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Article

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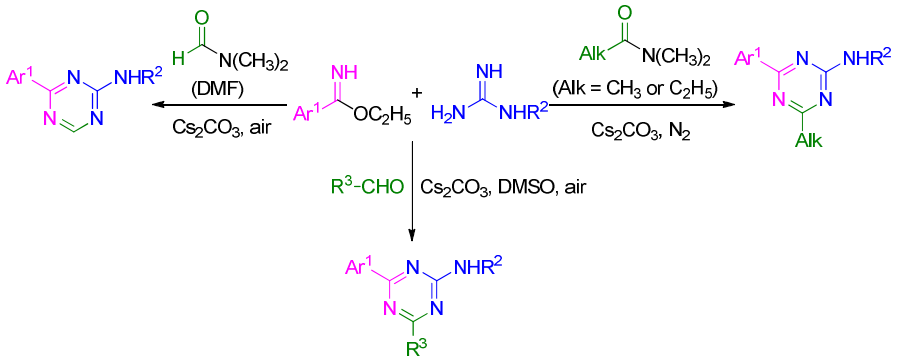
Base-mediated synthesis of unsymmetrical 1,3,5-triazin-2-amines via three-component reaction of imidates, guanidines and amides or aldehydes

Liyang Pan,[a,‡] Zhenxing Li,[b,‡] Tao Ding,[a] Xiaomin Fang,[a] Wenkai Zhang,[a] Hao Xu,*[,a,b] Yuanqing Xu*[,a]

[a] College of Chemistry and Chemical Engineering, Henan University, Kaifeng 475004, P. R. China.

[b] State Key Laboratory of Heavy Oil Processing, China University of Petroleum-Beijing, Beijing 102249, P. R. China.

E-mail : xuhao@henu.edu.cn; 18937822307@163.com



ABSTRACT: A simple and efficient method for the base-mediated synthesis of unsymmetrical 1,3,5-triazin-2-amines has been developed. The protocol uses readily available imidates, guanidines and amides or aldehydes as the starting materials, cesium carbonate as the base, no any catalyst or additive is required, and the three-component reaction provides diverse 1,3,5-triazin-2-amines in moderate to good yields with tolerance of wide functional groups.

INTRODUCTION

1,3,5-Triazines are important building blocks with wide application in pharmaceuticals, agrochemical and functional materials.[1] Direct synthesis of substituted 1,3,5-triazines from readily available substrates mainly relied on the nucleophilic displacement of cynauric chloride,[2] cyclotrimerization of nitriles,[3] and cyclization of aryl amidines with formylating reagents or others.[4] However, these methods were restricted to synthesis of symmetrical 1,3,5-triazines (Figure 1); because the unsymmetrical and symmetrical 1,3,5-triazines are always generated simultaneously during synthesis of unsymmetrical 1,3,5-triazines by the previous methods, and they are difficult to be separated for their very close value of R_f. Therefore, the direct synthesis of unsymmetrical 1,3,5-triazines from readily available substrates is still a great challenge.

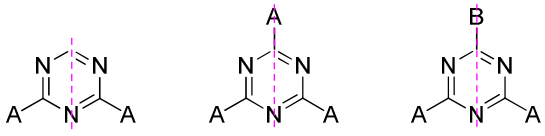
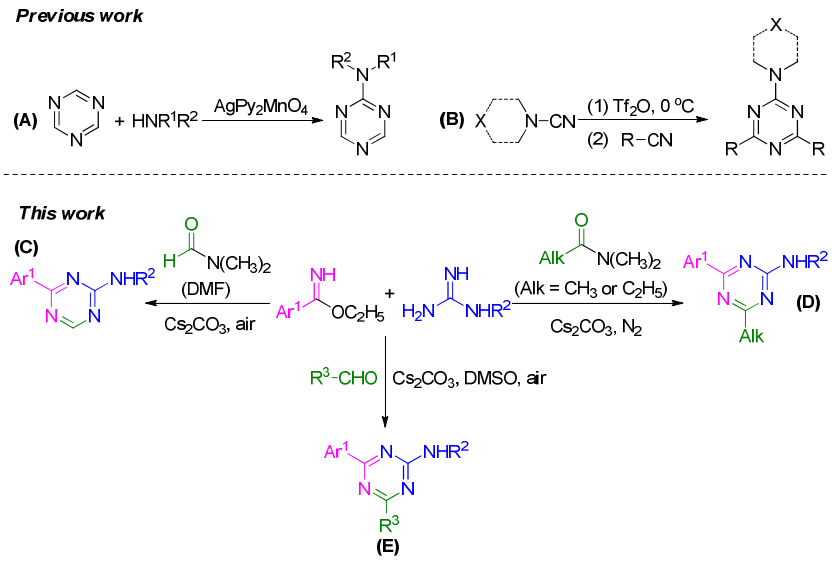


Figure 1. Symmetrical 1,3,5-triazines for traditional methods

Since 1,3,5-triazin-2-amines exhibit various biological and medicinal activities,[5] various methods for the synthesis of diverse 1,3,5-triazin-2-amines have been developed.[6] However, the direct synthesis of 1,3,5-triazin-2-amines from readily available substrates is rare. In 2007, Maes's group reported synthesis of 1,3,5-triazin-2-amines via oxidative amination of 1,3,5-triazine in excess of amine-ethanol solution using $AgPy_2MnO_4$ as the oxidant (Scheme 1A).[6a] In 2014, Martínez-Alvarez' group developed a simple and efficient method for triflic anhydride-mediated one-pot synthesis of 4,6-disubstituted 1,3,5-triazin-2-amines via coupling of two different nitriles (Scheme 1B).[6b] Nevertheless, it is difficult to directly prepare unsymmetrical 1,3,5-triazin-2-amines from readily available substrates. Meanwhile, the

synthesis of unsymmetrical 1,3,5-triazin-2-amines with different bioactive groups is significant for the research of new drugs and pesticides.



Scheme 1. Direct synthesis of 1,3,5-triazin-2-amines from readily available substrates

Transition-metal-catalyzed synthesis of *N*-heterocycles is still dominant; and transition-metal catalysts are usually needed in the formation of 1,3,5-triazine framework, when readily available substrates (such as DMF) are used.[2,3b,4b-4e] Nonetheless, transition-metal-catalyzed reactions have an insurmountable disadvantage, due to the intrinsic toxicity of most transition metals and the arduous removal of transition metal traces to the ppm- or even ppb-level which is often required for pharmaceutical intermediates or final products. Furthermore, molecular oxygen (O_2) has emerged as one of the most favorable oxidants as impressively demonstrated by nature in chemical transformations. In continuation of our endeavors to develop the simple synthetic methods of *N*-heterocycles from readily available substrates,[7] we herein report a base-mediated synthesis of unsymmetrical 1,3,5-triazin-2-amines via three-component reaction of imidates, guanidines and amides or aldehydes (Scheme 1C-1E).

