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New heteroaromatic aminations on 5-aryl-1,2,4-triazines and 1,2,4,5-tetrazines by palladium catalysis

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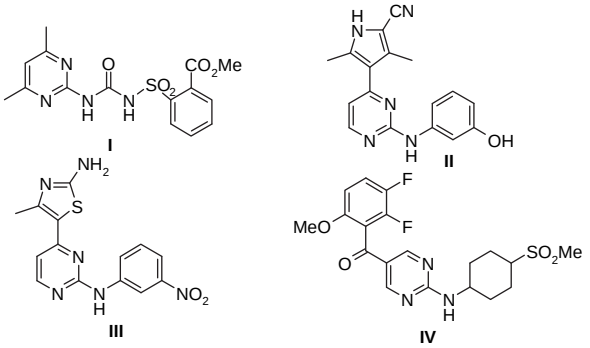
ABSTRACT

The efficient and original palladium-catalyzed amination of 5-Aryl-1,2,4-triazines and 1,2,4,5-tetrazines is reported. This Buchwald–Hartwig type reaction leads to the formation of aminated heterocycles via methylsulfur release. The reaction is optimized and a wide range of amines is used to determine the scope and limitations of this methodology.

1. Introduction

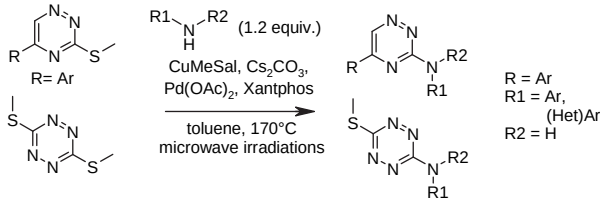
Pyrimidines are important scaffolds, which have attracted interest in the scientific community. Indeed this skeleton is present in many natural products and a variety of biologically active compounds. Among them, 2-aminopyrimidines cores are particularly interesting as they were found in molecules exhibiting promising antifungal, insecticide (Scheme 1, **I**),[1] antihistaminic, anti-anaphylactic,[2] antitumoral (**II**-**IV**),[3] and antidepressant activities.[4]



Scheme 1. Biologically active 2-aminopyrimidines.

Based on the interests of our group in the synthesis of biologically active compounds, we thought that a functionalized 3-amino-1,2,4-triazines and 3-amino-1,2,4,5-tetrazines,[5] could be considered as aza-bioisosters of 2-aminopyrimidines. We thus envisioned the development of methodologies giving access to such aminated heterocycles.

We recently described the *C*-3 palladium-catalyzed amination of 3-methylsulfanyl-1,2,4-triazines.[6,7] This desulfurative cross-coupling reaction[8] proved to be highly efficient in the presence of Cs_2CO_3, $Pd(OAc)_2$, Xantphos, and CuMeSal,[9] under microwave irradiations. Herein, we would like to complete our proposal and broaden this methodology to the use of accessible 5-aryl-3-methylsulfanyl-1,2,4-triazines and 3,6-dimethylsulfanyl-1,2,4,5-tetrazine as starting materials (Scheme 2).



Scheme 2. Desulfurative cross-coupling reaction in triazine and tetrazine series.

2. Results and discussion

2.1. Preparation of 5-aryl-3-SMe-1,2,4-triazines

3-SMe-1,2,4-triazines were thus chosen as new targets for our palladium-catalyzed amination. They were synthesized by the partial oxidation of the corresponding acetophenones by SeO_2, followed by the quench of the glyoxal intermediates (not isolated) with methylthiosemicarbazide, as limiting reactant, in basic media (Table 1).[10] The desired triazines were obtained in good to excellent yields, except for compound **3**, which was only isolated in 55% yield. Steric hindrance of the OMe group could explain this lack of reactivity.

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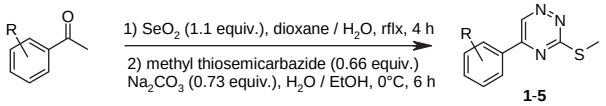
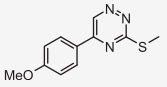
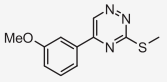
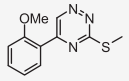
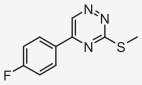
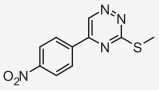
Table 1
Synthesis of derivatives **1**–**5**



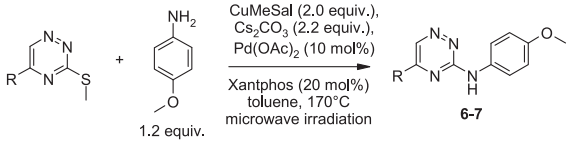
Entry	R	Product		Yield[a] (%)
1	*p*-OMe		**1**	Quant.
2	*m*-OMe		**2**	73
3	*o*-OMe		**3**	55
4	*p*-F		**4**	87
5	*p*-NO_2		**5**	72

[a] Yields are given for isolated products.

2.2. Optimization of the conditions for the preparation of derivative 7

With those five compounds in hand, we then tried to achieve the methylsulfur displacement of triazine **1** using the conditions we recently described for the synthesis of triazine **6** (Table 2, entry 1).[6,11]

Table 2
Optimization of the conditions for the preparation of derivative **7**



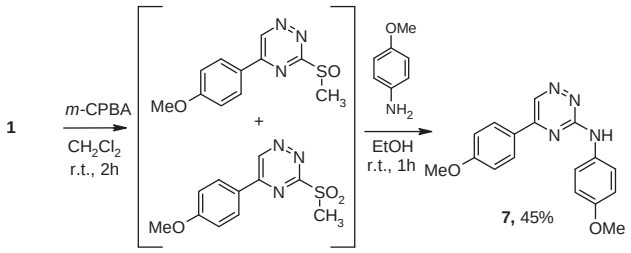
Entry	R	Time	Product	Yield (%)
1	H	2 h	**6**	91
2	*p*-OMe phenyl	25 min	**7**	13[a]
3	*p*-OMe phenyl	2 h	**7**	66[a]
4	*p*-OMe phenyl	3 h	**7**	81

[a] Some starting material was recovered.

Several assays were performed to optimize the reaction time for these new triazine series. Compound **1** and 4-methoxyaniline were irradiated in toluene at 170 °C for 25 min in the presence of Cs_2CO_3, copper(I) 3-methylsalicylate (CuMeSal), and $Pd(OAc)_2$/Xantphos (respectively 10 mol % and 20 mol %) as catalytic system. Only 13% of the desired aminotriazine **7** were isolated (entry 2) after purification. Fortunately, an increase of the reaction time to 2 h led to the isolation of 66% of **7** (entry 3). In each reaction some starting material was characterized, indicating an incomplete reaction.

Finally, 3-methylsulfanyltriazine **1** was fully consumed after 3 h of microwave irradiations, yielding to **7** in 81% yield (entry 4). No starting material was detected. The presence of the *C*-5 aryl group, bearing an electron-donating group, on the triazine seems to slightly decrease the reactivity of the *C*-3 sulfanylmethyl leaving group, as only 2 h were needed to obtain complete conversion with *C*-3 unsubstituted triazines (entry 1).[6] A similar behavior has already been observed with electron-enriched anilines in our last report.

