First Efficient Palladium-Catalyzed Aminations of Pyrimidines, 1,2,4-Triazines and Tetrazines by Original Methyl Sulfur Release

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Abstract: The efficient and original palladium-catalyzed amination of pyrimidines, 1,2,4-triazines and tetrazines is reported. Starting from triazine **1**, a Buchwald–Hartwig-type reaction leads to the formation of heterocycle **2** via methyl sulfur release. This reaction was generalized to the use of a wide range of amines in good to excellent yields.

Key words: aminations, cross-coupling, palladium, copper, sulfur

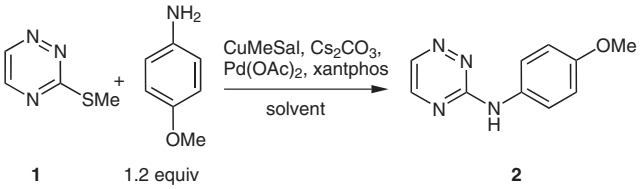
Six-membered heterocycles such as 1,2,4-triazines are widely used to design bioactive compounds. Indeed, these motifs are found in compounds showing a wide range of biological activities as antifungal,[1] antitumoral,[1] insecticide activities, etc.[2] As a result, chemist energy was recently highly mobilized to realize selective substitutions on those motifs.

Among the three available positions to offer molecular diversity, the C-3 position appeared to be the most attractive. For C-3 (het)arylations, the most commonly reported methods consist in the direct insertion of the residue during the triazine formation.[3] However palladium-catalyzed reactions are also attractive. Nevertheless C-3 halides or triflates are sometimes of limited availability and/or stability, especially in triazine series.

On the basis of our interests in heterocyclic synthesis, our laboratory recently described desulfurative cross-coupling reactions of methyl thiotriazines and cyclic thionocarbamates. It was therein established that these very efficient Stille,[4] Suzuki–Miyaura[5] and Sonogashira-type reactions[6] need a copper(I) cofactor to work.[7]

We then thought that the next interesting and missing protocol to be investigated would be the C-3 direct catalyzed amination. To our knowledge, only a few examples in the literature described an S_NAr reaction between a 3-methylthio-1,2,4-triazine and an amine.[8] Yields were generally poor and, in some cases, the SMe moiety even had to be oxidized as a methylsulfonyl group[9] and the amine activated as a formamide.[10] This method, which needs two activating steps including the formation of a sulfone, appeared to be difficult and capricious. We thus envisioned the direct and original displacement of the SMe group under palladium-catalyzed conditions.[11]

Considering Buchwald studies,[12] (het)aromatic aminations required a base (i.e. Cs_2CO_3), and $Pd(OAc)_2$–Xantphos as catalytic system. To achieve an alkylsulfur displacement we proved that a copper(I) source, copper(I) 3-methylsalicylate (CuMeSal) is required.[4–6] So we first used this cofactor to perform our assays (Scheme 1) and 4-methoxyaniline was chosen to explore the reactivity.



Scheme 1 Synthesis of derivative **2**

Using four equivalents of base, three equivalents of CuMeSal, 5 mol% of catalyst and 10 mol% of ligand in refluxing toluene, the desired compound **2** was formed after 20 hours, in an encouraging yield of 47% (Table 1, entry 1). To reduce the reaction time we then performed the reaction under microwave irradiation. At 170 °C, the reaction was completed in only two hours and the desired compound **2** was isolated in 66% yield (entry 2).[13]

The next assays concerned the optimization of all the different parameters. Changing the reaction solvent from toluene to dioxane decreased the yield down to 19% (entry 3). But adjustment of the temperature restored partially the reactivity (**2**, 43%, entry 4). We then investigated the copper(I) source: the use of copper(I) thiophene-2-carboxylate (CuTc) did not improve the yield and the soluble $CuBr{\cdot}Me_2S$ did not lead to the formation of **2**. We thus focused on the CuMeSal quantity and we were pleased to obtain the same 66% yield, even with a twofold reduction in its amount (entry 5).