RESULTS AND DISCUSSION

Initially, ethyl 4-methylbenzimidate **(1b)** and guanidine hydrochloride **(2a)** were chosen as model substrates to optimize the conditions including bases and temperatures. As shown in Table 1, nine bases (4 equiv., relative to amount of **1b**) were tested, Cs_2CO_3 showed the best activity (Table 1, entries 1-9). The reaction did not work in the absence of base (entry 10). The amount of base also affected its practical use; product **3a** was obtained in 88% yield when amount of Cs_2CO_3 was increased to 5 equivalents (entry 11); further increase of amount of Cs_2CO_3 did not lead to a higher yield (entry 12). Therefore, 5 equiv of Cs_2CO_3 was the best choice. Yield decreased when temperature was raised to 150 ^oC, owing to hydrolysis of a small amount of imidate **1b** (entry 14). It was noted that a high yield was also obtained when the reaction was performed under nitrogen atmosphere (entry 15). However, the oxidant was always needed in the formation of 1,3,5-triazine framework when DMF was used as the substrate in the previous synthetic method.[4d]

Table 1. Optimization of conditions on base-mediated synthesis of 4-(*p*-tolyl)-1,3,5-triazin-2-amine **(3b)** via three-component reaction of ethyl 4-methylbenzimidate **(1b)**, guanidine hydrochloride **(2a)** and DMF[a]

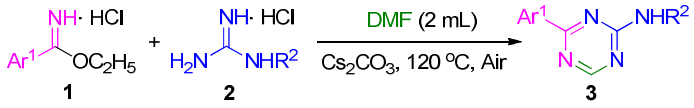
Entry	Base	Temp	Yield (%)[b]
1	*t*-BuONa	120	40
2	CsOH	120	19
3	NaOH	120	25
4	Cs_2CO_3	120	83
5	K_2CO_3	120	30
6	Na_2CO_3	120	trace
7	K_3PO_4	120	trace
8	CsOAc	120	30
9	NaOAc	120	17
10	--	120	trace

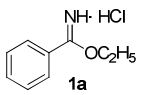
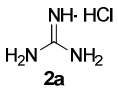
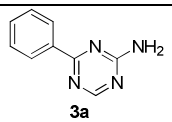
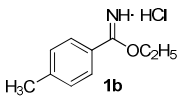
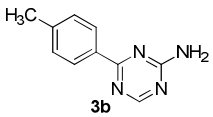
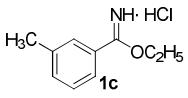
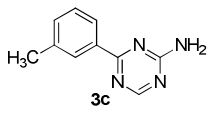
11[c]	**Cs_2CO_3**	**120**	**88**
12[d]	Cs_2CO_3	120	86
13[c]	Cs_2CO_3	100	52
14[c]	Cs_2CO_3	150	74
15[c,e]	Cs_2CO_3	120	79
16[c,f]	Cs_2CO_3	120	85

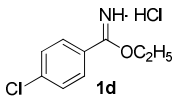
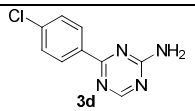
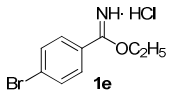
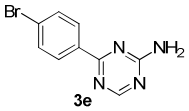
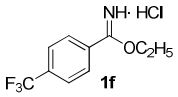
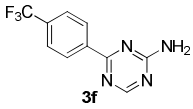
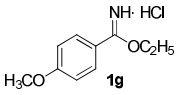
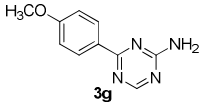
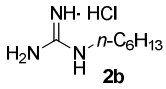
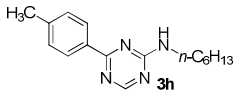
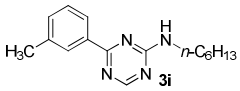
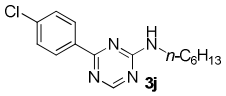
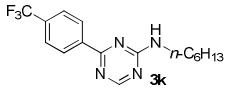
[a] Reaction condition: 4-methylbenzimidate **(1b)** (0.3 mmol), guanidine hydrochloride **(2a)** (0.33 mmol), base (1.2 mmol), DMF (2 mL), reaction time (24 h) in a sealed Schlenk tube without exclusion of air. [b] Isolated yield. [c] Base (1.5 mmol). [d] Base (1.8 mmol). [e] under nitrogen atmosphere (1 atm). [f] under oxygen atmosphere (1 atm).

Under the optimized conditions, various imidates and guanidines were used to investigate, and a series of 6-aryl-1,3,5-triazin-2-amines were synthesized in moderate to good yields (Table 2). The reaction worked well for *meta*- and *para*-substituted arylimidates (entries 2,3), and various electron-withdrawing groups (EWGs; Cl, Br, CF_3; entries 4-6) and electron-donating groups (EDGs, Me, OMe; entries 2, 3, 7) in the substituents were completely tolerated. Delightfully, substituted guanidine was also tolerated to afford **3h-3k** in moderate to good yields (entries 8-11).

Table 2. Base-mediated synthesis of 4-aryl-1,3,5-triazin-2-amines **3** via three-component reaction of imidates **1**, guanidines **2** and DMF[a]



Entry	1	2	3	Yield (%)[b]
1				90
2		**2a**		88
3		**2a**		75

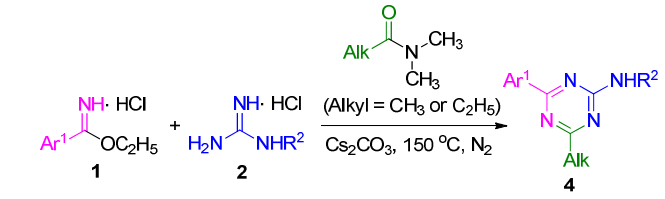
4	 1d	**2a**	 3d	71
5	 1e	**2a**	 3e	73
6	 1f	**2a**	 3f	72
7	 1g	**2a**	 3g	85
8	**1b**	 2b	 3h	58
9	**1c**	**2b**	 3i	54
10	**1d**	**2b**	 3j	68
11	**1f**	**2b**	 3k	62

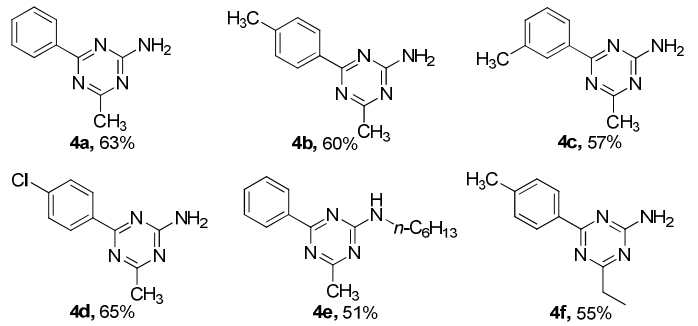
[a] Reaction condition: **1** (0.3 mmol), **2** (0.33 mmol), Cs_2CO_3 (1.5 mmol), DMF (2 mL), reaction time (24 h) at 120 °C in a sealed Schlenk tube without exclusion of air. [b] Isolated yield.

