An Efficient, "Green" Approach to Aryl Amination of Cyanuric Chloride Using Acetic Acid as Solvent

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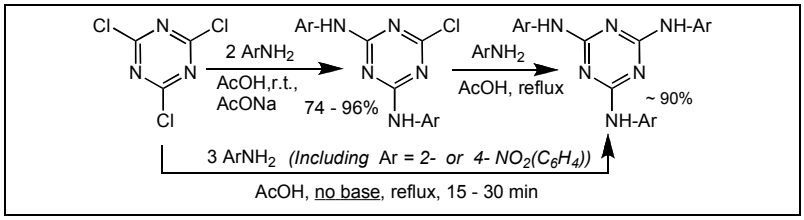

Acetic acid is an inexpensive and environmentally friendly solvent for facile, clean and high-yielding aryl amination of cyanuric chloride with aromatic amines, including nitroanilines. Aryl amination in acetic acid medium and isolation protocol are greatly simplified as compared to previously reported procedures. Under proper conditions, it is possible to attach the same or different aniline residues in a controlled way to obtain in excellent yields symmetrical and unsymmetrical 1,3,5-triazine derivatives, respectively.

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INTRODUCTION

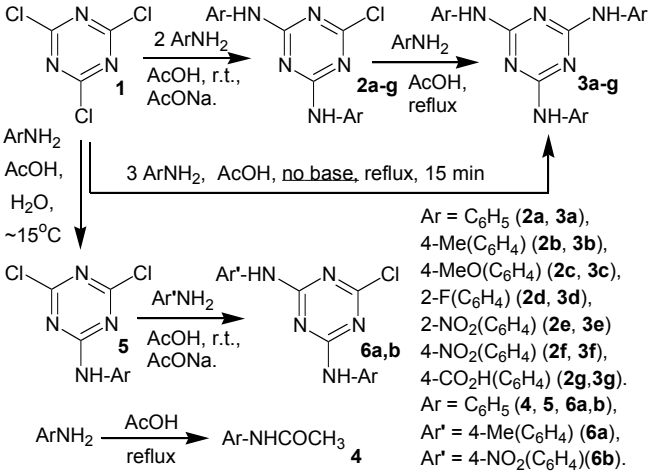
It has been known for 60 years that amines react with cyanuric chloride (2,4,6-trichloro-1,3,5-triazine (**1**, Scheme I)), providing access to amine-functionalized 1,3,5-triazine compounds [1]. 1,3,5-Triazine rings with *aryl* amine substituents (*e.g.*, **2** and **3**, Scheme I) are of particular interest because many of these compounds are biologically active [2]. Also, compounds with the general structure **3** (Scheme I) are potentially useful as inexpensive and non-toxic UV-absorbents [3] and pigments [4]. Finally, dendritic polymers, with potential materials applications, can be built from aromatic amine-functionalized 1,3,5-triazine rings [5].

Despite the merits of 1,3,5-triazine molecules with two or three aryl amine groups attached to the ring, existing syntheses of such compounds leave much to be desired. Compared to the reactions of *aliphatic* amines ($AlkNH_2$), [2,3] amination of **1** with less nucleophilic *aromatic* amines (anilines, $ArNH_2$) is more difficult to achieve, especially if trisubstituted (**3**) products are desired [3,9]. The difficulty is exacerbated if the aromatic group of the amine bears an electron-withdrawing group (*e.g.*, 4-nitroaniline, 4-$NO_2(C_6H_4)NH_2$), which further decreases the nucleophilicity of the amine. Thus, established synthetic routes to molecules of type **2** and **3** (Scheme I) generally involve long reaction times, elevated temperatures [1c] and give moderate yields after purification [5]. Further, all reported amination reactions of compound **1** utilize bases (normally heterogeneous) to remove hydrogen chloride generated as a byproduct, which complicates isolation of the aminated product.

No "green" (environmentally innocuous) syntheses of these compounds have been reported: previously published routes [1-6] to aminated 1,3,5-triazine rings have employed toxic organic solvents such as 1,4-dioxane or dimethylforamide (DMF).

Scheme I

Aryl Amination of Cyanuric Chloride (**1**) with Aromatic Amines in Acetic Acid Medium



In 2003, Sha and Dong [3] reported that the aryl amination reactions of **1** are drastically accelerated by microwave radiation, such that compounds of type **3** can be obtained in greatly reduced reaction times, compared to conventional approaches. As an illustrative example, it was claimed that **1** reacts with 3 equiv of 4-nitroaniline to give product **3f** (Ar = 4-$NO_2(C_6H_4)$, see Scheme I/Table 2 for structures) in *minutes*, while a previously reported synthesis (see below) of this compound required *hours* at elevated temperatures [5] to obtain complete reaction [1c].

While microwave-assisted routes to **2** and **3** might be promising, there are some drawbacks to the approach of Sha and Dong. For instance, microwave-assisted syntheses do not allow the selective formation of mono- (**5**) and diaminated (**2**) products; the triaminated products (**3**) form quickly to the exclusion of partially substituted derivatives. Also, isolation of aminated products requires (a) removal of high-boiling solvents (DMF or dioxane) under reduced pressure, (b) extraction of the solid residue with water to remove NaCl and $NaHCO_3$, and (c) recrystallization. It should be reiterated that similarly difficult purification procedures are common to all previously reported syntheses of aryl amine-functionalized 1,3,5-triazine compounds, where high-boiling solvents and HCl acceptors are required. Finally, the authors did not provide NMR spectroscopic data for compound **3f** and reported a melting point range of 154-160°C. Compound **3f** was originally made by Takagi and co-workers [5] by refluxing **1** and 4-$NO_2(C_6H_4)NH_2$ in dioxane for 17 h, in the presence of K_2CO_3. The isolated compound was characterized by ^{1}H NMR spectroscopy and was reported to have a melting point (presumably with decomposition) above 300°C. Our NMR data and melting point range for compound **3f**, synthesized by our new method (see below), agree with those presented by Takagi *et al* [5]. In light of these discrepancies, the efficacy of the microwave-assisted synthesis of **3f** is subject to scrutiny.