On the contrary, the yield dropped to 35% when the amount of the base was decreased by half (entry 6). To enhance the reactivity, we next increased the amount of the catalytic system, but the too heterogeneous system inhibited the mechanic stirring of the mixture. So we developed some new efforts to diminish the amount of the insolubles and to optimize the reaction time (not shown). In our

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Table 1 Optimization of the Conditions for the Formation of Derivative **2**

Entry	CuMeSal (equiv)	Cs_2CO_3 (equiv)	Xantphos (mol%)	$Pd(OAc)_2$ (mol%)	Solvent	Heating[a]	Temp.	Time	Yield (%)[b]
1	3.0	4.0	10	5	toluene	reflux	–	20 h	47%
2	3.0	4.0	10	5	toluene	MW	170 °C	2 h	66%
3	3.0	4.0	10	5	dioxane	MW	170 °C	2 h	19%
4	3.0	4.0	10	5	dioxane	MW	190 °C	2 h	43%
5	1.5	4.0	10	5	toluene	MW	170 °C	2 h	66%
6	3.0	2.0	10	5	toluene	MW	170 °C	2 h	35%
7	**2.2**	**2.0**	**20**	**10**	**toluene**	**MW**	**170 °C**	**2 h**	**91%**
8	–	–	–	–	toluene	MW	170 °C	2 h	ND
9	3.0	–	–	–	toluene	MW	170 °C	2 h	ND
10	3.0	4.0	–	–	toluene	MW	170 °C	2 h	ND
11	3.0	–	20	10	toluene	MW	170 °C	2 h	ND
12	–	4.0	20	10	toluene	MW	170 °C	2 h	ND
13	–	4.0	–	–	toluene	MW	170 °C	2 h	ND

[a] MW: microwave irradiation.
[b] Yields are given for isolated product; ND: not detected.

hand, as the best result, we found that the use of 2.2 equivalents of CuMeSal and two equivalents of Cs_2CO_3, 10 mol% of $Pd(OAc)_2$ and 20 mol% of Xantphos furnished triazine **2** in an excellent yield of 91% after two hours under microwave irradiation (entry 7).

In order to prove that the reaction is really a palladium-catalyzed reaction, we suppressed all the additives (entry 9). In this case no reaction occurred. The 4-methoxyaniline did not react with **1** under an S_NAr mechanism. We then suppressed them one by one and the four assays failed again (entries 10–13). As evidence, this new amination by original methyl sulfur release required all the described components without any exception.

All the spectral data are in concordance with the structure of compound **2**. In addition, isolation of a single crystal of **2** gave access to its X-ray structure analysis (Figure 1).[14]

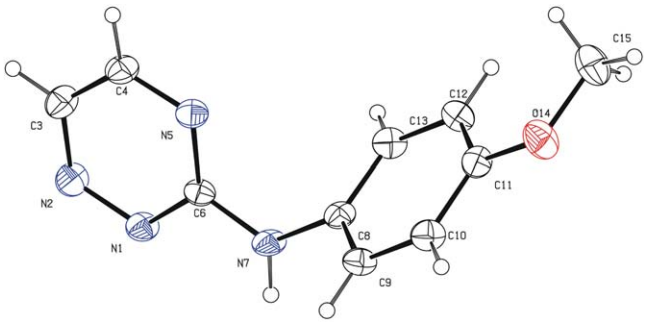


Figure 1 X-ray crystal structure of compound **2**

In order to explore the scope and limitation of our methodology, we next envisioned to modify the nature of the amine (Table 2) by using our optimized conditions.