In order to propose an alternative pathway giving access to **7**, we also envisioned its preparation by nucleophilic substitution. Under numerous reaction conditions, the direct reaction of **1** with *p*-OMe aniline failed, indicating that palladium catalysis is required for the sulfanylmethyl displacement. We then oxidized the sulfur atom of **1** at room temperature in the presence of *m*-CPBA. Nevertheless, a mixture of the corresponding sulfoxide and sulfone was obtained (Scheme 3). These compounds were too unstable to be purified and the crude mixture was engaged in the next step.



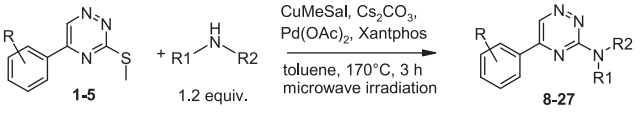
Scheme 3. Nucleophilic substitution leading to compound **7**.

The nucleophilic substitution with 4-methoxyaniline occurred but led to **7** in only 45% yield. Our convenient palladium-catalyzed methodology under microwave irradiation gave **7** with a better yield and with fewer steps.

2.3. Scope and limitations of aminations

In order to explore scope and limitations of this methodology, we next envisioned to modify the nature of the amine (Table 3) using our previously optimized conditions. The use of 3-methoxyaniline with **1** afforded the 3-aminotriazine **8** in 75% yield. The displacement of the electron-donating from the *C*-4 to the *C*-3 position of the aniline diminished the nitrogen nucleophilic effect and also the efficiency of the cross-coupling reaction (entries 1). The same behavior was observed with 4-methylaniline and aniline (entries 2 and 3).

Table 3
Synthesis of derivatives **8**–**27**



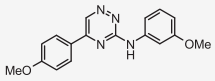
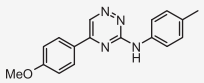
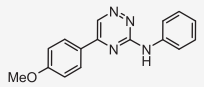
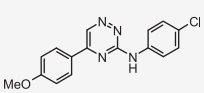
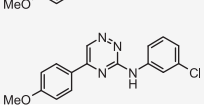
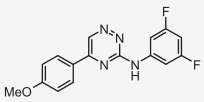
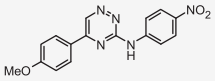
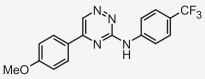
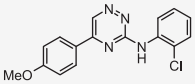
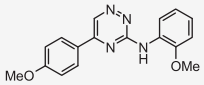
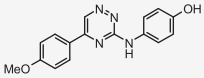
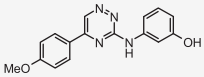
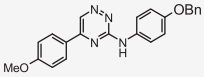
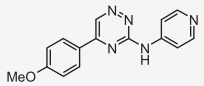
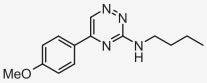
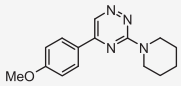
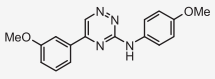
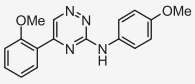
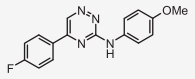
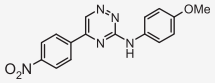
Entry	R	R1R2NH	Product	Yield (%)
1	*p*-OMe	*m*-OMe aniline		75
2	*p*-OMe	*p*-Me aniline		72
3	*p*-OMe	aniline		67
4	*p*-OMe	*p*-Cl aniline		64
5	*p*-OMe	*m*-Cl aniline		55

Table 3 (*continued*)

Entry	R	R1R2NH	Product	Yield (%)
6	*p*-OMe	3,5-difluoroaniline		62
7	*p*-OMe	*p*-NO_2 aniline		60
8	*p*-OMe	*p*-CF_3 aniline		59
9	*p*-OMe	*o*-Cl aniline		ND[a]
10	*p*-OMe	*o*-OMe aniline		ND[a]
11	*p*-OMe	*p*-OH aniline		ND[a]
12	*p*-OMe	*m*-OH aniline		ND[a]
13	*p*-OMe	*p*-OBn aniline		49[a]
14	*p*-OMe	4-aminopyridine		ND[a]
15	*p*-OMe	*n*-butylamine		ND[a]
16	*p*-OMe	piperidine		ND[a]
17	*m*-OMe	*p*-OMe aniline		85
18	*o*-OMe	*p*-OMe aniline		82
19	*p*-F	*p*-OMe aniline		68
20	*p*-NO_2	*p*-OMe aniline		72

[a] ND Not Detected, starting material was recovered.

Yields decreased again when we introduced an electron-withdrawing group on the aromatic aniline ring, nevertheless the desired triazines **11**–**15** were still obtained in a range of 55–62% using 3- or 4-chloro, 3,5-difluoro, 4-nitro, and 4-trifluoromethyl anilines (entries 4–8).

With sterically hindered anilines such as 2-chloro and 2-methoxy anilines (entries 9 and 10), the reactions were inefficient. Using 3- or 4-hydroxy anilines, the reactions did not work as well. Fortunately, the reactivity was restored starting from the *O*-benzyl protected 4-hydroxyaniline (entry 13). Less nucleophilic 4-aminopyridine, *n*-butylamine and piperidine, only led to starting material **1** (entries 14–16).

The Buchwald–Hartwig amination by *S*-alkyl displacement appeared as very efficient when steric effects and nucleophilic depletion are minored for the amine. The presence of acidic hydrogens deactivates the catalytic system.

To close our investigations on the 1,2,4-triazine series, we were then interested in the variation of the substitution on the *C*-5 aryl ring and thus used derivatives **2**–**5** with 4-OMe aniline (entries 17–20). Whatever the position and the electronic effect of the *C*-5 phenyl substituents were, the reactions were performed without any difficulties. Slight variations in yields were mainly due to the purification step.

All the NMR, IR, and HMRS spectral data are in concordance with the structure of the synthesized 3-aminotriazines **7**–**15**, **20**, **24**–**27**. In addition, X-ray crystallography of **10** confirmed that the amination was achieved (Fig. 1). The N(7) is in the sp^3 hybridation state with N(7)—C(8) and N(7)—C(6) single bonds at 1.361(2) and 1.405 (3) Å, respectively. A hydrogen bond occurs between N(7)(*x*,*y*,*z*) and N(12)(*x*−1,*y*,*z*) with N(7)···H(7)···N(12)=2.953(3) Å. The triazine ring is almost planar. The angle between plane I [C(1),C(2),C(3),C(4), C(5),C(6)] and plane II [C(8),N(9),C(10),C(11),N(12),N(13)] is 30,5 (1)°, and between plane II and plane III [C(14),C(15),C(16),C(17),C (18),C(19)] is 18.6(1)°.[12]

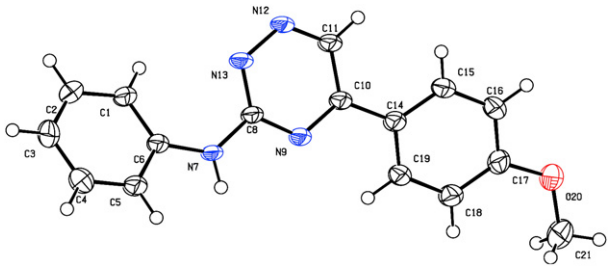
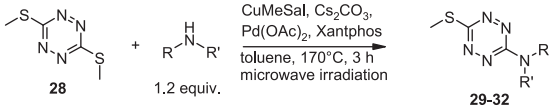


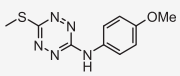
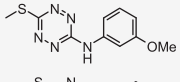
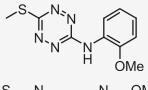
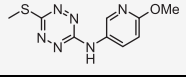
Figure 1. X-ray structure of compound **10**.