Our goal was to develop a new, more efficient approach to aryl amination of cyanuric chloride (**1**) with various aromatic amines in a controlled fashion. In particular, we sought to reduce reaction times, especially for the final third stage of substitution, simplify product isolation and increase yields. Also, we were motivated to find green, cost-effective routes to symmetrical and unsymmetrical aminated 1,3,5-triazine compounds, which are amenable to large-scale industrial processes. In this regard, protocols that do not require solvent, or that use non-toxic, inexpensive solvent(s), are particularly desirable.

RESULTS AND DISCUSSION

We first investigated solvent-free methods to generate amine-functionalized 1,3,5-triazine products but found this approach to be unfeasible. Problems with solvent-free syntheses include the large exotherms associated with amination of **1**, which pose safety concerns, especially when large-scale reactions are considered. Also, we found it impossible to achieve selectivity, with regard to the degree of amine substitution (*i.e.*, mixtures of mono- (**5**), di- (**2**) or tri-substituted products (**3**) were generated), in the absence of solvent. Further complications arise when the aniline starting material is a high-melting solid, or when high-melting solids are generated by the first or second substitution step. Finally, HCl salts of the aniline reagents are generated in the course of solvent-free reactions, which must be separated from unreacted aniline (used in excess) and aminated products.

Having ruled out solvent-free protocols, we began the search for a new solvent for the aryl amination reactions of **1**. In our view, amination of **1** is a special case of nucleophilic aromatic substitution. Polar solvents normally favor this type of reaction [8]. However, converting **1** to its trisubstituted aryl amine derivatives (compounds of type **3**) is generally slow [1c] in conventional polar (and toxic) organic solvents such as DMF, THF, and dioxane [5], even at elevated temperature. Note that DMSO, a polar and high-boiling solvent, reacts vigorously [9] with **1** and, therefore, can be ruled out as a solvent for these amination reactions. In the context of "green" solvents, water is an obvious choice, especially when high polarity is desired. However, water is also unsuitable as a solvent for these aryl amination reactions because the C-Cl bonds of **1** undergo hydrolysis [1c] at rates competitive with the desired amination reactions [10]. Also, the low solubility of the aniline reagents and the aminated products, led to further complications when water was used as solvent.

As shown above, potential solvents for the aryl amination reactions of **1** should be polar and high-boiling in order to facilitate the second or third substitution steps. Ideally, the solvent would also be inexpensive and inoffensive to the environment (*i.e.*, "green").

With these considerations in mind, we tested CH_3COOH/CH_3COONa as a solvent system for the aryl amination of **1**, where acetic acid would serve as solvent and sodium acetate would act as an acceptor of HCl. Initial results showed aryl amination of **1** does, indeed, occur in this medium. In fact, we discovered that the reaction in acetic acid proceeds even in the absence of CH_3COONa. Further, an excess of $ArNH_2$, which could potentially serve as an HCl acceptor, is not required. Upon combination of **1** with aromatic amines, reaction occurs immediately, as evidenced visually by the evolution of HCl. The progress of the reactions was monitored by TLC or HPLC. While mono- (**5**) and disubstituted (**2**) aryl amine derivatives of **1** are readily formed at or below room temperature, we found it necessary to heat (100°C) the reaction mixtures to obtain trisubstituted aryl amine species (**3**). For example, in the reaction between **1** and 3 equiv of aniline, conversion to trisubstituted **3a** (Ar = Ph) was not complete (60-70 % conversion) after 24 h at ambient temperature (20-25°C). However, **3a** was formed in high yield (up to 96%, isolated, see Table 1 and Experimental Section) by heating the reaction mixture to reflux (118°C) for 15 min or for 30 min at 100 °C. Table 1 compares the reactions of **1** with aniline ($PhNH_2$) or less reactive 2-nitroaniline (2-$NO_2(C_6H_4)NH_2$)) in various solvents. Note that, in contrast to conventional approaches, we did not use base

(to accept HCl) in these reactions. It is seen that, in all of the reactions examined, conversion to trisubstituted products (**3a** or **3e**) is fastest in acetic acid, compared to conventional, high-boiling organic solvents. The advantage of using acetic acid is more pronounced in the reactions of less nucleophilic 2-nitroaniline.

Table 1

Aryl Amination of Cyanuric Chloride[a] **1** in some high-boiling solvents at 100°C in the absence of base.

Solvent	Yields[b] (%) of Compounds **3a** or **3e**[c] (See Scheme I) in Reaction of **1** with 3 equiv of:	
	Aniline	2-Nitroaniline
Acetic acid	93	73
DMF	68	22
1,4-Dioxane	43	15
1-Butanol	25	12
Toluene	22	9

[a] – 3 equiv (3 mmol) of the aniline were added to 1 equiv (1 mmol) of 1 in the solvent (5 ml of 0.2 M solution) and then heated for 30 min at 100°C (no base added).
[b] – The yields of **3** were evaluated with 5 % accuracy by HPLC.
[c] – the rest of the chloride 1 formed disubstituted products **2**.

