ^{13}C NMR (500 MHz, DMSO): δ 166.8, 166.4, 164.5, 152.5, 140.8, 136.1, 132.5, 129.9, 128.7, 124.6, 122.2, 120.5, 98.1, 60.1, 55.8, 52.0. MS (ESI) *m/z* 427.1 $[M+1]^+$. ESI-HRMS *m/z* calcd for $C_{20}H_{23}N_6O_5^+$ $[M+H]^+$ 427.1730, found 427.1723.

*4.3.6. 2-(4-Amino-6-(3,4,5-trimethoxyphenylam-ino)-1,3,5-triazin-2-ylamino)-N-methylbenzamide (**2d**).* Yield 61.1%, white solid, mp 182 °C; ^{1}H NMR (250 MHz, DMSO): δ 2.80 (3H, d, CH_3), 3.63 (3H, s, OCH_3), 3.78 (6H, s, OCH_3), 6.82 (2H, s, NH_2), 7.01 (1H, t, ArH), 7.19 (2H, s, ArH), 7.41 (1H, t, ArH), 7.62 (1H, d, ArH), 8.61 (1H, s, NH), 8.81 (1H, d, ArH), 9.10 (1H, s, NH), 10.80 (1H, s, NH). ^{13}C NMR (500 MHz, DMSO): δ 169.1, 166.8, 164.3, 163.9, 152.5, 140.3, 136.2, 132.4, 131.3,

127.9, 120.4, 120.1, 119.8, 97.8, 60.1, 55.7, 26.1. MS (ESI) *m/z* 426.0 $[M+1]^+$. ESI-HRMS *m/z* calcd for $C_{20}H_{24}N_7O_4^+$ $[M+H]^+$ 426.1890, found 426.1885.

*4.3.7. N-(2-(4-Amino-6-(3,4,5-trimethoxyphenylam-ino)-1,3,5-triazin-2-ylamino)phenyl)methanesulfonamide (**2e**).* Yield 61.5%, white solid, mp 134 °C; ^{1}H NMR (250 MHz, DMSO): δ 3.01 (3H, d, CH_3), 3.62 (3H, s, OCH_3), 3.74 (6H, s, OCH_3), 6.57 (2H, s, NH_2), 6.84 (1H, d, ArH), 7.14 (2H, s, ArH), 7.20 (1H, t, ArH), 7.46 (1H, t, ArH), 7.69 (1H, d, ArH), 8.83 (1H, s, NH), 9.07 (1H, s, NH), 9.58 (1H, s, NH). ^{13}C NMR (500 MHz, DMSO): δ 176.3, 163.3, 164.0, 152.5, 135.9, 135.6, 133.1, 132.8, 130.7, 127.4, 125.9, 125.4, 98.1, 60.1, 55.7, 39.5. MS (ESI) *m/z* 462.1 $[M+1]^+$. ESI-HRMS *m/z* calcd for $C_{19}H_{24}N_7O_5S^+$ $[M+H]^+$ 462.1560, found 462.1567.

4.4. General procedure for the synthesis of tri-substituted triazines 5

To a 10 ml microwave vessel were added the corresponding compounds **4** (0.18 mmol, 1 equiv), 1-bromo-2-nitrobenzene or 4-iodotoluene (0.18 mmol, 1 equiv), $Pd(OAc)_2$ (7.2 μmol), xantphos (7.2 μmol) and Cs_2CO_3 (0.27 mmol, 1.5 equiv) and anhydrous dioxane (2 ml). The vessel was sealed and purged with argon. The mixture was subjected to microwave irradiation for 15–30 min at 150 °C using irradiation power of 150 W. On cooling to room temperature, the mixture was concentrated, and filtered. The crude product was purified by flash chromatography (silica gel, 5% methanol/CH_2Cl_2) to afford the desired product.

*4.4.1. 4-Methyl-6-morpholino-N-(2-nitrophenyl)-1,3,5-triazin-2-amine (**5a$_1$**).* Yield 82.2%, yellow solid, mp 156 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.42 (3H, s, CH_3), 3.80 (4H, t, 2× CH_2), 3.90 (4H, t, 2× CH_2), 7.12 (1H, t, ArH), 7.62 (1H, t, ArH), 8.22 (1H, d, ArH), 8.86 (1H, d, ArH), 10.02 (1H, s, NH). ^{13}C NMR (500 MHz, DMSO): δ 177.7, 166.1, 165.5, 138.2, 137.5, 136.4, 127.4, 123.9, 123.1, 68.2, 45.2, 27.1. MS (ESI) *m/z* 317.1 $[M+1]^+$. ESI-HRMS *m/z* calcd for $C_{14}H_{17}N_6O_3^+$ $[M+H]^+$ 317.1362, found 317.1347.

