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Easy Access to 3- or 5-Heteroarylamino-1,2,4-triazines by S_NAr, S_N^H, and Palladium-Catalyzed N-Heteroarylations

Ethel Garnier,[†,‡] Jérôme Audoux,[‡] Eric Pasquinet,[‡] Franck Suzenet,[†] Didier Poullain,[‡] Bruno Lebret,[‡] and Gérald Guillaumet*[,†]

Institut de Chimie Organique et Analytique (I.C.O.A.), UMR-CNRS 6005, LRC CEA M09, Université d'Orléans, Rue de Chartres, BP 6759, 45067 Orléans Cedex 2, France, and CEA Le Ripault, BP 16, 37260 Monts, France

gerald.guillaumet@univ-orleans.fr

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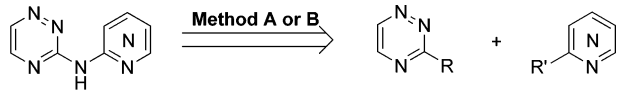
In this paper, N-arylations between two heteroaryl compounds were studied. Conditions were found to generate selectively either 3- or 5-heteroarylamino-1,2,4-triazines by investigating anionic processes (use of bases such as 2,2′,6,6′-tetramethylpiperidine/*t*BuOK/*n*BuLi) or Pd-catalyzed N-arylations [$Pd(OAc)_2$, xantphos]. These methods were successfully applied to a wide variety of heteroarylamines and allowed us to pursue our work on fused polynitrogen compounds synthesis.

Introduction

In the course of our studies on fused polynitrogen heterocycles synthesis, we were interested in the synthesis of heteroarylamino-1,2,4-triazines. First results on the amination reaction starting from different amino-1,2,4-triazines[1] led us to investigate base-promoted aminations versus Pd-catalyzed systems for C−N bond formation (Scheme 1). Our main interest was to study N-arylation reactions between two electron-poor heteroaromatic partners.

Palladium-catalyzed arylation of amines has attracted much attention in the past few years[2] and could offer convenient and versatile methods for the synthesis of heterocyclic compounds, as important builing blocks for drug discovery.[3] Whereas a variety of catalytic C−C bond-forming reactions[4] has been carried out using 1,2,4-triazine, there are many reasons for limitations of C−N palladium cross-coupling protocols, including the sensitivity of many functional groups to the combination of amine and base.[5] Nevertheless, catalytic aminations of aryl halides are an efficient method for the synthesis of anilines.[6] Moreover, there are some examples of Pd-catalyzed N-arylations with pyridinyl halides[7] achieved by using DPPP, BINAP, DPPF, or P(*t*Bu)$_3$ as ligand.[8] In the case of electron-poor aminopyridines,[9] ligands such as DCHPDMAB or XANTPHOS[10] are required. On the other hand, only few examples of N-arylations between two deactivated partners have been reported. [11]

SCHEME 1



Method A: Amination *via* metal amides R=LG*; R'=NH_2
Method B: Pd-catalyzed *N*-arylation R=NH_2; R'=LG*

*LG : Leaving group

In this paper, we describe the first regioselective N-arylations in the 5-position of the 3-methylsulfanyl-1,2,4-triazine **1a** using anionic conditions with various heteroarylamines, arising from a nucleophilic aromatic substitution of hydrogen mechanism (S_N^H). According to the employed base, we can also isolate the originally

[†] Université d'Orléans.
[‡] CEA Le Ripault.

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(8) DPPP = 1, 3-bis(diphenylphosphino)propane; BINAP = 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl; DPPF = 1,1′-bis(diphenylphosphino)ferrocene.

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(10) DCHPDMAB = 2-dicyclohexylphosphino-2′-(*N,N*-dimethylamino)biphenyl; XANTPHOS = 9,9-dimethyl-4,5-bis(diphenylphosphino)-xanthene.

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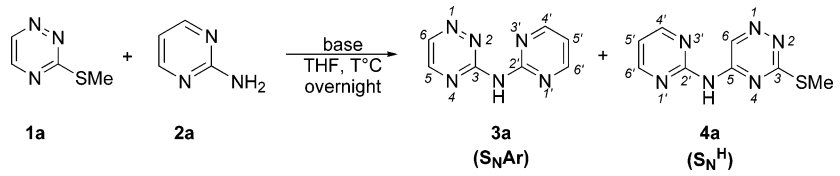
TABLE 1. Influence of Base and Temperature



1a **2a** **3a** (S_NAr) **4a** (S_N^H)

entry	base	temperature	yield of **3a**[a] (%)	yield of **4a**[b] (%)	recovered **1a**[a] (%)
1	NaH	rt	2	15	46
2	NaH	reflux	6	20	–
3	KH	rt	8	35	39
4	KH	reflux	11	65	–
5	LiTMP	rt	10	10	77
6	LiTMP	reflux	12	10	78
7	HTMP-*t*BuONa/*n*BuLi (NaTMP)	rt	58	20	8
8	HTMP-*t*BuONa/*n*BuLi (NaTMP)	reflux	49	22	–
9	HTMP-*t*BuOK/*n*BuLi (KTMP)	rt	5	75	–
10	HTMP-*t*BuOK/*n*BuLi (KTMP)	reflux	–	68	
11	LiHMDS	rt	38	4	56
12	LiHMDS	reflux	51	5	42
13	NaHMDS	rt	32	11	49
14	NaHMDS	reflux	46	15	–
15	KHMDS	rt	14	39	44
16	KHMDS	reflux	29	65	3