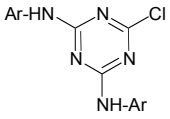
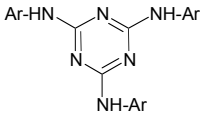
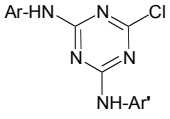
Clearly, if acetic acid is to be used as a solvent for the aryl amination reactions of **1**, then **1** must be reasonably stable in this medium. That is, if acetic acid induces cleavage of the C-Cl bonds in **1**, the rate of the decomposition pathway (solvolysis) must be much smaller than the rate of the desired amination reactions. It was reported [1c] that **1** undergoes solvolysis when refluxed in a large excess of acetic acid. However, we found that **1** is stable in acetic acid at room temperature; the ^{1}H or ^{13}C NMR spectra of **1** in CD_3COOD solution are invariant over 2 days at ambient temperature. When solutions of **1** are heated to reflux (118°C, 1 h) in acetic acid, solvolysis gives 70-80 % conversion to acetyl chloride and cyanuric acid (identified by mass spectrometry). Further experiments established that solvolysis of **1** is negligible, even at high temperatures, if a nucleophile, such as $ArNH_2$, is present, because amination occurs at a larger rate than the decomposition pathway. Another concern was the potential reactivity of hydrogen chloride (generated upon amination of **1**) towards acetic acid and aniline substrates. N-Acetyl anilines (**4**) were formed only in trace amounts; we propose that these acylated byproducts arise from the slight excess (5-10%) of aniline reagents used in preparative scale syntheses of compounds of type **3**. Indeed, aniline forms N-acetyl aniline **4** (Ar = Ph) with a high yield (> 80%) when refluxed in a large excess of acetic acid for 1 h in the absence of cyanuric chloride **1** (Scheme I). Perhaps most importantly, we did not observe the precipitation of HCl salts of aryl amine reagents in the course of amination of **1**. Presumably, the formation of aryl amine hydrochlorides is reversible in acetic acid. It is known that the acid strength of HCl is considerably lower in acetic acid medium than in water [8,11]. Also, the HCl salts are very likely to possess high solubility in polar protonic solvents. Note that the basicity of amino groups in compounds **2**, **3**, **5** and **6** is considerably decreased when attached to the 1,3,5-triazine core because of the electron withdrawing nature of this group. Hence, the aminated products, generated by amination of **1**, are not expected to be protonated by HCl to a significant extent [10]. As a result, yields are not negatively affected.

In our study, we investigated seven anilines, with a range of electronic properties, as substrates for the amination of **1** in acetic acid. For all seven substrates, including 4-aminobenzoic acid, 2- and 4-nitroanilines, we were able to selectively synthesize both di- (**2a-g**) and tri-substituted (**3a-g**) aryl amine 1,3,5-triazine compounds (Table 2) in high yields. As stated above, both of these classes of molecules are of interest for biological and/or materials applications. Compounds of type **2** are interesting reagents for combinatorial syntheses because they contain a reactive functional group CCl. Another reason to prepare compounds **2** was that, since the final third stage of substitution in **1** is normally difficult to achieve [1,5], we needed authentic samples of di-substituted compounds to check the purity of the corresponding tri-substituted compounds (**3**) by means of chromatographic analysis and spectroscopic study (see Experimental Section for details). Additionally, as reagents for possible combinatorial syntheses, other two new compounds of type **2** were prepared from 2,4- and 3,5-dimethylanilines (**2h** and **2i**, respectively).

Of the substrates examined in the aryl amination reactions of **1**, nitro-substituted anilines ($2\text{-}NO_2(C_6H_4)NH_2$ and $4\text{-}NO_2(C_6H_4)NH_2$) were the least reactive, as expected on the basis of their decreased nucleophilicity. The challenge in synthesizing compounds **2e** and **3e** (Ar = $2\text{-}NO_2(C_6H_4)$) from 2-nitroaniline is related to the low nucleophilicity of the aniline substrate ($2\text{-}NO_2(C_6H_4)NH_2$), which is impeded not only by the electron-withdrawing effect of the nitro group but also by steric hindrance in the vicinity of the nitrogen atom (see Table 1 for structures). It should be noted that compounds **2e** and **3e** (Ar = $2\text{-}NO_2(C_6H_4)$) have *not* been reported previously, while a considerable amount of other compounds of types **2** and **3**, with a wide range of substituents in benzene rings, have been synthesized by conventional methods [2]. Having obtained good results with the least reactive amine, we believe that, apart from the representative substrates (Table 2), our approach can be extended to aromatic amines of greater diversity.

Table 2

Aryl Amination of Cyanuric Chloride **1** with Aromatic Amines in Acetic Acid Medium.

Product structure	Compd №	Ar	Yield[a], (%), Method	
			A[c]	B[d]
	**2a**[b]	C_6H_5	96	65
	2b[b]	4-$CH_3(C_6H_4)$	94	74
	2c[b]	4-$CH_3O(C_6H_4)$	97	67
	2d[b]	2-$F(C_6H_4)$	92	62
	2e	2-$NO_2(C_6H_4)$	29	68
	2f[b]	4-$NO_2(C_6H_4)$	76	72
	2g[b]	4-$CO_2H(C_6H_4)$	74	69
	2h	2,4-*Di*-$CH_3(C_6H_3)$	95	70
	2i	3,5-*Di*-$CH_3(C_6H_3)$	93	76
	**3a**[b]	C_6H_5	93	
	3b[b]	4-$CH_3(C_6H_4)$	96	
	3c	4-$CH_3O(C_6H_4)$	94	
	3d[b]	2-$F(C_6H_4)$	89	
	3e	2-$NO_2(C_6H_4)$	86	
	3f[b]	4-$NO_2(C_6H_4)$	92[c]	
	3g[b]	4-$CO_2H(C_6H_4)$	88	
		Ar / Ar'		
	**6a**[b]	C_6H_5 / 4-$CH_3(C_6H_4)$	98	
	6b	C_6H_5 / 4-$NO_2(C_6H_4)$	91	

[a] – yields refer to isolated products with purity ≥ 98% (HPLC). [b] – known compounds; see ref. [3,5,6,12]. [c] – see Expt. Section for details. [d] – yields after recrystallization.