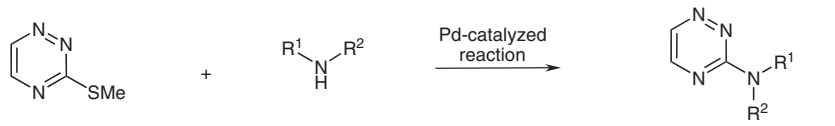
Displacement of the methoxy group from the C-4 to the C-3 position of the aniline diminished the electronic effect on nitrogen and the reactivity (entry 2), showing that the best yields were obtained with the more electron-rich amine.

This result was corroborated by the use of 4-methylaniline and aniline (entries 4 and 5) and anilines bearing an electron-withdrawing group (4-Cl or 4-NO_2, entries 6 and 7), for which yields decreased proportionally with the electronic depletion of the amine function. Assay failed for the 4-hydroxyaniline (entry 8), due to its degradation in basic media.

These electronic effects were majored using electron-deficient pyridinic amines (entries 12 and 13). In each reaction starting material **1** was recovered. Fortunately the electronic enrichment of the pyridine appeared as an efficient alternative; thus, starting from **1** and 2-methoxy-4-aminopyridine afforded compound **15** in fairly good yield (entry 14).

As last examples we tried benzylamines (entries 15 and 16) and aliphatic primary and secondary amines (entries 17–20). In each reaction, performed during two hours under microwave irradiation, no degradation was observed and the starting material **1** was identified as complementary organic material. Increase of the reaction time did not improve the yields. Nevertheless, triazines **16–21** were obtained in satisfying yields.

Table 2 Synthesis of Derivatives **2**–**21**[a]



1 1.2 equiv **2**–**21** R^1 = alkyl, benzyl; R^2 = H, alkyl

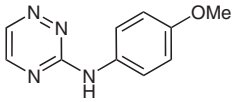
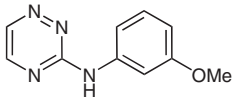
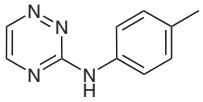
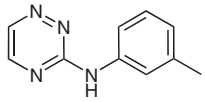
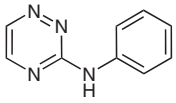
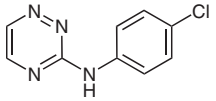
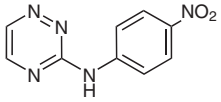
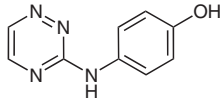
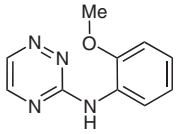
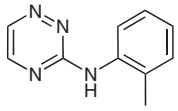
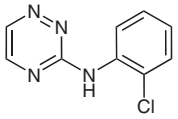
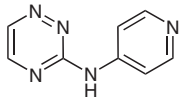
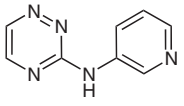
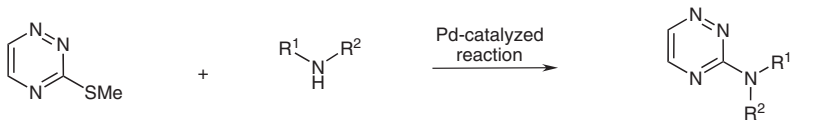
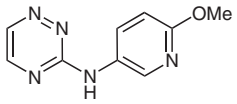
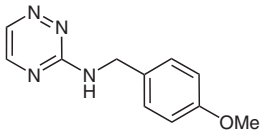
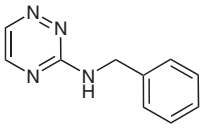
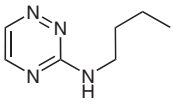
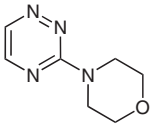
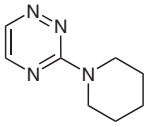
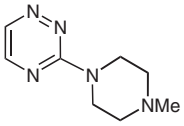
Entry	Amine	Product	Yield (%)
1	4-methoxyaniline	 **2**	91%
2	3-methoxyaniline	 **3**	79%
3	4-methylaniline	 **4**	75%
4	3-methylaniline	 **5**	69%
5	aniline	 **6**	72%
6	4-chloroaniline	 **7**	66%
7	4-nitroaniline	 **8**	51%
8	4-hydroxyaniline	 **9**	ND[b]
9	2-methoxyaniline	 **10**	ND[b]
10	2-methylaniline	 **11**	ND[b]
11	2-chloroaniline	 **12**	ND[b]
12	4-aminopyridine	 **13**	ND[b]
13	3-aminopyridine	 **14**	ND[b]