Considering that the reaction could be performed well in the absence of oxidant, we concluded that the formyl group of DMF participated in the formation of 1,3,5-trianine framework via addition and elimination of $-N(CH_3)_2$ (For details, see Scheme 5). Encouraged by the above results and speculated mechanism, *N,N*-dimethylacetamide (DMA) was used as the substrate to replace DMF, and we also optimized the reaction conditions (see Table S1 in the Supporting Information). Several 4-methyl-6-aryl-1,3,5-triazin-2-amines were prepared from imidates, guanidines and DMA (Scheme 2) under base-mediated conditions. Futhermore, 4-ethyl-6-aryl-1,3,5-triazin-2-amine derivative was also obtained in

moderate yield when *N,N*-dimethylpropionamide (DMP) was used as the substrate instead of DMA (**4f** in Scheme 2).

Scheme 2. Base-mediated synthesis of 4-alkyl-6-aryl-1,3,5-triazin-2-amines **4** *via* three-component reaction of imidates **1**, guanidines **2** and DMA or DMP[a]

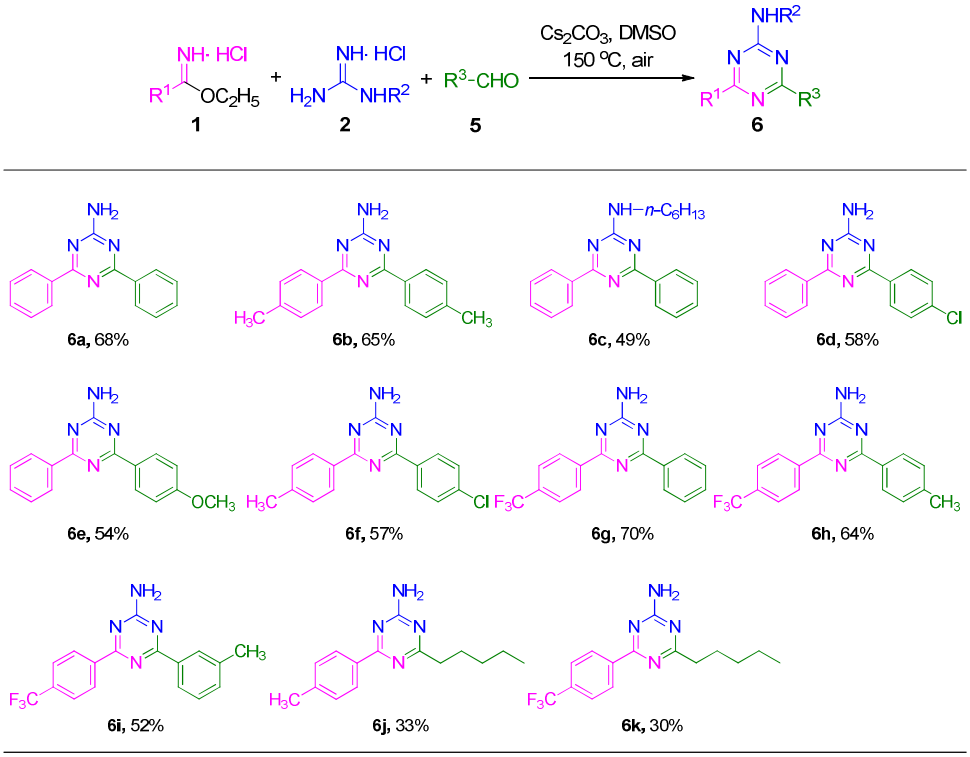




[a] Reaction condition: **1** (0.3 mmol), **2** (0.33 mmol), Cs_2CO_3 (1.5 mmol), anhydrous DMA (2 mL), reaction time (24 h) at 150 °C under nitrogen atmosphere (1 atm). [b] Isolated yield. [c] Using anhydrous DMP to replace DMA.

Subsequently, imidates **1**, guanidines **2** and aldehydes **5** were used as the substrates to prepare 4,6-disubstituted 1,3,5-triazin-2-amine derivatives (Scheme 3). Firstly, ethyl benzimidate **(1a)**, guanidine hydrochloride **(2a)** and benzaldehyde **(5a)** were chosen as the model substrates to optimize reaction conditions including bases, solvents, temperatures and atmospheres (Table S2 in the ESI). The molecular oxygen (O_2) in air was proved to be necessary to improve the yield of product **6a** (Table S2, compare entries 9-12). Under the optimized conditions, aryl-disubstituted 1,3,5-triazin-2-amines were prepared in moderate to good yields (**6a-i** in Scheme 3); and aromatic aldehydes were well tolerated under the base-mediated conditions. Furthermore, aliphatic aldehydes could also generate the relative products (**6j-k** in Scheme 3).

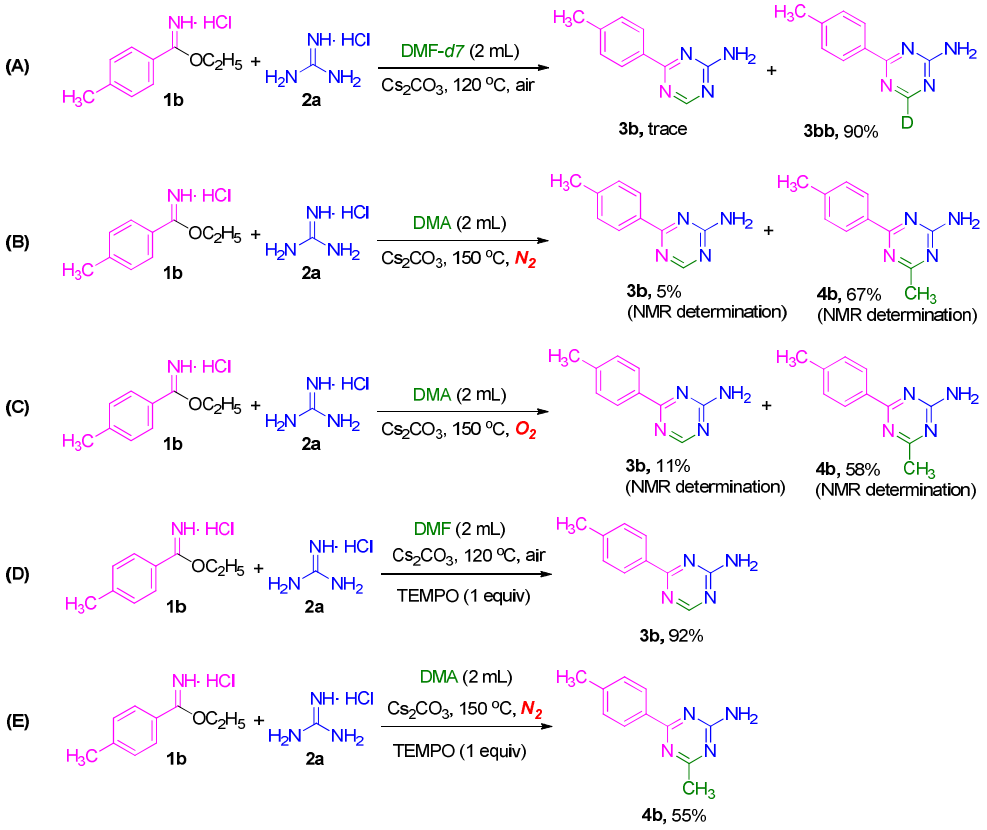
Scheme 3. Base-mediated synthesis of disubstituted 1,3,5-triazin-2-amines **6** *via* three-component oxidative reaction of ethyl imidates **1**, guanidines **2** and aldehydes **5**[a]



[a] Reaction condition: **1** (0.3 mmol), **2** (0.9 mmol), **5** (0.6 mmol), Cs_2CO_3 (2.1 mmol), DMSO (3 mL), reaction time (24 h) at 150 °C in a sealed Schlenk tube without exclusion of air. [b] Isolated yield.