2.4. Reactivity of the 1,2,4,5-tetrazine series

We then turned our attention to 3,6-dimethylsulfanyl-1,2,4,5-tetrazine **28**. We already used this tetrazine in our previous communication and showed, through a unique assay, that it is a good cross-coupling partner, as aminotetrazine **29** was obtained in 88% yield.[5] No additive reaction with the residual *C*-5 sulfanylmethyl group (Table 4, entry 1) was observed.

Table 4
Synthesis of derivatives **29**–**32**



Entry	RR'NH	Product		Yield (%)
1	4-OMe aniline		**29**	88%
2	3-OMe aniline		**30**	83%
3	2-OMe aniline		**31**	ND[a]
4	5-amino- 2-methoxypyridine		**32**	79%

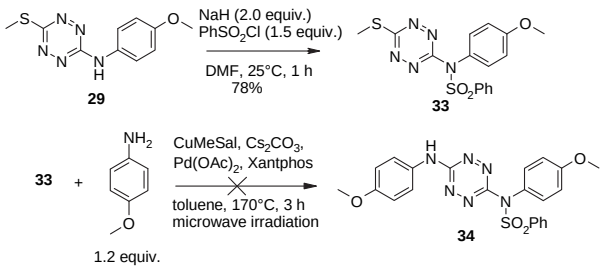
[a] ND Not Detected.

In order to confirm this first result, we envisioned to explore the reactivity of **28** with representative amines and present herein our findings. All reactions were achieved in only 3 h. Reaction with *3*-methoxyaniline gave the desired compound **30** in good yield (entry 2).[13] As described with 1,2,4-triazines, the amination failed with sterically hindered 2-methoxyaniline (entry 3) and 4-hydroxyaniline.

The same behavior was observed with 4-aminopyridine, but an assay run with the electron rich 5-amino-2-methoxy-pyridine furnished the attempted compound **32** in very good yield (entry 4).

In summary, the amination of 3,6-dimethylsulfanyl-1,2,4,5-tetrazine **28** thus depends on steric and electronic effects. Using our conditions, the coupling reaction only occurred on one methylsulfur moiety and the residual SMe group on **29**–**32** never gave additional reactions. It seems that the newly introduced amino group fully deactivated this function.

Having already established with 1,2,4-triazines that electron-poor methylsulfanyl-heteroaromatic derivatives gave better results, we thought that the reactivity of **29** could be restored by protecting the nitrogen of the newly installed amine with a benzenesulfonyl group (Scheme 4). Aminotetrazine **33** was thus obtained in 78% yield, when a solution of **29** in DMF was stirred at room temperature for 1 h in the presence of sodium hydride and phenylsulfonyl chloride. Unfortunately, the cross-coupling reaction proved to be inefficient, as only the starting material **33** was fully recovered.



Scheme 4. Amination starting from compound **33**.

3. Conclusion

In this paper, we have shown that our palladium-catalyzed amination with SMe release methodology could be applied to different *C*-5-aryl-1,2,4-triazines and 3,6-dimethylsulfanyl-1,2,4,5-tetrazine. Good to excellent yields were obtained with a wide range of amines. In general electron-rich aromatic amines gave the best results for both series. Several assays are in progress in fused triazinic and tetrazinic series and results will be published in due course.

4. Experimental section

4.1. General methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 250 or 400 MHz instrument using $CDCl_3$ or DMSO-d_6. The chemical shifts are reported in parts per million (δ scale) and all coupling constants (J) values are in hertz (Hz). The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet doublet). Melting points are uncorrected. IR absorption spectra were obtained on a Perkin Elmer PARAGON 1000 PC and values were reported in cm^{-1}. MS spectra (Ion Spray) were performed on a Perkin Elmer Sciex PI 300. HRMS were performed by the Centre Commun de Spectrométrie de Masse (Clermont Ferrand, France). Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F_{254}). Spots were visualized by UV light at 254 nm and 356 nm. Column chromatography were performed using silica gel 60 (0.063–0.200 mm, Merck).

*4.1.1. N-(4-Methoxyphenyl)-N-(6-(methylthio)-1,2,4,5-tetra zin-3-yl) benzenesulfonamide (**33**).* Under Argon atmosphere, NaH (22 mg, 0.56 mmol) was added to a solution of compound (**29**) (70 mg, 0.28 mmol) in dry DMF (10 mL) at 0 °C. Benzenesulfonyl chloride (71.0 μL, 0.56 mmol) was then added and the solution was stirred at room temperature until completion of the reaction (1 h). Water (20 mL) was added and the resulting mixture was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed several times with water (10 mL) and brine (10 mL), dried on $MgSO_4$, and evaporated under reduced pressure. Compound **33** was isolated without further purification as a reddish solid (85 mg, 78%). R_f (CH_2Cl_2/MeOH 95/5) 0.51; mp 156–158 °C; IR (ATR Diamond, cm^{-1}) ν 3055, 2942, 1587, 1438, 1269, 1225, 1141; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.67 (s, 3H), 3.85 (s, 3H), 6.97 (d, J=8.7 Hz, 2H), 7.21–7.26 (m, 2H), 7.53–7.59 (m, 2H), 7.63–7.70 (m, 1H), 8.11 (d, J=8.7 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.5 (CH_3), 55.5 (CH_3), 115.0 (CH), 128.9 (2×CH), 129.1 (Cq), 129.3 (2×CH), 131.3 (2×CH), 133.8 (2×CH), 138.7 (Cq), 160.4 (Cq), 161.5 (Cq), 172.6 (Cq); HRMS (EIMS): m/z calcd for $C_{16}H_{16}N_5O_3S_2$: 390.0672 [M+H$^+$], found: 390.0668.

4.2. General procedure A for the preparation of compounds 1–5

In a 250 mL round bottom flask, selenium dioxide was dissolved in a mixture of dioxane/water (30/1) at 60 °C. The appropriate acetophenone was then added. The resulting mixture was refluxed for 4 h, cooled to room temperature and filtered through a Celite® pad, which was washed with acetone till Celite® became white. The combined organic layers were concentrated under reduced pressure. The crude reddish brown oil was then dissolved in water and then methylthiosemicarbazide and Na_2CO_3 were added. The resulting mixture was cooled to 0 °C and stirred for 6 h. Ethanol was added to avoid solidification of the solution. The mixture was filtered at room temperature to give a yellow solid, which was dried and isolated without further purification.