The compounds synthesized in this study are summarized in Table 2. All products were characterized by $^1H/^{13}C$ NMR, and IR spectroscopy, high resolution mass spectrometry and by melting point determination. In addition, elemental analyses were done to all new compounds. Our melting point data for known compounds (**2a**, **2b**, **2c**, **2d**, **2f**, **2g**, **3a**, **3b**, **3d**, **3f, 3g**, and **6a**) agreed with literature reports [3,5,6,12]. As seen in Experimental Section, one can easily distinguish the tri-substituted derivatives (**3**) from the di-substituted ones (**2**) by means of ^{13}C NMR spectroscopy. In particular, for compounds **2**, the characteristic signals belonging to carbon atoms C6, attached to the chlorine (see Table 2 for structures), were observed in the low-field (163 – 165 ppm) area. Despite the informativity nature of the method, none of those compounds has been characterized by ^{13}C NMR spectroscopy so far. Products of type **2**, **3** and **6** were conveniently isolated by filtration; in all cases these species are only sparingly soluble in acetic acid. Thus, purification requires only washing the solid precipitates with boiling water to remove the acetic acid. As seen in Table 2, isolated yields for all compounds range from good to excellent, for the reactions conducted in acetic acid. Even though the second and the third steps of the substitution do proceed in the absence of bases, as we established, better isolated yields of compounds **2** were achieved when sodium acetate was used as HCl acceptor, and some water was added to assist product precipitation and thus omit recrysctallization from suitable solvents. (Compare conditions for Methods A and B in Experimental Section). Method A, which utilizes CH_3COONa, requires shorter time to complete the reactions and, as seen in Table 2, gives better yields for all the aniline substrates, except 2-nitroaniline. In fact, both procedures are homogeneous, and crystalline solids start to precipitate soon after the reagents are combined. In Method A, sodium chloride (byproduct) remains in the solution.

Meanwhile, we found that the final third stage of substitution in **1**, when performed in acetic acid, is very slightly influenced by the addition of CH_3COONa or pyridine. As we expected, all the di-substituted compounds **2** formed the corresponding tri-substituted compounds **3** with high (≥ 90%) yields simply upon heating (118°C) with 1 equiv of the corresponding aniline substrates in acetic acid for 15 min (Scheme I). Clearly, it is more convenient to prepare compounds **3** straight from cyanuric chloride (**1**) by heating it with 3 equiv of the aniline substrates in acetic acid to reflux (see Experimental Section for General Procedure).

In addition to compounds of type **2** and **3**, where the aryl amine groups attached to the 1,3,5-triazine scaffold are identical, we were able to apply our acetic acid method to the syntheses of unsymmetrical 6-chloro-*N,N*'-diaryl-[1,3,5]triazine-2,4-diamines (type **6**). With three different groups (CCl, NHAr and NHAr') on the 1,3,5-triazine moiety, these molecules are very interesting for combinatorial applications; again, it should be possible to generate libraries of new amine-substituted 1,3,5-triazines with potential biological activity and/or materials applications. We made these unsymmetrical species (type **6**) by installation of a single aryl amine group of the triazine ring, to give compounds of type **5**, followed by another aryl amine substitution step to generate molecules with the general structure **6**. We found that both substitution steps can be accomplished in acetic acid, with high selectivity/yields, as seen in Table 2 (see Experimental Section for conditions). While mono-substituted compounds **5** are accessible by classical procedures (*via* temperature-controlled reactions between **1** and $ArNH_2$ in acetone/water [1]), our alternative syntheses in acetic acid have the advantages of higher yields and greater ease of work-up.

CONCLUSIONS

In summary, we have developed efficient synthetic approaches to mono- (**5**), di- (symmetrical (**2**) and unsymmetrical (**6**) and tri- (**3**) aryl amine functionalized 1,3,5-triazines. Under proper conditions, it is possible to selectively add different anilines in a controlled fashion to cyanuric chloride (**1**) to get unsymmetrical triazines in excellent yields; even with non-nucleophillic anilines. This approach utilizes acetic acid as solvent, which is inexpensive and non-toxic (environmentally friendly) and, therefore, amenable to large-scale industrial processes. Low flammability is also very important. Also, acetic acid is volatile, miscible with water and most organic solvents. Therefore, it is much easier to completely remove residual acetic acid from solid reaction products than such popular "green" solvents as polyethylene glycol or ionic liquids [7]. Further, in the context of industrial applications, the acetic acid could easily be recycled: once the acetic acid-insoluble aminated products are removed from the reaction medium by filtration, only HCl-saturated acetic acid remains. The hydrogen chloride can be removed from the solvent conveniently under reduced pressure or by boiling/bubbling air through the liquid. Further purification (if necessary) can be achieved by means of fractional freezing/thawing (freezing point of acetic acid = 17°C). The chemistry described here is exceptionally clean; all products were isolated in good to excellent yields, with shorter reaction times, compared to conventional approaches. Importantly, in our method, purification/isolation of aminated products is greatly simplified, relative to previously reported syntheses of aminated triazine compounds. Because hydrogen chloride acceptors are not required, and aryl amine products are insoluble in acetic acid, product isolation requires only filtration. On-going investigations are focused on determining why acetic acid is superior to conventional polar organic solvents in the aryl amination.