Some control experiments were performed to probe the mechanism. Reaction of **1b**, **2a** and DMF-*d7* gave the deuterated product **3bb** in 90 % yield (Scheme 4A), and only trace amount of non-deuterated product was observed in the H^1 NMR spectrum (Figure S1,S2 in the Supporting Information); this result proved that DMF participated in the formation of 1,3,5-triazine framework, and served as the C-H source. Reaction of **1b**, **2a** and DMA gave product **4b** in 67 % yield (NMR determination, Figure S3 in Supporting Information) under standard conditions (N_2, 1 atm), and only 5 % yield (NMR determination, Figure S3 in Supporting Information) of **3b** was obtained (Scheme 4B); the result proved that the acyl group of the DMA serve as the C-CH_3 source in the formation of **4b**. Under oxygen atmosphere, more **3b** was obtained although **4b** was still the main product (Scheme 4C; Figure S4,S5 in Supporting Information); the methyl of DMA served as the C-H source in the formation of little **3b** under oxygen atmos-

phere, and a single-electron oxidation process could happen in the formation of **3b** (examined by addition of TEMPO; Figure S6 in Supporting Information).[4d,8] Furthermore, addition of 1 equiv of TEMPO (radical scavenger) had no effect for the formation of **3b** or **4b** under the standard conditions (Scheme 4D,4E); these results implied that the reaction underwent a nucleophilic addition-elimination process in the formation of products **3** and **4**.

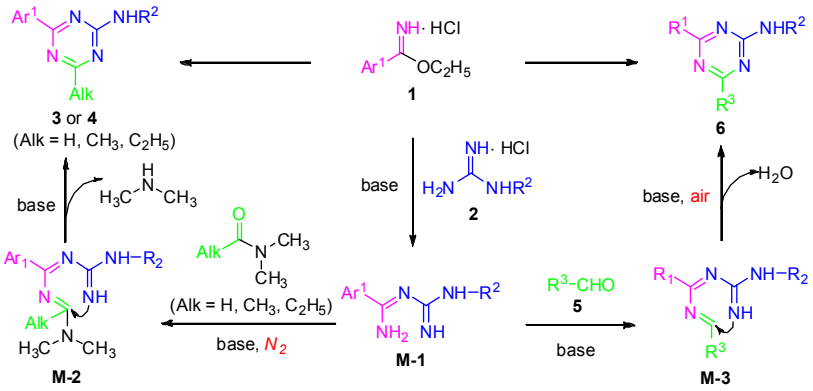


Scheme 4. (A) Base-mediated three-component reaction of imidates **1b**, guanidines **2a** and deuterated DMF under standard conditions; (B) Base-mediated three-component reaction of imidates 1b, guanidines **2a** and DMA under standard conditions (N_2, 1 atm); (C) Base-mediated three-component reaction of imidates 1b, guanidines **2a** and DMA under oxygen atmosphere (1 atm); (D) Addition of 1 equiv of TEMPO (radical scavenger) for the synthesis of **3b** under standard conditions; (E) Addition of 1 equiv of TEMPO (radical scavenger) for the synthesis of **4b** under standard conditions.

Interestingly, under copper-catalyzed conditions, the methyl of DMF could serve as the C-H source to afford *N*-heterocyclic compounds, such as symmetrical 1,3,5-triazines[4d,4e] or 1,2,4-triazoles.[4e] However,

under metal-free base-mediated condition, the acyl group of DMF, DMA and DMP respectively served as the C-H, C-CH_3 and C-C_2H_5 source in our work.

On the basis of the above control experiments and previous reports,[4] a plausible reaction mechanism is proposed in Scheme 5. At first, nucleophilic attack of guanidine **2** to imidate **1** leads to intermediate **M-1** in the presence of Cs_2CO_3; then the amino group of **M-1** attacks the acyl group of the amide to form the intermediate **M-2**; finally, intramolecular cyclization of **M-2** gives the target product **3** or **4** via an intramolecular addition-elimination process. When aldehyde **5** is used as the substrate and DMSO as the solvent, the amino group of **M-1** attacks the aldehyde **5** to form the intermediate **M-3**; then intramolecular oxidative dehydration/cyclization of **M-3** provides the target product **6** under base-mediated and oxygen-oxidized conditions.



Scheme 5. Possible mechanism for the synthesis of products **3, 4** and **6**

CONCLUSION

In conclusion, we have developed a simple and efficient method for the base-mediated synthesis of unsymmetrical 1,3,5-triazin-2-amines via three-component reaction of imidates, guanidines and amides or aldehydes under transition metal-free conditions. The unsymmetrical 1,3,5-triazine derivatives were inaccessible to prepare directly from readily available substrates in the previous methods. The corresponding mechanism is proposed for the synthesis of 4-aryl-1,3,5-triazin-2-amines from imidates, guan-

idines and DMF; the formyl group of DMF serves as the C-H source in our work, which is different from the previous reports that the methyl of DMF served as the C-H source for the formation of 1,3,5-triazine framework. Based on the mechanism, we also use other amides and aldehydes to replace DMF, and unsymmetrically disubstituted 1,3,5-triazin-2-amine derivatives are synthesized successfully. This method can tolerate various functional groups, and presents a simple and efficient protocol for the direct synthesis of unsymmetrical 1,3,5-triazin-2-amine derivatives from readily available substrates. Meanwhile, this method will have a promising application in the direct synthesis of unsymmetrical 1,3,5-triazin-2-amine drugs and pesticides.

EXPERIMENTAL SECTION

General experimental procedures: Reagents were purchased and used without further purification. Reactions were monitored by thin layer chromatography (TLC) and the products were obtained by column chromatography on silica gel. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$ as the internal standard (^{1}H NMR: TMS at 0.00 ppm,$CHCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm) or were recorded using tetramethylsilane (TMS) in the solvent of DMSO-d_6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, DMSO at 2.50 ppm; ^{13}C NMR: DMSO at 39.51 ppm).

General procedure for synthesis of compounds (3a-k): Substituted benzimidate hydrochloride **1** (0.3 mmol), guanidine hydrochloride **2** (0.33 mmol), Cs_2CO_3 (1.5 mmol, 489 mg) and DMF (2 mL) were added to a 25 mL Schlenk tube charged with a magnetic stirrer. The reaction mixture was stirred at 120 ^{o}C for 24 h without exclusion of air. The resulting solution was concentrated on a rotary evaporator, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to give the desired product **3a-k**.