*4.2.1. 5-(4-Methoxyphenyl)-3-(methylthio)-1,2,4-triazine (**1**).* Compound **1** was obtained as a yellow solid (6.2 g, 100%) following general procedure A with 4-methoxyacetophenone (4 g, 26.6 mmol), selenium dioxide (3.3 g, 29.3 mmol), dioxane (30 mL), water (1 mL), methylthiosemicarbazide (3.52 g, 17.7 mmol), sodium bicarbonate (1.75 g, 19.5 mmol), water (150 mL), ethanol (5 mL). R_f (CH_2Cl_2/MeOH 95/5) 0.35; mp 124–125 °C; IR (ATR Diamond, cm^{-1}) ν 3079, 3004, 2929, 2840, 1601, 1504, 1394, 1241, 1173; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.71 (s, 3H, SMe), 3.90 (s, 3H, OMe), 7.04 (d, J=9.0 Hz, 2H), 8.14 (d, J=9.0 Hz, 2H), 9.30 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.8 (CH_3), 55.5 (CH_3), 114.8 (2×CH), 125.2 (Cq), 129.4 (2×CH), 141.4 (CH), 153.9 (Cq), 163.4 (Cq), 173.3 (Cq); HRMS (EIMS): m/z calcd for $C_{11}H_{11}N_3OSNa$: 256.0521 [M+Na$^+$], found: 256.0529.

*4.2.2. 5-(3-Methoxyphenyl)-3-(methylthio)-1,2,4-triazine (**2**).* Compound **2** was obtained as a yellow solid (4.5 g, 73%) following general procedure A with 3-methoxyacetophenone (4.0 g, 26.6 mmol), selenium dioxide (3.3 g, 29.3 mmol), dioxane (30 mL), water (1 mL), methylthiosemicarbazide (3.52 g, 17.7 mmol), sodium bicarbonate (1.75 g, 19.5 mmol), water (150 mL), ethanol (5 mL). R_f (CH_2Cl_2/MeOH 95/5) 0.35; mp 112–113 °C; IR (ATR Diamond, cm^{-1}) ν 3079, 3004, 2929, 2840, 1601, 1504, 1394, 1241, 1173; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.73 (s, 3H), 3.90 (s, 3H), 7.13 (dd, J=5.3, 5.0 Hz,

1H), 7.46 (t, J=5.0 Hz, 1H), 7.68–7.71 (m, 2H), 9.35 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.9 (CH_3), 55.5 (CH_3), 112.6 (CH), 118.5 (CH), 119.9 (CH), 130.3 (CH), 134.5 (Cq), 142.0 (CH), 154.3 (Cq), 160.3 (Cq), 173.7 (Cq); HRMS (EIMS): m/z calcd for $C_{11}H_{11}N_3OSNa$: 256.0521 [M+Na$^+$], found: 256.0519.

*4.2.3. 5-(2-Methoxyphenyl)-3-(methylthio)-1,2,4-triazine (**3**).* Compound **3** was obtained as a yellow solid (3.4 g, 55%) following general procedure A with 2-methoxyacetophenone (4.0 g, 26.6 mmol), selenium dioxide (3.3 g, 29.3 mmol), dioxane (30 mL), water (1 mL), methylthiosemicarbazide (3.52 g, 17.7 mmol), sodium bicarbonate (1.75 g, 19.5 mmol), water (150 mL), ethanol (5 mL). R_f (CH_2Cl_2/MeOH 95/5) 0.78; mp 84–85 °C; IR (ATR Diamond, cm^{-1}) ν 1525, 1488, 1300, 1239, 1019; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.71 (s, 3H, SMe), 3.96 (s, 3H, OMe), 7.04(d, J=8.4 Hz, 1H), 7.11 (td, J=8.4, J=1.6 Hz, 1H), 7.53 (td, J=8.4, J=1.6 Hz, 1H), 8.12 (dd, J=8.0 J=1.6 Hz, 1H), 9.63 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.8 (CH_3), 55.7 (CH_3), 111.6 (CH), 121.5 (CH), 122.3 (Cq), 131.5 (CH), 133.7 (CH), 145.9 (CH), 154.4 (Cq), 158.6 (Cq), 173.2 (Cq); HRMS (EIMS): m/z calcd for $C_{11}H_{11}N_3OSNa$: 256.0521 [M+Na$^+$], found: 256.0518.

*4.2.4. 5-(4-Fluorophenyl)-3-(methylthio)-1,2,4-triazine (**4**).* Compound **4** was obtained as a yellow solid (5.57 g, 87%) following general procedure A with 4-fluoroacetophenone (3.5 mL, 26.6 mmol), selenium dioxide (3.3 g, 29.3 mmol), dioxane (30 mL), water (1 mL), and methylthio- semicarbazide (4.5 g, 19.3 mmol), sodium bicarbonate (1.75 g, 19.5 mmol), water (150 mL), ethanol (5 mL). R_f (CH_2Cl_2/MeOH 95/5) 0.34; mp 140–141 °C; IR (ATR Diamond, cm^{-1}) ν 1598, 1504, 1490, 1234, 1160, 1140; ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.66 (s, 3H, SMe), 7.39–7.49 (m, 2H), 8.34–8.42 (m, 2H), 9.79 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 13.3 (CH_3), 116.7 (d, J=21.9 Hz, 2×CH), 129.3 (d, J=2.8 Hz, Cq), 130.8 (d, J=9.3 Hz, 2×CH), 142.7 (CH), 153.2 (Cq), 165.1 (d, J=250.1 Hz, Cq), 172.5 (Cq); HRMS (EIMS): m/z calcd for $C_{10}H_8N_3SF$: 244.0321 [M+Na$^+$], found: 244.0333.

*4.2.5. 5-(4-Nitrophenyl)-3-(methylthio)-1,2,4-triazine (**5**).* Compound **5** was obtained as a yellow solid (4.32 g, 72%) following general procedure A with 4-nitroacetophenone (4.0 g, 24.2 mmol), selenium dioxide (2.69 g, 24.2 mmol), dioxane (30 mL), water (1 mL), methylthiosemicarbazide (3.76 g, 16.1 mmol), sodium bicarbonate (1.88 g, 17.8 mmol), water (150 mL), ethanol (5 mL). R_f (CH_2Cl_2/MeOH 95/5) 0.78; mp 222–223 °C; IR (ATR Diamond, cm^{-1}) ν 1519, 1494, 1344, 1328, 1301, 1241, 1136; ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.71 (s, 3H, SMe), 8.42 (d, J=9.0 Hz, 2H), 8.56 (d, J=9.0 Hz, 2H), 9.93 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 13.2 (CH_3), 124.1 (2×CH), 129.3 (2×CH), 138.8 (Cq), 143.1 (CH), 149.7 (Cq), 152.2 (Cq), 172.7 (Cq); HRMS (EIMS): m/z calcd for $C_{10}H_8N_4O_2SNa$: 271.0266 [M+Na$^+$], found: 271.0280.

4.3. General procedure B for the preparation of compounds 7–15, 20, 24–27, 29, 30–32

In a 2–5 mL sealed microwave vial were successively added the SMe derivative, the amine (1.2 equiv), copper(I) methylsalicylate (2.0 equiv), Cs_2CO_3 (2.2 equiv), Pd(OAc)$_2$ (10 mol %), and Xantphos (20 mol %). Dry toluene was added and the suspension was subjected to microwave irradiations at 170 °C for 3 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude material was immediately purified by chromatography on silica gel to afford the attempted compound.