EXPERIMENTAL

General. All chemicals were purchased from Aldrich Chemical Company and used as received. Progress of the reactions was monitored by HPLC or TLC on silica gel SIL G/UV 254 plates. The chromatograms were developed in chloroform/hexanes (4:1 v/v) or chloroform/acetone (15:1 v/v) (for reactions involving nitro- substituted derivatives). HPLC was performed using 5500 Varian Vista chromatograph equipped with Waters Symmetry C-18 reverse-phase column (4.6/150 mm, 5μ particle size, methanol/water 80:20 v/v as liquid phase). Mass-spectra were recorded on Micromass 70S-250 sector mass and IR – on Shimadzu FTIR 8700 spectrometers. NMR spectra were taken using Varian spectrometer at 300 MHz (H^1) and 75 MHz (C^{13}). Elemental analyses were carried out at Guelph Laboratories, Guelph ON, Canada. Melting points were measured in capillary tubes and are uncorrected. Acetic acid (Aldrich, ACS reagent grade, 99.7%) was freshly distilled and subjected to fractional crystallization for initial experiments. Later, in all the procedures described below acetic acid was used without purification.

General Procedure for Aryl Amination of Cyanuric Chloride with 3 Equiv of Aromatic Amines in Acetic Acid Medium to Give Compounds of Type 3. (See Table 2 for the yields). Cyanuric chloride **1** (1.84 g, 0.01 mol) was added in one portion to a stirred solution of the aromatic amine (aniline) substrate (0.033 mol) in 75 mL of glacial acetic acid (AcOH), and the mixture was heated (30 min, steam bath (100°C) or 15 min, reflux (118°C)) immediately after the addition of aniline. The products precipitated from solution as white or yellow solids and were recovered by filtration. The solid products were washed with boiling water (approximately 20 mL x 3) to neutral pH and dried at 90°C in air to afford compounds **3** with high purity (≥ 98 %; HPLC, NMR). See below for characterization data/spectral assignments. Analytical samples of compounds 3 were recrystallized from suitable solvents (see below), boiled with water to completely remove the solvents and dried under vacuum.

***N,N',N''*-Triphenyl-[1,3,5]triazine-2,4,6-triamine (3a).** Colorless crystals; mp 229–230°C (isopropanol); reported mp 232 °C [3]; ir (KBr): 3260, 1570, 1521, 1230 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.12 (t, *J* = 7.5 Hz, 1H, Ph), 7.70 (d, *J* = 7.5Hz, 2H, Ph), 7.34 (t, *J* = 7.8Hz, 2H, Ph), 10.31 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 122.47, 124.87, 128.97, 129.17, 137.62; MS (EI, 70 e V): *m/z* (%) = 354 (100, M^+), 262 (25, M^+– Ph-NH); HRMS (EI) Calcd. for (M^+) $C_{21}H_{18}N_6$ 354.1593. Found: 354.1601.

***N,N',N''*-Tri-*p*-tolyl-[1,3,5]triazine-2,4,6-triamine (3b).** Colorless crystals; mp 236–237°C (isopropanol); reported 238–239 °C [3]; ir (KBr): 3260, 1570, 1521, 1230 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 7.52 (d, *J* = 6,6Hz, 2H, *p*-C_6H_4), 7.13 (d, *J* = 6,6Hz, 2H, *p*-C_6H_4), 10.34 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 21.11 (CH_3), 122.41 (br.), 129.41, 134.14, 134.88; MS (EI, 70 e V): *m/z* (%) = 396 (100, M^+), 305 (25, M^+– Tol), 106 (45, M^+– Tol-NH); HRMS (EI) Calcd. for (M^+) $C_{24}H_{24}N_6$ 396.2062. Found: 396.2059.

***N,N',N''*-Tris-(4-methoxyphenyl)-[1,3,5]triazine-2,4,6-triamine (3c).** Colorless crystals; mp 214–216 °C (isopropanol); ir (KBr): 3230, 1580, 1510, 1240 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.78 (s, 3H, OCH_3), 6.87 (m, 2H, *p*-C_6H_4), 7.54 (m, 2H, *p*-C_6H_4), 10.29, (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 55.41 (OCH_3), 113.95, 122.87, 124.05, 130.49, 156.81 (C_{Ar}-OCH_3); MS (EI, 70 e V): *m/z* (%) = 444 (100, M^+), 429 (35, M^+– CH_3), 412 (5, M^+– OCH_3), 322 (10, M^+– NHPh-OCH_3); HRMS (EI) Calcd. for (M^+) $C_{24}H_{24}N_6O_3$ 444.1910, Found: 444.1915; *Anal.* Calcd.: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.51; H, 5.49; N, 18.74.

***N,N',N''*-Tris-(2-fluorophenyl)-[1,3,5]triazine-2,4,6-triamine (3d).** Colorless crystals; mp 169–170°C (isopropanol); reported 173–174 °C [3]; ir (KBr): 3230, 1580, 1530, 1255 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.21 – 7.84 (m, $3H_{Ar}$), 7.85 (m, $1H_{Ar}$), 8.61 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 115.43, 115.69, 124.20, 124.05, 127.28, 127.43, 168.21 (C-F); MS (EI, 70 e V): *m/z* (%) = 408 (25, M^+), 389 (100, M^+ – F), 370 (20, M^+ – 2F), 298(10, M^+– NH-Ph-F); HRMS (EI) Calcd. for (M^+) $C_{21}H_{15}F_3N_6$ 408.1310. Found: 408.1312.

***N,N',N''*-Tris-(2-nitrophenyl)-[1,3,5]triazine-2,4,6-triamine (3e).** Yellow crystals (isopropanol); t. decomp. ≥ 300 °C; ir (KBr): 3360, 1620, 1590, 1510, 1330, 1240 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.31 (m, $1H_{Ar}$), 7.68 (m, $1H_{Ar}$), 8.05

(m, $2H_{Ar}$), 9.88 (s, 1H, NH). ^{13}C nmr (DMSO-d_6): δ 104.79, 115.40, 119.59, 125.70, 131.04, 135.37, 146.62; MS (EI, 70 e V): *m/z* (%) = 489 (30, M^+), 443 (100, $M^+ - NO_2$), 397 (10, $M^+ - 2NO_2$), 351 (12, $M^+ - 3NO_2$); HRMS (EI) Calcd. for (M^+) $C_{21}H_{15}N_9O_6$ 489.1145. Found 489.1150; *Anal*. Calcd.: C, 51.54; H, 3.09; N, 25.76. Found: C, 51.33; H, 2.92; N, 25.48.