4-Phenyl-1,3,5-triazin-2-amine (3a).[9] Eluent: petroleum ether/ethyl acetate (4:1). Yield 46.5 mg (90 %). White solid, mp 203-204 °C (lit.[9] mp 203-204 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.63 (s, 1H), 8.38-8.33 (m, 2H), 7.68-7.50 (m, 5H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 170.4, 167.1, 136.4, 132.5, 129.0, 128.4. GC-MS $[M+H]^+$ m/z 172.36.

4-(*p*-Tolyl)-1,3,5-triazin-2-amine (3b).[10] Eluent: petroleum ether/ethyl acetate (4:1). Yield 49.2 mg (88 %). White solid, mp 235.9-237.3 °C (lit.[10] mp 235-236 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.56 (s, 1H), 8.22 (d, J = 8.2 Hz, 2H), 7.58 (s, 2H), 7.33 (d, J = 8.0 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 170.4, 167.0, 142.5, 133.7, 129.6, 128.4, 21.6. APCI-MS $[M+H]^+$ m/z 186.96.

4-(*m*-Tolyl)-1,3,5-triazin-2-amine (3c). Eluent: petroleum ether/ethyl acetate (4:1). Yield 41.9 mg (75 %). White solid, mp 184.7-186.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.62 (s, 1H), 8.21-8.13 (m, 2H), 7.67 (s, 2H), 7.41 (m, 2H), 2.40 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 170.5, 167.0, 138.2, 136.3, 133.1, 128.9, 125.6, 21.5. ESI-MS $[M+H]^+$ m/z 186.94. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{10}H_{11}N_4$ 187.0984, found 187.0993.

4-(4-Chlorophenyl)-1,3,5-triazin-2-amine (3d). Eluent: petroleum ether/ethyl acetate (4:1). Yield 44.0 mg (71 %). White solid, mp 229.3-230.5 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.63 (s, 1H), 8.36-8.33 (m, 2H), 7.70 (s, 2H), 7.62-7.58 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 169.5, 167.1, 167.0, 137.3, 135.2, 130.1, 129.2. APCI-MS $[M+H]^+$ m/z 206.95. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_9H_8ClN_4$ 207.0437, found 207.0447.

4-(4-Bromophenyl)-1,3,5-triazin-2-amine (3e).[11] Eluent: petroleum ether/ethyl acetate (4:1). Yield 55.0 mg (73%). White solid, mp 241.4-242.6 °C (lit.[11] mp 242-244 °C). ^{1}H NMR (DMSO-d_6, 400 MHz,

25 °C) δ 8.63 (s, 1H), 8.27 (d, *J* = 8.6 Hz, 2H), 7.79-7.71 (m, 4H). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz, 25 °C) δ 169.6, 167.2, 167.0, 135.6, 132.1, 130.3, 126.4. APCI-MS $[M+H]^+$ m/z 251.01.

4-[4-(Trifluoromethyl)phenyl]-1,3,5-triazin-2-amine (3f). Eluent: petroleum ether/ethyl acetate (4:1). Yield 51.9 mg (72%). White solid, mp 201.7-202.9 °C. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz, 25 °C) δ 8.68 (s, 1H), 8.52 (d, *J* = 8.2 Hz, 2H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.84 (s, 2H). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz, DMSO) δ 169.2, 167.3, 167.0, 140.2, 132.1 (q, *J* = 31.8 Hz), 129.0, 126.1, 126.0, 125.9, 123.1. APCI-MS $[M+H]^+$ m/z 241.05. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{10}H_8F_3N_4$ 241.0701, found 241.0709.

4-(4-Methoxyphenyl)-1,3,5-triazin-2-amine (3g).[11] Eluent: petroleum ether/ethyl acetate (4:1). Yield 51.6 mg (85%). White solid, mp 223.8-224.7 °C (lit.[11] mp 225-228 °C). ^{1}H NMR (DMSO-*d*$_6$, 400 MHz, 25 °C) δ 8.56 (s, 1H), 8.34-8.28 (m, 2H), 7.56 (s, 2H), 7.10-7.05 (m, 2H), 3.85 (s, 3H). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz, 25 °C) δ 170.0, 166.9, 162.9, 130.3, 128.6, 114.4, 55.8. APCI-MS $[M+H]^+$ m/z 202.97.

***N*-hexyl-4-(*p*-tolyl)-1,3,5-triazin-2-amine (3h).** Eluent: petroleum ether/ethyl acetate (4:1). Yield 47.0 mg (58%). White solid, mp 88.5-89.4 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.64-8.42 (m, 1H), 8.30-8.13 (m, 2H), 7.29-7.09 (m, 2H), 6.30-5.68 (m, 1H), 3.50-3.33 (m, 2H), 2.38-2.30 (m, 3H), 1.60-1.45 (m, 2H), 1.36-1.15 (m, 6H), 0.87-0.75 (m, 3H). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz, 25 °C) δ 170.1, 169.8, 166.9, 166.4, 165.4, 165.3, 142.6, 142.5, 133.8, 133.6, 129.6, 128.5, 128.4, 40.7, 31.5, 31.4, 29.2, 29.0, 26.5, 22. 6, 22.5, 21.6, 14.4. ^{13}C NMR (DMSO-*d*$_6$, 150 MHz, 80 °C) δ 170.4, 166.9, 166.4, 165.7, 142.43, 134.1, 129.5, 128.5, 40.9, 31.5, 29.2, 26.5, 22.5, 21.5, 14.2. APCI-MS $[M+H]^+$ m/z 271.25. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{16}H_{23}N_4$ 271.1923, found 271.1927.

***N*-hexyl-4-(*m*-tolyl)-1,3,5-triazin-2-amine (3i).** Eluent: petroleum ether/ethyl acetate (4:1). Yield 43.8 mg (54%). White solid, mp 69.0-71.1 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.69-8.49 (m, 1H), 8.25-8.05 (t, J = 11.2 Hz, 3H), 7.40 (s, 2H), 3.46-3.29 (m, 2H), 2.40 (s, 3H), 1.64-1.49 (m, 2H), 1.37-1.19 (m, 6H), 0.92-0.81 (m, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 170.2, 169.9, 167.0, 166.4, 165.4, 165.3, 138.1, 136.5, 136.3, 133.2, 133.1, 128.9, 125.7, 125.6, 56.5, 49.1, 40.7, 31.5, 31.4, 29.2, 29.0, 26.5, 22.6, 22.5, 21.5, 19.0, 14.4. ^{13}C NMR (DMSO-d_6, 150 MHz, 80 °C) δ 166.9, 166.4, 165.7, 138.1, 133.0, 129.0, 128.8, 125.8, 40.9, 31.5, 29.2, 26.5, 22.5, 21.5, 14.2. APCI-MS $[M+H]^+$ m/z 271.13. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{16}H_{23}N_4$ 271.1923, found 271.1940.