*4.3.1. 5-(4-Methoxyphenyl)-N-(4-methoxyphenyl)-1,2,4-triazin-3-amine (**7**).* Compound **7** was obtained as a yellow solid (107 mg, 81%) following general procedure B with compound **1** (100 mg, 0.43 mmol), 4-methoxyaniline (64 mg, 0.52 mmol), CuMeSal (216 mg, 0.860 mmol), Cs_2CO_3 (279 mg, 0.94 mmol), Pd(OAc)$_2$ (10 mg, 0.043 mmol), Xantphos (50 mg, 0.086 mmol), toluene (5 mL). R_f (CH_2Cl_2/MeOH 95/5) 0.40; mp>250 °C; IR (ATR Diamond, cm^{-1}) ν 3016, 2921, 2841, 1603, 1505, 1439, 1248, 1172, 1024; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.75 (s, 3H), 3.86 (s, 3H), 6.95 (d, J=9.0 Hz, 2H), 7.15 (d, J=9 Hz, 2H), 7.69 (d, J=9.0 Hz, 2H), 8.24 (d, J=9.0 Hz, 2H), 9.37 (s, 1H), 9.87 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 55.0 (CH_3), 55.2 (CH_3), 113.7 (2×CH), 114.4 (2×CH), 121.2 (2×CH), 125.7 (Cq), 128.8 (2×CH), 132.4 (Cq), 137.6 (CH), 152.3 (Cq), 154.7 (Cq), 154.8 (Cq), 162.3 (Cq); HRMS (EIMS): m/z calcd for $C_{17}H_{17}N_4O_2$: 309.1352 [M+H$^+$], found: 309.1347.

*4.3.2. 5-(4-Methoxyphenyl)-N-(3-methoxyphenyl)-1,2,4-triazin-3-amine (**8**).* Compound **8** was obtained as a yellow solid (99 mg, 75%) following general procedure B with compound **1** (100.0 mg, 0.43 mmol), 3-methoxyaniline (64.0 mg, 0.52 mmol), CuMeSal (216 mg, 0.860 mmol), Cs_2CO_3 (279 mg, 0.94 mmol), Pd(OAc)$_2$ (10 mg, 0.04 mmol), Xantphos (50 mg, 0.08 mmol), toluene (5 mL). R_f (CH_2Cl_2/MeOH 95/5) 0.41; mp 213 °C; IR (ATR Diamond, cm^{-1}) ν 3049, 2965, 1509, 1459, 1296, 1252, 1174; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.78 (s, 3H), 3.87 (s, 3H), 6.61 (d, J=8.0 Hz, 1H), 7.16 (d, J=9.6 Hz, 2H), 7.25 (t, J=8.0 Hz, 1H), 7.38 (d, J=8.0 Hz, 1H), 7.55 (s, 1H), 8.27 (d, J=9.6 Hz, 2H), 9.44 (s, 1H), 10.07 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 54.9 (CH_3), 55.5 (CH_3), 105.0 (CH), 107.4 (CH), 111.6 (CH), 114.7 (2×CH), 125.6 (CH), 129.3 (2×CH), 129.4 (Cq), 138.4 (Cq), 140.8 (Cq), 154.1 (CH), 159.5 (Cq), 159.8 (Cq), 162.6 (Cq); HRMS (EIMS): m/z calcd for $C_{17}H_{17}N_4O_2$: 309.1352 [M+H$^+$], found: 309.1361.

*4.3.3. 5-(4-Methoxyphenyl)-N-(4-tolyl)-1,2,4-triazin-3-amine (**9**).* Compound **9** was obtained as a yellow solid (91 mg, 72%) following general procedure B with 5-(4-methoxyphenyl)-3-(methylthio)-1,2,4-triazine **1** (100 mg, 0.43 mmol), 4-methylaniline (55 mg, 0.52 mmol), CuMeSal (216 mg, 0.860 mmol), Cs_2CO_3 (279 mg, 0.946 mmol), Pd(OAc)$_2$ (10 mg, 0.043 mmol), Xantphos (50 mg, 0.086 mmol), toluene (5 mL). R_f (CH_2Cl_2/MeOH 95/5) 0.43; mp 263 °C; IR (ATR Diamond, cm^{-1}) ν 3015, 2919, 1506, 1433, 1249, 1028; ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.28 (s, 3H), 3.87 (s, 3H), 7.15 (d, J=8.7 Hz, 2H), 7.16 (d, J=8.7 Hz, 2H), 7.68 (d, J=8.7 Hz, 2H), 8.25 (d, J=8.7 Hz, 2H), 9.40 (s, 1H), 9.95 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 20.4 (CH_3), 55.5 (CH_3), 114.7 (2×CH), 119.5 (2×CH), 125.8 (Cq), 129.1 (2×CH), 129.4 (2×CH), 131.0 (Cq), 137.1 (Cq), 138.2 (CH), 154.2 (Cq), 159.9 (Cq), 162.6 (Cq); HRMS (EIMS): m/z calcd for $C_{17}H_{17}N_4O$: 293.1402 [M+H$^+$], found: 293.1412.

*4.3.4. 5-(4-Methoxyphenyl)-N-(phenyl)-1,2,4-triazin-3-amine (**10**).* Compound **10** was obtained as a yellow solid (89 mg, 67%) following general procedure B with compound **1** (100 mg, 0.43 mmol), aniline (48 mg, 0.52 mmol), CuMeSal (216 mg, 0.86 mmol), Cs_2CO_3 (279 mg, 0.94 mmol), Pd(OAc)$_2$ (10.0 mg, 0.04 mmol), Xantphos (50.0 mg, 0.08 mmol), toluene (5 mL). R_f (CH_2Cl_2/MeOH 95/5) 0.41; mp 266 °C; IR (ATR Diamond, cm^{-1}) ν 3242, 3015, 2921, 1505, 1430, 1250, 1027; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.87 (s, 3H), 7.03 (t, J=7.3 Hz, 1H), 7.16 (d, J=8.8 Hz, 2H), 7.36 (t, J=7.3 Hz, 2H), 7.83 (d, J=7.3 Hz, 2H), 8.27 (d, J=8.8 Hz, 2H), 9.43 (s, 1H), 10.06 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 55.2 (CH_3), 114.4 (2×CH), 119.3 (2×CH), 121.8 (CH), 125.6 (Cq), 128.1 (2×CH), 128.9 (2×CH), 138.0 (Cq), 139.3 (CH), 154.0 (Cq), 159.7 (Cq), 162.4 (Cq); HRMS (EIMS): m/z calcd for $C_{16}H_{15}N_4O$: 279.1246 [M+H$^+$], found: 279.1257.