4,4',4''-([1,3,5]-Triazine-2,4,6-triyltriimino)tribenzoic acid (3g). Colorless crystals (isopropanol); t. decomp. ≥ 330 °C; reported mp 378–380 °C [12]; ir (KBr): 3300 – 3100 (br. m), 1610, 1560, 1530, 1330, 1240 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.96 (d, *J* = 8 Hz, 2H, *p*-C_6H_4), 8.12 (d, *J* = 8 Hz, 2H, *p*-C_6H_4), 10.11 (br. s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 120.44, 122.31, 124.14, 135.14, 139.71, 192.30 (CO_2H); MS (EI, 70 e V): *m/z* (%) = 486 (15, M^+), 442 (100, $M^+ - CO_2$), 398 (10, $M^+ - 2\ CO_2$); HRMS (EI) Calcd. for (M^+) $C_{24}H_{18}N_6O_6$ 486.1288, Found: 486.1281.

***N,N',N''*-Tris-(4-nitrophenyl)-[1,3,5]triazine-2,4,6-triamine (3f)** was prepared as follows: The solution of **1** (1.84 g, 0.01 mol) in 30 mL of AcOH was added within 3 min to a boiling solution of 6.20 g (0.045 mol) of 4-nitroaniline in 60 mL of AcOH. The mixture was refluxed for 30 min, a yellow precipitate was filtered and boiled with ~ 100 mL of water to remove the solvent to give 92% of **3f** as yellow crystalline powder (analytical sample was recrystallized from DMF – isopropanol). Properties: t. decomp. ≥ 300 °C (as reported previously [5]); ir (KBr): 3340, 1630, 1590, 1510, 1340, 1240 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.11 (d, *J* = 8 Hz, 2H, *p*-C_6H_4), 8.17 (d, *J* = 8 Hz, 2H, *p*-C_6H_4), 10.23 (s, 1H, NH); (in accordance with reported [5]). ^{13}C nmr (DMSO-d_6): δ 119.99, 120.44, 124.99, 125.06, 146.61; MS (EI, 70 e V): *m/z* (%) = 489 (12, M^+), 443 (100, $M^+ - NO_2$), 397 (7, $M^+ - 2\ NO_2$); HRMS (EI) Calcd. for (M^+) $C_{21}H_{15}N_9O_6$ 489.1145, Found: 489.1149.

General Procedure for Aryl Amination of Cyanuric Chloride with 2 Equiv of Aromatic Amines in Acetic Acid Medium to Give Compounds of Type 2. (See Table 2 for the yields). **Method A.** (With sodium acetate as HCl acceptor, and water added. Provides excellent yields for all the compounds **2**, except *ortho*-nitro derivative **2e**; See Table 2)

A solution of 1 (18.4 g, 0.1 mol) in 300 mL of AcOH and solutions of 0.21 mol of the aniline substrates with 34 g (0.25 mol) of sodium acetate trihydrate ($CH_3COONa \times 3H_2O$) in the mixture of 100 mL of AcOH and 100 mL of H_2O were combined at r.t. and then slightly cooled to maintain the temperature below 25°C. The resulting solutions were left for 2–4 h or overnight (for compound 2f (Ar = 4-$NO_2(C_6H_4)$); the completion of the reactions was checked by TLC. The precipitates were separated by filtration and washed with boiling water (150 mL × 2) to neutral pH. All the chlorides of type **2** were isolated with high purity (≥ 98 %; HPLC, NMR) after filtration. Analytical samples were recrystallized from suitable solvents and dried under vacuum.

Method B. (In glacial acetic acid, with no HCl acceptors added. Provides good yield for 6-chloro-N,N'-bis-(2-nitrophenyl)-[1,3,5]triazine-2,4-diamine (**2e**) and for the rest of compounds **2**; See Table 2).

Solutions of **1** (1.84 g, 0.01 mol) in 30 mL of AcOH and the aniline substrates (0.02 mol, (2 equiv each)) in 30 mL of AcOH were combined at room temperature and then left overnight. The precipitates were collected and recrystallized from isopropyl alcohol or acetone to afford pure (≥ 98 %; HPLC, NMR) compounds.

6-Chloro-*N,N'*-diphenyl-[1,3,5]triazine-2,4-diamine (2a). Colorless crystals; mp 197–198 °C (benzene); reported mp 191°C [5]; ^1H nmr (DMSO-d_6): δ 7.03 (t, *J* = 7.8 Hz, 1H, Ph), 7.28 (t, *J* = 7.8 Hz, 2H, Ph), 7.70 (br. s, 2H, Ph), 10.16 (s,1H, NH); ^{13}C nmr (DMSO-d_6): δ 121.31, 123.43, 128.55, 139.00, 164.31(C-Cl).

6-Chloro-*N,N'*-di-*p*-tolyl-[1,3,5]triazine-2,4-diamine (2b). Colorless crystals; mp 199–201 °C (isopropanol); reported 204–206 °C [6]; ir (KBr): 3260, 1570, 1521, 1230 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 7.21 (d, *J* = 6,3 Hz , 2H, *p*-C_6H_4), 7.61 (d, *J* = 6,3 Hz, 2H, *p*-C_6H_4), 10.38 (s,1H, NH);^{13}C nmr (DMSO-d_6) δ 20.53 (CH_3), 121.11, 129.03 (br.), 123.69, 135.81, 163.87 (C-Cl); MS (EI, 70 e V): *m/z* (%) = 325 (100, M^+), 234 (15, M^+ – Tol), 290 (55, M^+– Cl), 219 (10, M^+ – Tol-NH); HRMS (EI) Calcd. for (M^+) $C_{17}H_{16}ClN_5$ 325.1094. Found 325.1096.