*4.4.2. 4-Methyl-6-morpholino-N-p-tolyl-1,3,5-triazin-2-amine (**5a$_2$**).* Yield 60.2%, white solid, mp 199 °C; ^{1}H NMR (250 MHz, DMSO): δ 2.24 (3H, s, CH_3), 2.26 (3H, s, CH_3), 3.66 (4H, t, 2× CH_2), 3.75 (4H, t, 2× CH_2), 7.1 (2H, d, ArH), 7.58 (2H, d, ArH), 9.49 (1H, s, NH). ^{13}C NMR (500 MHz, DMSO): δ 176.5, 166.3, 165.6, 139.0, 132.9, 130.8, 121.9, 67.8, 45.2, 27.1, 22.3. MS (ESI) *m/z* 286.1 $[M+1]^+$. ESI-HRMS *m/z* calcd for $C_{15}H_{20}N_5O^+$ $[M+H]^+$ 286.1668, found 286.1659.

*4.4.3. N-(2-Nitrophenyl)-6-(trifluoromethyl)-N-(3,4,5-trimethoxyphenyl)-1,3,5-triazine-2,4-diamine (**5b$_1$**).* Yield 74.1%, yellow solid, mp 184 °C; ^{1}H NMR (250 MHz, DMSO, 363 K): δ 3.69 (9H, s, OCH_3), 7.0 (2H, s, ArH), 7.43 (1H, t, ArH), 7.72 (1H, t, ArH), 7.94 (1H, d, ArH), 8.05 (1H, d, ArH), 9.95 (2H, s, NH). ^{13}C NMR (500 MHz, DMSO, 363 K): δ 166.7, 165.9, 165.2, 154.7, 144.6, 137.3, 136.0, 135.7, 133.8, 128.8, 127.6, 127.0, 121.8, 119.6, 102.5, 62.1, 58.2. MS (ESI) *m/z* 467.1 $[M+1]^+$. ESI-HRMS *m/z* calcd for $C_{19}H_{18}F_3N_6O_5^+$ $[M+H]^+$ 467.1291, found 467.1277.

*4.4.4. 6-Methyl-N-(2-nitrophenyl)-N-(3,4,5-trimethoxyphenyl)-1,3,5-triazine-2,4-diamine (**5b$_2$**).* Yield 80.1%, yellow solid, mp 214 °C; ^{1}H NMR (250 MHz, DMSO): δ 2.27 (3H, s, CH_3), 3.62 (3H, s, OCH_3), 3.66 (6H, s, OCH_3), 7.06 (2H, s, ArH), 7.35 (1H, t, ArH), 7.72 (1H, t, ArH), 8.02 (2H, m, ArH), 9.66 (1H, s, NH), 9.94 (1H, s, NH). ^{13}C NMR (500 MHz, DMSO): δ 177.7, 166.5, 165.8, 154.7, 144.3, 137.2, 136.1, 135.5, 133.6, 128.5, 127.7, 127.0, 102.4, 62.1, 58.2, 26.7. MS (ESI) *m/z* 413.1 $[M+1]^+$. ESI-HRMS *m/z* calcd for $C_{19}H_{21}N_6O_5^+$ $[M+H]^+$ 413.1573, found 413.1559.

4.5. General procedure for the synthesis of *N*-4-substituted 1,3,5-triazine-2,4-diamine 4

A mixture of sodium methoxide (0.75 mmol, 1.5 equiv) prepared from Na and methanol, arylbiguanide hydrochloride (0.5 mmol, 1 equiv) and ester (1.5 mmol, 3 equiv) in dry THF (3 ml) was introduced into a 50 ml round-bottomed flask equipped with a condenser and a magnetic stirring bar. The flask was placed in the microwave cavity and exposed to microwave irradiation for 20 min at 70 °C using irradiation power of 100 W. On cooling to room temperature, the mixture was evaporated under vacuum, and the residue was subjected to flash chromatography (silica gel, 5% methanol/CH_2Cl_2) to afford the desired product as a white solid.

*4.5.1. 6-Methyl-N-morpholino-1,3,5-triazine-2,4-diamine (**4a**).* Yield 88%, white solid, mp 192 °C; ^{1}H NMR (250 MHz, DMSO): δ 2.13 (3H, s, CH_3), 3.6 (4H, t, 2× CH_2), 3.67 (4H, t, 2× CH_2), 6.75 (2H, s, NH_2). ^{13}C NMR (500 MHz, DMSO): δ 176.3, 168.6, 166.5, 68.0, 45.0, 27.0. MS (ESI) *m/z* 196.1 $[M+1]^+$. ESI-HRMS *m/z* calcd for $C_8H_{14}N_5O^+$ $[M+H]^+$ 196.1198, found 196.1185.

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Supplementary data

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