4-(4-Chlorophenyl)-*N*-hexyl-1,3,5-triazin-2-amine (3j). Eluent: petroleum ether/ethyl acetate (4:1). Yield 59.3 mg (68%). White solid, mp 105.5-106.3 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.66-8.51 (m, 1H), 8.37-8.26 (m, 2H), 8.20 (t, J = 5.7 Hz, 1H), 7.56 (d, J = 7.6 Hz, 2H), 3.42-3.27 (m, 2H), 1.61-1.45 (m, 2H), 1.37-1.18 (m, 6H), 0.90-0.77 (m, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 169.2, 168.9, 167.1, 166.5, 165.3, 165.2, 137.4, 137.3, 135.4, 135.2, 130.1, 129.1, 40.7, 31.5, 31.4, 29.1, 29.0, 26.5, 22.6, 14.4. ^{13}C NMR (DMSO-d_6, 150 MHz, 80 °C) δ 169.5, 169.2, 167.0, 166.5, 165.6, 137.4, 135.6, 135.5, 130.2, 129.1, 40.9, 31.4, 29.1, 26.5, 22.5, 14.2.APCI-MS $[M+H]^+$ m/z 291.20. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{15}H_{20}ClN_4$ 291.1376, found 291.1382.

***N*-hexyl-4-[4-(trifluoromethyl)phenyl]-1,3,5-triazin-2-amine (3k).** Eluent: petroleum ether/ethyl acetate (4:1). Yield 60.3 mg (62%). White solid, mp 99.2-100.6 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.69-8.56 (m, 1H), 8.53-8.44 (m, 2H), 8.34-8.24 (m, 1H), 7.88-7.81 (m, 2H), 3.43-3.28 (m, 2H), 1.60-1.47 (m, 2H), 1.34-1.19 (m, 6H), 0.86-0.77 (m, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 168.9, 168.6, 167.2, 166.6, 165.3, 140.4, 140.2, 132.2 (q, J = 31.9 Hz), 132.1 (q, J = 31.9 Hz), 129.0, 125.9, 123.1, 40.7, 40.5, 31.5, 31.4, 29.1, 29.0, 26.5, 22.5, 14.3. ^{13}C NMR (DMSO-d_6, 150 MHz, 80 °C) δD6) δ 169.2, 169.0, 167.2, 166.6, 165.7, 140.7, 140.5, 132.7, 132.5, 132.4, 132.3, 132.2, 132.1, 132.0,

129.2, 125.9, 123.7, 40.9, 31.4, 29.1, 26.5, 22.4, 14.2. APCI-MS $[M+H]^+$ m/z 325.25. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{16}H_{20}F_3N_4$ 325.1640, found 325.1653.

4-(*p*-Tolyl)-1,3,5-triazin-6-*d*-2-amine (3bb). Eluent: petroleum ether/ethyl acetate (4:1). Yield 47.7 mg (85%). White solid, mp 235.9-237.3 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ = 8.22 (d, J = 8.1, 2H), 7.58 (s, 2H), 7.33 (d, J = 8.0, 2H), 2.38 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 170.4, 167.0, 166.7 (t), 142.5, 133.7, 129.6, 128.4, 40.6, 40.4, 40.2, 40.0, 39.8, 39.5, 39.3, 21.6. ESI-MS $[M+H]^+$ m/z 188.07. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{10}H_{10}DN_4$ 188.1041, found 188.1051.

General procedure for synthesis of compounds (4a-f). Substituted benzimidate hydrochloride **1** (0.3 mmol), guanidine hydrochloride **2** (0.33 mmol), Cs_2CO_3 (1.5 mmol, 488 mg), anhydrous DMA or DMP (2 mL) were added to a 25 mL Schlenk tube charged with a magnetic stirrer. The reaction mixture was stirred at 150 °C for 24 h under nitrogen atmosphere (1 atm). The resulting solution was concentrated on a rotary evaporator, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to give the desired product **4a-f**.

4-Methyl-6-phenyl-1,3,5-triazin-2-amine (4a).[10] Eluent: petroleum ether/ethyl acetate (4:1). Yield 35.2 mg (63%). White solid, mp 158.5-160.2°C (lit.[10] mp 159-160 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.36 (d, J = 7.2 Hz, 2H), 7.61-7.48 (m, 5H), 2.40 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 176.2, 170.5, 167.5, 136.6, 132.2, 128.9, 128.4, 25.7. ESI-MS $[M+H]^+$ m/z 187.02.

4-Methyl-6-(*p*-tolyl)-1,3,5-triazin-2-amine (4b).[10] Eluent: petroleum ether/ethyl acetate (4:1). Yield 36.0 mg (60%). White solid, mp 175.4-176.6 °C (lit.[10] mp 185 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.23 (d, J = 8.1 Hz, 2H), 7.44 (s, 2H), 7.31 (d, J = 8.0 Hz, 2H), 2.37 (d, J = 7.4 Hz, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 176.1, 170.4, 167.4, 142.2, 133.9, 129.6, 128.4, 25.7, 21.6. ESI-MS $[M+H]^+$ m/z 201.06.

4-Methyl-6-(*m*-tolyl)-1,3,5-triazin-2-amine (4c). Eluent: petroleum ether/ethyl acetate (4:1). Yield 34.2 mg (57%). White solid, mp 169.1-170.1 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.17 (s, 1H), 8.15-8.10 (m, 1H), 7.50 (s, 2H), 7.41-7.36 (m, 2H), 2.41-2.37 (m, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 176.1, 170.5, 167.4, 138.07, 136.6, 132.9, 128.9, 128.8, 125.6, 25.7, 21.5. ESI-MS $[M+H]^+$ m/z 201.06. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{11}H_{13}N_4$ 201.1140, found 201.1156.

4-(4-Chlorophenyl)-6-methyl-1,3,5-triazin-2-amine (4d).[11] Eluent: petroleum ether/ethyl acetate (4:1). Yield 43.0 mg (65%). White solid, mp 248.8-249.1 °C (lit.[11] mp 250-252 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.32 (d, J = 8.3 Hz, 2H), 7.64-7.50 (m, 4H), 2.38 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 176.3, 169.5, 167.4, 137.1, 135.4, 130.1, 129.1, 25.7. ESI-MS $[M+H]^+$ m/z 220.99.

***N*-hexyl-4-methyl-6-phenyl-1,3,5-triazin-2-amine (4e).** Eluent: petroleum ether/ethyl acetate (4:1). Yield 41.4 mg (51%). White solid, mp 48.6-51.2 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.41-8.29 (m, 2H), 8.05-7.92 (m, 1H), 7.61-7.46 (m, 3H), 3.44-3.30 (m, 2H), 2.42-2.33 (m, 3H), 1.62-1.48 (m, 2H), 1.38-1.21 (m, 6H), 0.89-0.82 (m, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 176.2, 175.5, 170.1, 169.8, 165.9, 136.7, 136.5, 132.3, 132.2, 128.9, 128.5, 128.4, 31.4, 31.4, 29.2, 26.5, 26.5, 26.2, 25.6, 22.5, 14.4. APCI-MS $[M+H]^+$ m/z 271.19. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{16}H_{23}N_4$ 271.1923, found 271.1925.

4-Ethyl-6-(*p*-tolyl)-1,3,5-triazin-2-amine (4f).[12] Eluent: petroleum ether/ethyl acetate (4:1). Yield 35.4 mg (55%). White solid, mp 169.2-169.7 °C (lit.[12] mp 164-165 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.30 (d, J = 8.1 Hz, 2H), 7.50 (s, 2H), 7.37 (d, J = 8.1 Hz, 2H), 2.69 (q, J = 7.6 Hz, 2H), 2.44 (s, 3H), 1.31 (t, J = 7.6 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 179.8, 170.4, 167.5, 142.2, 134.0, 129.6, 128.4, 31.9, 21.6, 12.0. ESI-MS $[M+H]^+$ m/z 215.08.