*4.3.5. 5-(4-Methoxyphenyl)-N-(4-chlorophenyl)-1,2,4-triazin-3-amine (**11**).* Compound **11** was obtained as a yellow solid (85 mg, 64%) following general procedure B with compound **1** (100 mg, 0.43 mmol), 4-chloroaniline (66 mg, 0.52 mmol), CuMeSal (216 mg,

0.86 mmol), Cs_2CO_3 (279 mg, 0.94 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), Xantphos (50 mg, 0.08 mmol), toluene (5 mL). R_f (CH_2Cl_2/MeOH 95/5) 0.43; mp>250 °C; IR (ATR Diamond, cm^{-1}) ν 3238, 3017, 2949, 1603, 1553, 1510, 1490, 1254, 1027; ^1H NMR (250 MHz, DMSO-d_6) δ 3.87 (s, 3H), 7.15 (d, J=9.0 Hz, 2H), 7.41 (d, J=9.0 Hz, 2H), 7.86 (d, J=9.0 Hz, 2H), 8.27 (d, J=9.0 Hz, 2H), 9.47 (s, 1H), 10.20 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 55.1 (CH_3), 114.4 (2×CH), 120.6(2×CH), 125.4 (Cq), 127.9 (2×CH), 128.9 (2×CH), 138.2 (CH), 138.3 (Cq), 148.6 (Cq), 151.2 (Cq), 153.9 (Cq), 162.4 (Cq); HRMS (EIMS): m/z calcd for $C_{16}H_{14}N_4OCl$: 313.0856 [M+H$^+$], found: 313.0845.

*4.3.6. 5-(4-Methoxyphenyl)-N-(3-chlorophenyl)-1,2,4-triazin-3-amine (**12**).* Compound **12** was obtained as a yellow solid (74 mg, 55%) following general procedure B with compound **1** (100 mg, 0.43 mmol), 3-chloroaniline (66 mg, 0.52 mmol), CuMeSal (216 mg, 0.86 mmol), Cs_2CO_3 (279 mg, 0.94 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), Xantphos (50 mg, 0.08 mmol), toluene (5 mL). R_f (CH_2Cl_2/MeOH 95/5) 0.43; mp 226–227 °C; IR (ATR Diamond, cm^{-1}) ν 3235, 3019, 2951, 1603, 1506, 1322, 1253, 1026; ^1H NMR (250 MHz, DMSO-d_6) δ 3.87 (s, 3H), 7.07 (dd, J=8.0, 2.0 Hz, 1H), 7.17 (d, J=9.0 Hz, 2H), 7.37 (t, J=8.0 Hz, 1H), 7.75 (dd, J=8.0, 2.0 Hz, 1H), 8.04 (s, 1H), 8.28 (d, J=9.0 Hz, 2H), 9.50 (s, 1H), 10.27 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 55.6 (CH_3), 114.8 (2×CH), 117.6 (CH), 121.5 (CH), 125.5 (CH), 129.5 (2×CH),130.3 (Cq), 133.0 (CH), 139.1 (Cq), 141.3 (Cq), 154.5 (CH), 159.7 (Cq), 162.8 (Cq), 167.1 (Cq); HRMS (EIMS): m/z calcd for $C_{16}H_{14}N_4OCl$: 313.0856 [M+H$^+$], found: 313.0869.

*4.3.7. 5-(4-Methoxyphenyl)-N-(3,5-difluorophenyl)-1,2,4-triazin-3-amine (**13**).* Compound **13** was obtained as a yellow solid (84 mg, 62%) following general procedure B with compound **1** (100 mg, 0.43 mmol), 3,5-difluoroaniline (66 mg, 0.52 mmol), CuMeSal (216 mg, 0.86 mmol), Cs_2CO_3 (279 mg, 0.94 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), Xantphos (50 mg, 0.08 mmol), toluene (5 mL). R_f (CH_2Cl_2/MeOH 95/5) 0.43; mp 256 °C; IR (ATR Diamond, cm^{-1}) ν 3263, 3213, 3054, 2968, 1572, 1432, 1256, 1113; ^1H NMR (250 MHz, DMSO-d_6) δ 3.88 (s, 3H), 6.84 (t, J=8.5 Hz, 1H), 7.18 (d, J=9.1 Hz, 2H), 7.61 (d, J=8.5 Hz, 2H), 8.27 (d, J=9.1 Hz, 2H), 9.55 (s, 1H), 10.49 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 55.6 (CH_3), 96.8 (CH), 101.7 (2×CH), 114.9 (2×CH), 125.4 (Cq), 129.5 (2×CH), 139.6 (Cq), 142.5 (Cq), 154.6 (CH), 159.6 (Cq), 161.4 (Cq, J=60 Hz), 162.9 (Cq), 163.9 (Cq); HRMS (EIMS): m/z calcd for $C_{16}H_{13}F_2N_4O$: 315.1057 [M+H$^+$], found: 315.1061.

*4.3.8. 5-(4-Methoxyphenyl)-N-(4-nitrophenyl)-1,2,4-triazin-3-amine (**14**).* Compound **14** was obtained as a yellow solid (83 mg, 60%) following general procedure B with compound **1** (100 mg, 0.43 mmol), 4-nitroaniline (71 mg, 0.52 mmol), CuMeSal (216 mg, 0.86 mmol), Cs_2CO_3 (279 mg, 0.94 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), Xantphos (50 mg, 0.08 mmol), toluene (5 mL). R_f (CH_2Cl_2/MeOH 95/5) 0.43; mp>250 °C; IR (ATR Diamond, cm^{-1}) ν 3262, 3044, 2976, 1499, 1467, 1319, 1256, 1194, 1074, 1027; ^1H NMR (250 MHz, DMSO-d_6) δ 3.90 (s, 3H), 7.17 (d, J=8.6 Hz, 2H), 8.11 (d, J=8.6 Hz, 2H), 8.25 (d, J=9.3 Hz, 2H), 8.29 (d, J=9.3 Hz, 2H), 9.53 (s, 1H), 10.59 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 55.2 (CH_3), 114.5 (2×CH), 118.1 (2×CH), 124.4 (2×CH), 125.1 (Cq), 129.3 (2×CH), 139.6 (CH), 140.9 (Cq), 145.9 (Cq), 154.4 (Cq), 159.2 (Cq), 162.7 (Cq); HRMS (EIMS): m/z calcd for $C_{16}H_{14}N_5O_3$: 324.1097 [M+H$^+$], found: 324.1092.

*4.3.9. 5-(4-Methoxyphenyl)-N-(4-trifluoromethylphenyl)-1,2,4-triazin-3-amine (**15**).* Compound **15** was obtained as a yellow solid (74 mg, 59%) following general procedure B with compound **1** (100 mg, 0.43 mmol), 4-trifluoromethylaniline (83 mg, 0.52 mmol), CuMeSal (216 mg, 0.86 mmol), Cs_2CO_3 (279 mg, 0.94 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), Xantphos (50 mg, 0.08 mmol), toluene (5 mL). R_f (CH_2Cl_2/MeOH 95/5) 0.43; mp>270 °C; IR (ATR Diamond, cm^{-1}) ν 3017, 2922, 1604, 1507, 1434, 1321, 1250, 1114; ^1H NMR (250 MHz, DMSO-d_6) δ 3.88 (s, 3H), 7.18 (d, J=8.8 Hz, 2H), 7.72 (d, J=8.8 Hz, 2H), 8.06 (d, J=8.7 Hz, 2H), 8.31 (d, J=8.7 Hz, 2H), 9.54 (s, 1H), 10.49 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 55.2 (CH_3), 114.5 (2×CH), 118.7 (2×CH), 125.4 (q, J=7.8 Hz, 2×CH), 129.1 (CH), 138.9 (Cq), 154.2 (Cq), 159.4 (q, J=4.6 Hz, 2×CH), 162.6 (Cq); HRMS (EIMS): m/z calcd for $C_{17}H_{14}F_3N_4O$: 347.1120 [M+H$^+$], found: 347.1106.