Table 2 Synthesis of Derivatives **2**–**21**[a] (continued)



1 1.2 equiv **2–21** R^1 = alkyl, benzyl; R^2 = H, alkyl

Entry	Amine	Product	Yield (%)
14	5-amino-2-methoxypyridine	 **15**	83%
15	4-methoxybenzylamine	 **16**	62%
16	benzylamine	 **17**	55%
17	*n*-butylamine	 **18**	53%
18	morpholine	 **19**	71%
19	piperidine	 **20**	82%
20	*N*-methylpiperazine	 **21**	78%

[a] For reagents and conditions see also Table 1, entry 7; ND: not detected.
[b] Starting material was recovered.

To close this first report, the last parameter to modify was the nature of the methyl sulfur derivative (Table 3). Each reaction was carried out with the efficient 4-methoxyaniline under our previously optimized conditions (vide supra Table 1). As attempted, with the methylphenylsulfane, the reaction failed. Same results were obtained by performing the reaction with the 2-pyridine or the pyrazine core (entries 1–3).

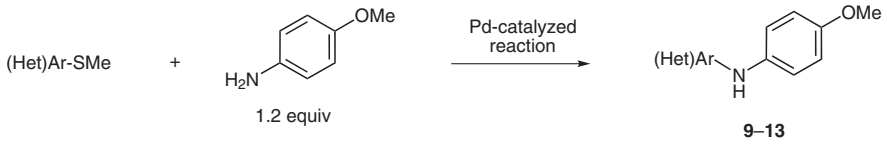
Fortunately, the efficiency of the reactivity was fully restored by using the more deactivated 2-thiomethylpyrimidine and compound **22** was isolated in 73% yield. As a last assay, we started with the 3,6-bis(methylthio)-1,2,4,5-tetrazine, and product **23** was obtained as the only isolated compound in an excellent yield of 88%. Only a mono reaction occurred indicating that a SMe discrimination would be conceivable.

In this Letter we have described efficient aromatic and alkyl aminations under palladium catalytic conditions. Several parameters are essential such as microwave activation, the presence of Cs_2CO_3 and CuMeSal additives to obtain good yields. In addition, the heteroaromatic derivative must be deactivated, with the SMe group adjacent to two nitrogen atoms, whereas electron-rich amines gave the best results. This new method would be suitable for designing more complex heterocyclic structures such as bioactive derivatives containing deactivated nitrogen heterocycles.

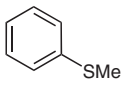
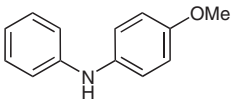
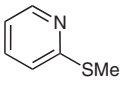
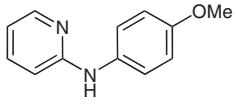
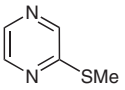
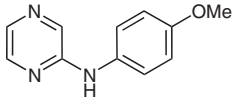
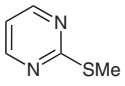
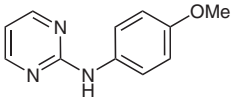
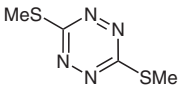
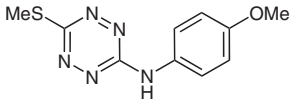
Acknowledgment

We thank the Cancéropôle Grand Ouest and the Ligue Contre le Cancer Region Centre for the financial support.