General procedure for synthesis of compounds (6a-l). Substituted benzimidate hydrochloride **1** (0.3 mmol), guanidine hydrochloride **2** (0.9 mmol), aldehyde **5** (0.6 mmol), Cs_2CO_3 (2.1 mmol, 684 mg), anhydrous DMSO (3 mL) were added to a 25 mL Schlenk tube charged with a magnetic stirrer. The reaction mixture was stirred at 150 °C for 24 h without exclusion of air. The resulting solution was concentrated on a rotary evaporator, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to give the desired product.

4,6-diphenyl-1,3,5-triazin-2-amine (6a)[9]. Eluent: petroleum ether/ethyl acetate (10:1). Yield 50.7 mg (68%). White solid, mp 172.2-172.9 °C (lit.[9] mp 167-169 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.55-8.48 (m, 4H), 7.71 (s, 2H), 7.64-7.55 (m, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 171.0, 168.0, 136.7, 132.5, 129.0, 128.6. ESI-MS $[M+H]^+$ m/z 249.17.

4,6-di-*p*-tolyl-1,3,5-triazin-2-amine (6b).[13] Eluent: petroleum ether/ethyl acetate(10:1). Yield 53.9 mg (65%). White solid, mp 225.2-226.3 °C (lit.[13] mp 231 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.40 (d, J = 8.1 Hz, 4H), 7.62 (s, 2H), 7.37 (d, J = 8.0 Hz, 4H), 2.41 (s, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 170.9, 167.9, 142.4, 134.1, 129.6, 128.6, 21.6. APCI-MS $[M+H]^+$ m/z 277.07.

***N*-hexyl-4,6-diphenyl-1,3,5-triazin-2-amine (6c).** Eluent:petroleum ether/ethyl acetate(10:1). Yield 48.9 mg (49%).Yellowish solidiquid mixture. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.61-8.49 (m, 4H), 8.22-8.12 (m, 1H), 7.65-7.55 (m, 6H), 3.56-3.44 (m, 2H), 1.70-1.55 (m, 2H), 1.40-1.23 (m, 6H), 0.91-0.78 (m, 3H). ^{13}C NMR(DMSO-d_6, 100 MHz, 25 °C) δ 170.7, 170.4, 166.4, 136.9, 136.8, 132.5, 132.4, 129.0, 128.6, 128.5, 40.7, 31.5, 29.2, 26.6, 22.6, 14.4. ESI-MS $[M+H]^+$ m/z 333.41. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{21}H_{25}N_4$ 333.2079, found 333.2079.

4-(4-Chlorophenyl)-6-phenyl-1,3,5-triazin-2-amine (6d). Eluent: petroleum ether/ethyl acetate (10:1). Yield 49.2 mg (58%). White solid, mp 190.3-190.8 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ

8.53-8.44 (m, 4H), 7.77 (s, 2H), 7.67-7.55 (m, 5H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 171.1, 170.0, 167.9, 137.3, 136.5, 135.6, 132.6, 130.3, 129.2, 129.1, 128.6. ESI-MS $[M+H]^+$ m/z 283.19. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{15}H_{12}ClN_4$ 283.0750, found 283.0752.

4-(4-Methoxyphenyl)-6-phenyl-1,3,5-triazin-2-amine (6e). Eluent: petroleum ether/ethyl acetate(10:1). Yield 45.1 mg (54%). White solid, mp 201.0-201.5 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.52-8.41 (m, 4H), 7.68-7.51 (m, 5H), 7.11 (d, J = 9.0 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 170.8, 170.6, 167.8, 162.9, 136.8, 132.4, 130.4, 129.0, 128.5, 114.4, 55.9. APCI-MS $[M+H]^+$ m/z 279.07. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{16}H_{15}N_4O$ 279.1246, found 279.1270.

4-(4-Chlorophenyl)-6-(*p*-tolyl)-1,3,5-triazin-2-amine (6f). Eluent: petroleum ether/ethyl acetate(10:1). Yield 50.7 mg (57%). White solid, mp 216.2-217.4 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.55-8.49 (m, 2H), 8.42 (d, J = 8.2 Hz, 2H), 7.74 (s, 2H), 7.70-7.65 (m, 2H), 7.41 (d, J = 8.1 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 171.0, 167.0, 167.9, 142.6, 137.2, 135.6, 133.8, 130.3, 129.7, 129.2, 128.6, 21.6. APCI-MS $[M+H]^+$ m/z 297.05. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{16}H_{14}ClN_4$ 297.0907, found 297.0911.

4-Phenyl-6-(4-(trifluoromethyl)phenyl)-1,3,5-triazin-2-amine (6g). Eluent: petroleum ether/ethyl acetate (10:1). Yield 66.4 mg (70%). White solid, mp 158.6-159.3 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 8.57 (d, J = 8.1 Hz, 2H), 8.50-8.41 (m, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.53-7.38 (m, 3H), 5.59 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 171.1, 169.7, 166.6, 138.6, 134.9, 132.4 (q, J = 32.4 Hz), 131.3, 127.9, 127.6, 127.5, 124.3, 124.3, 121.6. ESI-MS $[M+H]^+$ m/z 317.25. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{16}H_{12}F_3N_4$ 317.1014, found 317.1017.

4-(*p*-Tolyl)-6-(4-(trifluoromethyl)phenyl)-1,3,5-triazin-2-amine (6h). Eluent: petroleum ether/ethyl acetate(10:1). Yield 63.4 mg (64%). White solid, mp 176.6-177.8 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25

°C) δ 8.66 (d, *J* = 8.1 Hz, 2H), 8.39 (d, *J* = 8.2 Hz, 2H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.79 (s, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 171.2, 169.7, 167.9, 142.8, 140.7, 133.7, 132.1 (q, *J* = 31.7 Hz), 129.7, 129.2, 128.6, 126.0, 125.9, 123.2, 21.6. APCI-MS $[M+H]^+$ m/z 331.12. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{17}H_{14}F_3N_4$ 331.1171, found 331.1169.

4-(*m*-Tolyl)-6-(4-(trifluoromethyl)phenyl)-1,3,5-triazin-2-amine (6i). Eluent: petroleum ether/ethyl acetate(10:1). Yield 51.5 mg (52%). White solid, mp 145.2-146.4 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.66 (d, *J* = 8.1 Hz, 2H), 8.30 (d, *J* = 8.9 Hz, 2H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.82 (s, 2H), 7.50-7.42 (m, 2H), 2.44 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 171.3, 169.8, 167.9, 140.6, 138.3, 136.4, 133.3, 133.0, 132.7, 132.1 (q, *J* = 31.8 Hz), 129.3, 129.1, 129.0, 126.0, 125.9, 123.2, 21.5. APCI-MS $[M+H]^+$ m/z 331.15. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{17}H_{14}F_3N_4$ 331.1171, found 331.1174.