*4.3.10. 5-(4-Methoxyphenyl)-N-(4-benzyloxyphenyl)-1,2,4-triazin-3-amine (**20**).* Compound **20** was obtained as a yellow solid (81 mg, 49%) following general procedure B with compound **1** (100 mg, 0.43 mmol), 4-benzyloxyaniline (102 mg, 0.52 mmol), CuMeSal (216 mg, 0.860 mmol), Cs_2CO_3 (279 mg, 0.94 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), Xantphos (50 mg, 0.08 mmol), toluene (5 mL). R_f (dichloromethane/MeOH 95/5) 0.55; mp>250 °C; IR (ATR Diamond, cm^{-1}) ν 3247, 3017, 1603, 1505, 1435, 1250, 1232, 1172, 1023; ^1H NMR (250 MHz, DMSO-d_6) δ 3.87 (s, 3H), 5.10 (s, 2H), 7.03 (d, J=8.3 Hz, 2H), 7.15 (d, J=8.5 Hz, 2H), 7.37–7.48 (m, 5H), 7.69 (d, J=8.5 Hz, 2H), 8.24 (d, J=8.3 Hz, 2H), 9.37 (s, 1H), 9.88 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 55.1 (CH_3), 69.5 (CH_2), 114.4 (2×CH), 114.8 (2×CH), 121.1 (2×CH), 125.7 (Cq), 127.0 (2×CH), 127.2 (CH), 127.9 (2×CH), 128.8 (2×CH), 132.7 (Cq), 137.0 (Cq), 137.6 (CH), 153.7 (Cq), 153.9 (Cq), 159.7 (Cq), 162.3 (Cq); HRMS (EIMS): m/z calcd for $C_{23}H_{21}N_4O_2$: 385.1665 [M+H$^+$], found: 385.1680.

*4.3.11. 5-(3-Methoxyphenyl)-N-(4-methoxyphenyl)-1,2,4-triazin-3-amine (**24**).* Compound **24** was obtained as a yellow solid (112 mg, 85%) following general procedure B with compound **2** (100 mg, 0.43 mmol), 4-methoxyaniline (64 mg, 0.52 mmol), CuMeSal (216 mg, 0.860 mmol), Cs_2CO_3 (279 mg, 0.94 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), Xantphos (50 mg, 0.08 mmol), toluene (5 mL). R_f (dichloromethane/MeOH 95/5) 0.43; mp 215–216 °C; IR (ATR Diamond, cm^{-1}) ν 3263, 3204, 3056, 2961, 1504, 1464, 1230, 1084, 1034; ^1H NMR (250 MHz, DMSO-d_6) δ 3.75 (s, 3H), 3.86 (s, 3H), 6.95 (d, J=9.0 Hz, 2H), 7.19 (dd, J=8.0, 2.9 Hz, 1H), 7.51 (t, J=8.0 Hz, 1H), 7.70 (d, J=9.0 Hz, 2H), 7.78 (s, 1H), 7.81 (t, J=8.0 Hz, 1H), 9.43 (s, 1H), 9.98 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 55.2 (CH_3), 55.3 (CH_3), 112.3 (CH), 113.8 (2×CH), 118.1 (CH), 119.8 (CH), 121.3 (2×CH), 130.3 (CH), 132.5 (Cq), 135.2 (Cq), 138.5 (CH), 154.4 (Cq), 154.8 (Cq), 159.8 (Cq), 160.1 (Cq); HRMS (EIMS): m/z calcd for $C_{17}H_{17}N_4O_2$: 309.1352 [M+H$^+$], found: 309.1339.

*4.3.12. 5-(2-Methoxyphenyl)-N-(4-methoxyphenyl)-1,2,4-triazin-3-amine (**25**).* Compound **25** was obtained as a yellow solid (108 mg, 82%) following general procedure B with compound **3** (100 mg, 0.43 mmol), 4-methoxyaniline (64 mg, 0.52 mmol), CuMeSal (216 mg, 0.86 mmol), Cs_2CO_3 (279 mg, 0.94 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), Xantphos (50 mg, 0.08 mmol), toluene (5 mL). R_f (dichloromethane/MeOH 95/5) 0.43; mp 195–196 °C; IR (ATR Diamond, cm^{-1}) ν 3262, 3204, 3056, 2962, 1614, 1509, 1232, 1108, 1017; ^1H NMR (250 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.95 (s, 3H), 6.93 (d, J=8.5 Hz, 2H), 7.03 (d, J=8.0 Hz, 1H), 7.12 (td, J=8.0, 1.2 Hz, 1H), 7.51 (td, J=8.0 Hz, J=1.2 Hz, 1H), 7.63 (d, J=8.5 Hz, 2H), 7.76 (s, 1H), 8.04 (dd, J=8.0 Hz, J=2.0 Hz, 1H), 9.35 (s, 1H); ^{13}C NMR: (62.5 MHz, $CDCl_3$) δ 55.8 (CH_3), 55.9 (CH_3), 111.8 (CH), 114.4 (2×CH), 121.6 (CH), 121.9 (2×CH), 123.5 (Cq), 131.5 (CH), 132.1 (Cq), 133.3 (CH), 142.9 (CH), 155.8 (Cq), 156.0 (Cq), 158.7 (Cq), 160.7 (Cq); HRMS (EIMS): m/z calcd for $C_{17}H_{17}N_4O_2$: 309.1352 [M+H$^+$], found: 309.1348.

*4.3.13. 5-(4-Fluorophenyl)-N-(4-methoxyphenyl)-1,2,4-triazin-3-amine (**26**).* Compound **26** was obtained as a yellow solid (91 mg, 68%) following general procedure B with compound **4** (100 mg, 0.45 mmol), 4-methoxyaniline (67 mg, 0.54 mmol), CuMeSal

(208 mg, 0.90 mmol), Cs_2CO_3 (324 mg, 0.99 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), Xantphos (52 mg, 0.09 mmol), toluene (5 mL). R_f (dichloromethane/MeOH 95/5) 0.43; mp>250 °C; IR (ATR Diamond, cm^{-1}) ν 3243, 3010, 2929, 2838, 1599, 1503, 1436, 1317, 1264; ^1H NMR (250 MHz, DMSO-d_6) δ 3.77 (s, 3H), 6.95 (d, J=9.0 Hz, 2H), 7.40 (t, J=9.0 Hz, 2H), 7.68 (d, J=9.0 Hz, 2H), 8.28 (td, J=9.0 Hz, J=2.0 Hz, 2H), 9.34 (s, 1H), 9.67 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 55.0 (CH_3), 113.7 (2×CH), 115.7 (d, J=22.0 Hz, 2×CH), 121.3 (2×CH), 129.6 (d, J=9.0 Hz, 2×CH), 130.7 (d, J=3.0 Hz, Cq), 132.2 (Cq), 137.7 (CH), 153.3 (Cq), 154.8 (Cq), 159.8 (Cq), 164.2 (d, J=249.0 Hz, Cq); HRMS (EIMS): m/z calcd for $C_{16}H_{14}FN_4O$: 297.1152 [M+H$^+$], found: 297.1147.