6-Chloro-*N,N'*-bis-(4-methoxyphenyl)-[1,3,5]triazine-2,4-diamine (2c). Colorless crystals; mp 198–189°C (isopropanol); reported 202–203 °C [6]; ir (KBr): 3230, 1580, 1510, 1240 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.81(s, 3H, OCH_3), 6.93 (d, *J* = 9 Hz, 2H, *p*-C_6H_4), 7.61 (d, *J* = 9 Hz, 2H, *p*-C_6H_4), 10.35 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 55.31 (OCH_3), 113.79, 122.31, 122.85, 131.31, 155.74, (C_{Ar}-OCH_3), 163.84 (CCl); MS (EI, 70 e V): *m/z* (%) = 357 (100, M^+), 342 (35, $M^+ - CH_3$), 322 (30, M^+ – Cl), 234 (10, M^+ – NH-Ph-OCH_3); HRMS (EI) Calcd. for (M^+) $C_{17}H_{16}ClN_5O_2$: 357.0993. Found 357.0988.

6-Chloro-*N,N'*-bis-(2-fluorophenyl)-[1,3,5]triazine-2,4-diamine (2d). Colorless crystals; mp 144–146 °C (isopropanol); ir (KBr): 3230, 1580, 1530, 1255 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.22-7.41 (m, $3H_{Ar}$), 7.96 (br. s, $1H_{Ar}$) 8.72 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 115.69, 115.95, 124.22, 125.23, 125.38, 126.97 (br), 164.91, (C-Cl), 168.91 (C-F); MS (EI, 70 e V): *m/z* (%) = 333 (100 M^+), 314 (55, M^+- F), 298 (40, M^+– Cl), 223 (10, M^+– NHPh-F); HRMS (EI) Calcd. for (M^+) $C_{15}H_{10}ClF_2N_5$: 333.05927. Found: 333.05980.

6-Chloro-*N,N'*-bis-(2-nitrophenyl)-[1,3,5]triazine-2,4-diamine (2e). Colorless crystals; mp 199 –201 °C (isopropanol); ir (KBr): 3360, 1620, 1590, 1510, 1330, 1240 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.56 (m, $1H_{Ar}$), 7.78 (m, $1H_{Ar}$), 8.05(m, $2H_{Ar}$), 11.42 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 125.66, 127.76, 128.04, 129.99, 134.47, 144.13, 164.89, (C-Cl); MS (EI, 70 e V): *m/z* (%) = 387 (100, M^+), 341 (65, M^+- NO_2), 351 (10, M^+ – Cl), 249 (10, M^+ – NHPh-NO_2); HRMS (EI) Calcd. for (M^+) $C_{15}H_{10}ClN_7O_4$ 387.04829, Found: 387.04963; *Anal*. Calc.: C, 46.46; H, 2.60; N, 25.29; Found: C, 46.13; H, 2.48; N, 24.89.

Chloro-*N,N'*-bis-(4-nitrophenyl)-[1,3,5]triazine-2,4-diamine (2f). Colorless crystals; mp 264–266°C (acetone), reported 273 °C [3]; ir (KBr): 3340, 1630, 1590, 1510, 1340, 1240 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.90 (d, *J* = 9.3Hz, 2H, *p*-C_6H_4), 8.22 (d, *J* = 9.3Hz, 2H, *p*-C_6H_4), 10.44 (s, 1H, NH); (in accordance with reported) [3]; ^{13}C nmr (DMSO-d_6): δ 120.36, 121.08, 125.05, 125.12, 143.85, 164.32 (C-Cl); MS (EI, 70 e V): *m/z* (%) = 387 (100, M^+), 351 (45, M^+– Cl), 341 (60, $M^+ - NO_2$), 249 (30, M^+ – NHPh-NO_2); HRMS (EI) Calcd. for (M^+) $C_{15}H_{10}ClN_7O_4$ 387.04829. Found: 387.04997.

4,4'-[(6-Chloro-1,3,5-triazine-2,4-diyl)diimino]dibenzoic acid (2g). Colorless crystals (isopropanol); t. decomp. ≥ 330 °C; reported mp 345–348°C [12]; ir (KBr): 3300 – 3100 (br. m), 1610, 1560, 1530, 1330, 1240 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.88 (d, *J* = 8 Hz, 2H, *p*-C_6H_4), 8.06 (d, *J* = 8 Hz, 2H, *p*-C_6H_4), 10.10 (br. s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 120.44, 122.56, 124.14, 135.11, 139.83, 164.66 (C-Cl), 192.30 (CO_2H); MS (EI, 70 e V): *m/z* (%) = 385 (10, M^+), 350 (30, M^+ – Cl), 341 (100, $M^+ - CO_2$); HRMS (EI) Calcd. for (M^+) $C_{17}H_{12}ClN_5O_4$ 385.0578, Found: 385.0569.

6-Chloro-*N*,*N*'-bis-(2,4-dimethylphenyl)-[1,3,5]triazine-2,4-diamine (2h). Colorless crystals; mp 213–214 °C (isopropanol); ir (KBr): 3260, 1570, 1520, 1230 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.31, 2.36 (2s, 6H, $2CH_3$), 7.15 (s, $1H_{Ar}$), 7.23 (m, $1H_{Ar}$), 7.63 (m, $1H_{Ar}$) 10.38 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 20.32 (CH_3), 20.81(CH_3), 121.13, 129.05 (br), 132.69, 135.86, 163.87 (C-Cl); MS (EI, 70 e V): *m/z* (%) = 353 (100, M^+), 318 (40, M^+ – Cl), 248 (20, M^+– $C_6H_4(CH_3)_2$), 233 (10, M^+– $C_6H_3(CH_3)_2NH$); HRMS (EI) Calcd. for (M^+) $C_{19}H_{20}ClN_5$ 353.1407. Found: 353.1398. *Anal*. Calcd.: C, 64.49; H, 5.70; N, 19.79. Found C, 64.16; H, 5.58; N, 19.58.