4-Pentyl-6-(*p*-tolyl)-1,3,5-triazin-2-amine (6j). Eluent: petroleum ether/ethyl acetate(10:1). Yield 25.4 mg (33%). White solid, mp 130.5-132.1 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.23 (d, *J* = 8.2 Hz, 2H), 7.42 (s, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 2.62-2.56 (m, 2H), 2.38 (s, 3H), 1.78-1.69 (m, 2H), 1.44-1.19 (m, 4H), 0.93-0.85 (m, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 179.1, 170.4, 167.5, 142.2, 134.0, 129.6, 128.4, 38.7, 31.5, 27.2, 22.4, 21.6, 14.4. ESI-MS $[M+H]^+$ m/z 257.22. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{15}H_{21}N_4$ 257.1766, found 257.1776.

4-Pentyl-6-[4-(trifluoromethyl)phenyl]-1,3,5-triazin-2-amine (6k). Eluent: petroleum ether/ethyl acetate (10:1). Yield 27.9 mg (30%). White solid, mp 118.9-120.4°C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.51 (d, *J* = 8.1 Hz, 2H), 7.90 (d, *J* = 8.3 Hz, 2H), 7.65 (s, 2H), 2.67-2.61 (m, 2H), 1.84-1.67 (m, 2H), 1.33 (m, *J* = 7.1, 3.6 Hz, 4H), 0.91-0.84 (m, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 179.5, 169.3, 167.5, 140.6, 131.9 (q, *J* = 31.8 Hz), 129.1, 126.0, 125.9, 123.2, 38.6, 31.5, 27.2, 22.4,

14.3. ESI-MS $[M+H]^+$ m/z 311.31. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{15}H_{18}F_3N_4$ 311.1484, found 311.1486.

ASSOCIATED CONTENT

Supporting Information. Optimization tables of reaction conditions for the products **4** and **6**, the ^1H and ^{13}C NMR spectra of these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* E-mail : xuhao@henu.edu.cn; 18937822307@163.com.

ORCID

Hao Xu: 0000-0002-6069-3246

Author Contributions

‡ Liyang Pan and Zhenxing Li contributed equally to this work.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Patel, R. V.; Keum, Y. -S.; Park, S. W. *Mini-Rev. Med. Chem.* **2014**, *14*, 768. (b) Giacomelli, G.; Porcheddu, A.; de Luca, L. *Curr. Org. Chem.* **2004**, *8*, 1497. (c) Gamez, P.; Reedijk, J. *Eur. J. Inorg. Chem.* **2006**, 29. (d) Taeuber, K.; Dani, A.; Yuan, J. -Y. *ACS Macro Lett.* **2017**, *6*, 1.

(2) (a) Blotny, G. *Tetrahedron* **2006**, *62*, 9507. (b) Hayashi, M.; Yamasaki, T.; Kobayashi, Y.; Imai, Y.; Watanabe, Y. *Eur. J. Org. Chem.* **2009**, 4956. (c) Isfahani, A. L.; Mirkhani, V.; Khosropour, A. R.; Moghadam, M.; Tangestaninejad, S.; Kia, R. *Adv. Synth. Catal.* **2013**, *355*, 957.

(3) (a) Diaz-Ortiz, A.; de la Hoz, A.; Moreno, A.; Migallon, A. S.; Valiente, G. *Green Chem.* **2002**, *4*, 339. (b) Xu, F.; Sun, J. H.; Yan, H. B.; Shen, Q. *Synth. Commun.* **2000**, *30*, 1017.

(4) (a) Wessig, P.; Schwarz, J. *Monatsh. Chem.* **1995**, *126*, 99. (b) Xie, F.; Chen, M.; Wang, X.; Jiang, H.; Zhang, M. *Org. Biomol. Chem.* **2014**, *12*, 2761. (c) You, Q.; Wang, F.; Wu, C.; Shi, T.; Min, D.; Chen, H.; Zhang, W. *Org. Biomol. Chem.* **2015**, *13*, 6723. (d) Xu, X. -W.; Zhang, M.; Jiang, H. -F.; Zheng, J.; Li, Y. -Q. *Org. Lett.* **2014**, *16*, 3540. (e) Huang, H. -W.; Guo, W.; Wu, W. -Q.; Li, C. -J.; Jiang, H. -F. *Org. Lett.* **2015**, *17*, 2894. (f) Tiwari, A. R.; Bhanage, B. M. *Green Chem.* **2016**, *18*, 144.

(5) Tang, P. C. T.; Yang, C.; Li, R. W. -S.; Lee, S. M. -Y.; Hoi, M. P. -M.; Chan, S. -W.; Kwan, Y. -W.; Tse, C. -M.; Leung, G. P. -H. *Eur. J. Pharmacol.* **2016**, *791*, 544.

(6) (a) Gulevskaya, A. V.; Maes, B. U. W.; Meyers, C. *Synlett* **2007**, *71*. (b) Herrera, A.; Riaño, A.; Moreno, R.; Caso, B.; Pardo, Z. D.; Fernández, I.; Sáez, E.; Molero, D.; Sánchez-Vázquez, A.; Martínez-Alvarez, R. *J. Org. Chem.* **2014**, *79*, 7012. (c) Huffman, K. R.; Schaefer, F. C. *J. Org. Chem.* **1963**, *28*, 1816. (d) Xiao, L.; Poethig, A.; Hintermann, L. *Monatsh. Chem.* **2015**, *146*, 1529.

(7) (a) Xu, H.; Li, S. -F.; Liu, H. -X.; Fu, H.; Jiang, Y. -Y. *Chem. Commun.* **2010**, *46*, 7617. (b) Xu, H.; Fu, H. *Chem. Eur. J.* **2012**, *18*, 1180. (c) Xu, H.; Ma, S.; Xu, Y. -Q.; Bian, L. -X.; Ding,T.; Fang, X. -X.; Zhang, W. -K.; Ren, Y. -R. *J. Org. Chem.* **2015**, *80*, 1789. (d) Li, H. -Y.; Jie, J. -Y.; Wu, S. -X.; Yang, X. -B.; Xu, H. *Org. Chem. Front.* **2017**, *4*, 250. (e) Su, H. -M.; Wang, L. -Y.; Rao, H. -H.; Xu, H. *Org. Lett.* **2017**, *19*, 2226.

(8) (a) Zhang, C.; Tang, C.-H.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. (b) Zhao, M. -N.; Hui, R.-R.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z. -H. *Org. Lett.* **2014**, *16*, 3082.

(9) Huffman, K. R.; Schaefer, F. C. *J. Org. Chem.* **1963**, *28*, 1812.

(10) Nagasaka, H.; Ichikawa, E.; Odo, K. *J. Synth. Chem.* (*Yuki Gosei Kagaku Kyokaishi*), **1967**, *25*, 1048.

(11) Lin, Y. I.; Fields, T. L. *J. Heterocyclic Chem.,* **1982**, *19*, 613.

(12) Seo, T.; Hoga, T.; Kakurai, T. *Chem. Soc. Jpn. (Nippon Kagaku Kaishi),* **1982**, 485.

(13) Weidinger H., Kranz, J. DE 1135477, **1962**.