*4.3.14. 5-(4-Nitrophenyl)-N-(4-methoxyphenyl)-1,2,4-triazin-3-amine (**27**).* Compound **27** was obtained as a yellow solid (94 mg, 72%) following general procedure B with compound **5** (100 mg, 0.40 mmol), 4-methoxyaniline (60 mg, 0.48 mmol), CuMeSal (185 mg, 0.80 mmol), Cs_2CO_3 (289 mg, 0.88 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), Xantphos (47.0 mg, 0.08 mmol), toluene (5 mL). R_f (dichloromethane/MeOH 95/5) 0.43; mp>250 °C; IR (ATR Diamond, cm^{-1}) ν 3246, 3027, 2957, 1607, 1509, 1437, 1349, 1234, 1026; ^1H NMR (250 MHz, DMSO-d_6) δ 3.76 (s, 3H), 6.96 (d, J=8.5 Hz, 2H), 7.69 (d, J=8.5 Hz, 2H), 8.42 (d, J=8.5 Hz, 2H), 8.48 (d, J=8.5 Hz, 2H), 9.52 (s, 1H), 10.16 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 55.2 (CH_3), 113.9 (2×CH), 121.5 (2×CH), 124.2 (2×CH), 128.9 (2×CH), 132.2 (Cq), 138.5 (CH), 140.0 (Cq), 149.4 (Cq), 152.7 (Cq), 155.0 (Cq), 160.1 (Cq); HRMS (EIMS): m/z calcd for $C_{16}H_{14}N_5O_3$: 324.1097 [M+H$^+$], found: 324.1106.

*4.3.15. N-(4-Methoxyphenyl)-6-(methylthio)-1,2,4,5-tetrazin-3-amine (**29**).* Compound **29** was obtained as a yellow solid (126 mg, 88%) following general procedure B with compound **28** (100 mg, 0.57 mmol), 4-methoxyaniline (85 mg, 0.68 mmol), CuMeSal (264 mg, 1.14 mmol), Cs_2CO_3 (411 mg, 1.25 mmol), $Pd(OAc)_2$ (13 mg, 0.05 mmol), Xantphos (66 mg, 0.11 mmol), toluene (5 mL). R_f (CH_2Cl_2/MeOH 95/5) 0.44; mp 177–178 °C; IR (ATR Diamond, cm^{-1}) ν 3263, 3090, 1616, 1571, 1510, 1249, 1233, 1029; ^1H NMR (400 MHz, DMSO-d_6) δ 2.65 (s, 3H), 3.75 (s, 3H), 7.57 (d, J=9.1 Hz, 2H), 6.95 (d, J=9.1 Hz, 2H), 10.49 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.1 (CH_3), 55.2 (CH_3), 114.0 (2×CH), 121.5 (2×CH), 131.2 (Cq), 155.3 (Cq), 160.0 (Cq), 166.1 (Cq). HRMS (EIMS): m/z calcd for $C_{10}H_{12}N_5OS$: 250.0734 [M+H$^+$], found: 250.0733.

*4.3.16. N-(3-Methoxyphenyl)-6-(methylthio)-1,2,4,5-tetrazin-3-amine (**30**).* Compound **30** was obtained as a yellow solid (119 mg, 83%) following general procedure B with compound **28** (100 mg, 0.57 mmol), 3-methoxyaniline (85 mg, 0.68 mmol), CuMeSal (264 mg, 1.14 mmol), Cs_2CO_3 (411 mg, 1.25 mmol), $Pd(OAc)_2$ (13 mg, 0.05 mmol), Xantphos (66 mg, 0.10 mmol), toluene (5 mL). R_f (CH_2Cl_2/MeOH 95/5) 0.43; mp 175–177 °C; IR (ATR Diamond, cm^{-1}) ν 3263, 3056, 1504, 1464, 1230, 1084, 1034; ^1H NMR (250 MHz, $CDCl_3$) δ 2.71 (s, 3H), 3.85 (s, 3H), 6.71 (dd, J=5.3, 1.5 Hz, 1H), 7.19 (dd, J=5.2, 2.0 Hz, 1H), 7.28–7.33 (m, 2H), 7.50 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.7 (CH_3), 55.4 (CH_3), 105.5 (CH), 109.6 (CH), 111.8 (CH), 120.0 (Cq), 130.1 (CH), 138.4 (Cq), 159.8 (Cq), 160.4 (Cq); HRMS (EIMS): m/z calcd for $C_{10}H_{12}N_5OS$: 250.0734 [M+H$^+$], found: 250.0741.

*4.3.17. N-(6-Methoxypyridin-3-yl)-6-(methylthio)-1,2,4,5-tetrazin-3-amine (**32**).* Compound **32** was obtained as a yellow solid (113 mg, 79%) following general procedure B with compound **28** (100 mg, 0.40 mmol), 6-methoxypyridin-3-amine (64 mg, 0.48 mmol), CuMeSal (185 mg, 0.80 mmol), Cs_2CO_3 (289 mg, 0.88 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), Xantphos (47.0 mg, 0.08 mmol), toluene (5 mL). R_f (CH_2Cl_2/MeOH 95/5) 0.43; mp 182–184 °C; IR (ATR Diamond, cm^{-1}) ν 3221, 3022, 1545, 1474, 1238, 1087, 1030; ^1H NMR (250 MHz, $CDCl_3$) δ 2.68 (s, 3H), 3.95 (s, 3H), 6.80 (d, J=8.5 Hz, 1H), 7.41–7.42 (m, 1H), 7.96 (dd, J=9.0, 3.0 Hz, 1H), 8.32 (d, J=1.0 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.6 (CH_3), 55.7 (CH_3), 110.9 (CH), 132.5 (CH), 133.7 (Cq), 139.3 (CH), 160.0 (Cq), 161.2 (Cq), 168.9 (Cq); HRMS (EIMS): m/z calcd for $C_9H_{11}N_6OS$: 250.0621 [M+H$^+$], found: 250.0618.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.03.099.

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11. More than 20 h were needed to get full completion when the reaction was run under reflux conditions. See Ref. 5.
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13. Fields and Boger described that *N*-substituted 6-(methylthio)-1,2,4,5-tetrazin-3-amines could be obtained through the direct displacement of the SMe moiety by amines, without the use of palladium catalysis. However the reported yields were poor. See: (a) Fields, S. C.; Parker, M.; Erickson, W. R. *J. Org. Chem.* **1994**, *59*, 8284; (b) Boger, D. L.; Schaum, R. P.; Garbaccio, R. M. *J. Org. Chem.* **1998**, *63*, 6329 and references quoted therein. Besides control experiments run without Pd $(OAc)_2$/CuMeSal, in the 1,2,4-triazine and 1,2,4,5-tetrazine series failed in our hands.