Table 3 Synthesis of Derivatives **22** and **23**[a]



9–13

Entry	(Het)ArSMe	Product	Yield (%)
1			ND
2			ND
3			ND
4			**22** (73%)
5			**23** (88%)

[a] For reaction conditions see Table 1, entry 7.
[b] ND: not detected.

References and Notes

(1) (a) Lacefield, W. B. U.S. Patent, US 3948894, **1974**; *Chem. Abstr.* 1974, *85*, 33089. (b) Wang, H.; Lim, K. L.; Yeo, S. L.; Xu, X.; Sim, M. M.; Ting, A. E.; Wang, Y.; Yee, S.; Tan, Y. H.; Pallen, C. J. *J. Nat. Prod.* **2000**, *63*, 1641. (c) Nagamatsu, T.; Yamasaki, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 130.

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(13) General Procedure for the Heterocyclic Amination: In a 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%). Anhydrous toluene was added and the suspension was subjected to MW irradiation at 170 °C for 2 h. The reaction mixture was cooled to r.t. and the solvent was

removed under reduced pressure. The crude material was immediately purified by chromatography on silica gel (CH_2Cl_2) to afford the attempted compound. Compound 2: R_f 0.65 (CH_2Cl_2–MeOH, 95:5); mp 164–165 °C (CH_2Cl_2). IR (ATR diamond): 3196, 2961, 1595, 1574, 1507, 1447, 1323, 1291, 1107, 1025, 890, 810 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 6.93 (d, *J* = 9.0 Hz, 2 H), 7.54 (d, *J* = 9.0 Hz, 2 H), 7.78 (br s, 1 H), 8.22 (d, *J* = 2.3 Hz, 1 H), 8.68 (d, *J* = 2.3 Hz, 1 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 55.5 (Me), 114.3 (2 × CH), 122.5 (2 × CH), 130.9 (Cq), 141.8 (CH), 149.1 (CH), 156.3 (Cq), 160.9 (Cq). HRMS (EI–MS): *m/z* [M + H^+] calcd for $C_{10}H_{11}N_4O$: 203.0933; found: 203.0946.

(14) Crystallographic Study: The structure of compound 2 has been established by X-ray crystallography (Figure 1). Colorless single crystals of 2 were obtained by slow evaporation from a methanol–chloroform (20:80) solution. The unit cell dimensions were determined using the least-squares fit from 25 reflections (25° < *c* < 35°): *a* = 5.628 (1) Å, *b* = 8.211 (5) Å, *c* = 10.741 (2) Å, α = 101.05 (3)°, β = 84.27 (1)°, γ = 91.47 (3)°. Space group: P–1, Z = 2, μ(Cu, *K*α) = 0.783 mm^{-1}. 1740 unique reflections were measured; final R = 4.27% (all data). Intensities were collected with an Enraf-Nonius CAD-4 diffractometer using the CuKα radiation and a graphite monochromator up to *c* = 68.91°. The data were corrected for Lorentz and polarization effects and for empirical absorption correction.[15] The structure was solved by direct methods Shelx 86 and refined using Shelx 97 suite of programs.[16,17] An intermolecular hydrogen bond partially contributed to the crystal cohesion. Indeed, the linker N7 (I) acts as a donor to the N1 (II) of the triazine moiety. The distance between N7 (I) and N1 (II), and the N7–H7 (I)···N1 (II) angle were found to be 2.978 (2) Å and 168.55°, respectively. Symmetry code of intermolecular hydrogen bond is: I (x, y, z); II (1–x, 1–y, 1–z).
CCDC 726564 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.uk/conts/retrieving.html (or from Cambridge Crystallographic Data Centre, University Chemical Lab, 12 Union Road, Cambridge,CB2 1EZ, U.K.; E-mail: deposit@ccdc.cam.ac.uk.).

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