6-Chloro-*N*,*N*'-bis-(3,5-dimethylphenyl)-[1,3,5]triazine-2,4-diamine (2i). Colorless crystals; mp 189–191°C (isopropanol); ir (KBr): 3260, 1570, 1520, 1230 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.34 (s, 6H, $2CH_3$), 7.34 (s, $1H_{Ar}$), 7.63 (s, $2H_{Ar}$), 10.34 (s, 1H, NH). ^{13}C nmr (DMSO-d_6): δ 21.23 (CH_3), 121.13, 129.05(br), 132.69, 135.56, 163.91(C-Cl); MS (EI, 70 e V): *m/z* (%) = 353 (100, M^+), 318 (50, M^+ – Cl), 248 (15, M^+– $C_6H_4(CH_3)_2$), 233 (10, M^+– $C_6H_3(CH_3)_2NH$); HRMS (EI) Calcd. for (M^+) $C_{19}H_{20}ClN_5$ 353.1407. Found: 353.1394. *Anal*. Calc.: C, 64.49; H, 5.70; N, 19.79. Found C, 64.09; H, 5.56; N, 19.61.

4,6-Dichloro-[1,3,5]triazin-2-yl-phenylamine (5). To a stirred solution of **1** (9.2 g, 0.05 mol) in 150 mL of acetic acid 4.65 g (0.05 mol) of aniline in a mixture of 20 mL of AcOH and 80 mL of H_2O was added dropwise within 15 min at 15-17°C (not letting AcOH to freeze). The reaction mixture was left for 1h at this temperature and then diluted with 1 L of brine. The solid was collected, dried in the open air and recrystallized from 400 ml of heptane (insoluble impurities were filtered off the hot solution) to afford 67 % of pure compound **5** whose melting point (136-137°C) was in accordance with previously reported [1,10]. We found that the compound reacted with DMSO and therefore NMR spectrum was taken in acetone-d_6: ^1H nmr (Acetone-d_6): δ 7.25 (t, *J* = 9 Hz, 1H, Ph) 7.46 (t, *J* = 8 Hz, 2H, Ph), 7.77 (br. s, 2H, Ph), 9.90 (br. s, 1H, NH); ^{13}C nmr (Acetone-d_6): δ 121.62, 125.19, 128.93, 137.07, 164.56 (C-Cl)

"Unsymmetrical" derivatives – 6-Chloro-*N*,*N*'-diaryl-[1,3,5]triazine-2,4-diamines (6a, 6b). (See Table 2 for the yields). Compound **5** (1.20 g , 5 mmol) was dissolved in the mixture of 40 mL of AcOH and 10 mL of H_2O. The aromatic amines (5.5 mmol) and 0.81 g (6 mmol) of $CH_3COONa \times 3H_2O$ was then added. The solution was stirred until the solids dissolved and left overnight. Crystalline products were filtered, washed with boiling water (10 mL × 3) and dried to afford pure compounds **6a** and **6b**. Analytical samples were recrystallized from isopropanol.

6-Chloro-*N*-phenyl-*N*'-p-tolyl-[1,3,5]triazine-2,4-diamine (6a). Colorless crystals; mp 178–179 °C (isopropanol); reported mp 176.5 – 177.5 °C [6]; ir (KBr): 3260, 1570, 1521, 1230 cm^{-1}; ^1H nmr (Acetone-d_6): δ 2.34 (s, CH_3), 7.22–7.13 (m, 3H, Ph), 7.39 (t, *J* = 8Hz, 2H, Ph), 7.81 (d, *J* = 7Hz, 2H, *p*-C_6H_4), 7.66 (d, *J* = 8Hz, 2H, *p*-C_6H_4), 9.04 (br. s, 2H, NH); ^{13}C nmr (Acetone-d_6): 20.06 (CH_3), 121.20 (br), 123.70, 128.26, 133.25, 135.93, 138.62, 164.66 (C-Cl) MS (EI, 70 e V): *m/z* (%) = 311 (100, M^+), 276 (25, M^+- Cl), 219 (10, M^+– Tol), 205 (7, M^+– Tol-NH); HRMS (EI) Calcd. for (M^+) $C_{16}H_{14}ClN_5$ 311.093. Found: 311.0929.

6-Chloro-*N*-(4-nitro-phenyl)-*N*'-phenyl-[1,3,5]triazine-2,4-diamine (6b). Yellow crystals; mp 221–2 °C (acetone); ir (KBr): 3320, 1630, 1590, 1510, 1340, 1240 cm^{-1}; ^1H nmr (Acetone-d_6): δ 7.22 (m, $1H_{Ar}$), 7.77 (m, $2H_{Ar}$), 7.45 (m, $2H_{Ar}$), 8.10 (m, $2H_{Ar}$), 8.25 (m, $2H_{Ar}$), 9.30 (br. s, 1H, NH), 9.69 (br. s, 1H, NH); ^{13}C nmr (Acetone-d_6): δ = 119.87, 122.85 (br.), 124.54, 128.77, 138.11, 142.81, 145.04, 164.65(C-Cl); MS (EI, 70 e V): *m/z* (%) = 342 (100, M^+), 297 (70, M^+– NO_2), 307 (10, M^+– Cl); HRMS (EI) Calcd. for (M^+) $C_{15}H_{11}ClN_6O_2$ 342.0623. Found: 342.0632; *Anal*. Calcd.: C, 52.56; H, 3.23; N, 24.52. Found: C, 52.24; H, 3.31; N, 24.63.

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