[a] Yield of pure, isolated product. [b] S_NAr compound **3a** and the starting 2-aminopyrimidine **2a** having the same polarity, we isolated the mixture **2a** + **3a** by silica gel column of chromatography. Thus, yields were assessed by ^1H NMR integration. Nevertheless, preparative HPLC conditions were optimized to isolate and fully characterize compound **3a**.

expected nucleophilic aromatic substitution compound (S_NAr) albeit in moderate yields. We also describe in this paper the coupling reaction between 3-amino-1,2,4-triazine **2d** and different heteroaryl halides using Pd-catalyzed reactions. This sequence constitutes a valuable alternative to S_NAr reaction and led to the isolation of 3-heteroarylamino-1,2,4-triazine derivatives in good yields.

Results and Discussion

Nucleophilic Aromatic Substitution (S_NAr). According to our laboratory experience,[1] we knew that the 3-amino-1,2,4-triazine **2d** was nonreactive toward diazotization reactions or condensation reactions with β-diketo compounds such as malonaldehyde. So we decided to generate the C−N bond by nucleophilic displacement of a leaving group in the 3-position of the triazine ring. In opposition to 1,2,4-triazinyl halides, the synthesis and the reactivity of the 3-methylsulfanyl-1,2,4-triazine **1a** is well-described.[12] Thus, we tried to use 2-aminopyrimidine **2a** as the electron-poor amine reference product and decided to generate the corresponding metal amide with sodium hydride as base in refluxing THF. In those conditions, two different products, **3a** and **4a**, were isolated (Table 1, entry 2) in 6% and 20% yield, respectively. Although only S_NAr compound **3a** was expected,[13] the major product **4a**, corresponding to nucleophilic aromatic substitution of hydrogen (S_N^H) in the 5-position of the 1,2,4-triazine moiety, was suprisingly isolated (Table 1). The S_N^H compound was characterized by ^1H and ^{13}C NMR. ^{15}N NMR analyses (nitrogen chemical shifts[14] and N−H correlation) were carried out to confirm on which position (5 or 6) addition had occurred. In the literature,[15] only one example of S_N^H with an amine is described with the 3-methylsulfanyl-1,2,4-triazine **1a** using ammonia in methanol (Chichibabin conditions). The authors needed to oxidize the final product with potassium permanganate to get back aromaticity; in our case, no further oxidizing reagent was necessary to isolate **4a**. For this reason, we supposed that the formation of this compound followed an oxidative nucleophilic substitution of hydrogen (ONSH) mechanism: the metal amide first added the 1,2,4-triazine ring in position 5 and the oxidative sequence then proceeded spontaneously.

To study the scope and limitations of this reaction, we tried different experimental conditions to get the highest regioselectivity toward S_NAr or S_N^H. For this reason, we first performed the amination reaction by modifying the base and the temperature conditions (Table 1).

We deliberately chose three different series of bases: metal hydrides (M^+H^-), metal 1,1,1,3,3,3-hexamethyldisilazides (M^+HMDS^-), LiTMP and two superbasic mixtures, 2,2′,6,6′-tetramethylpiperidine/*t*BuONa/*n*BuLi, and 2,2′,6,6′-tetramethylpiperidine/*t*BuOK/*n*BuLi.[16] Al-

(11) (a) For examples of cross-couplings between pyridine and diazine derivatives, see: Jonckers, T. H. M.; Maes, B. U. W.; Lemière, G. L. F.; Dommisse, R. *Tetrahedron* **2001**, *57*, 7027. (b) Košmrlj, J.; Maes, B. U. W.; Lemière, G. L. F.; Haemers, A. *Synlett* **2000**, 1581. For references of coupling between two nucleosides purines, see: (c) De Riccardis, F.; Johnson, F. *Org. Lett.* **2000**, *2*, 293. (d) Shoffers, E.; Olsen, P. D.; Means, J. C. *Org. Lett.* **2001**, *3*, 4221. For an example of N-arylation with a substituted 3-amino-1,2,4-triazine, see: (e) Yin, J.; Zhao, M. M.; Huffman, M. A.; McNamara, J. M. *Org. Lett.* **2002**, *4*, 3481.

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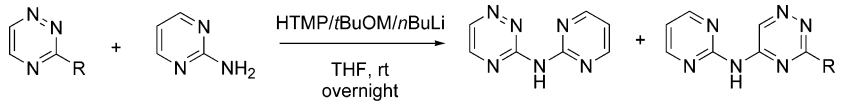
(14) For chemical schifts attribution, see: Martin, G. J.; Martin, M. L.; Gouesnard, J.-P. In *^{15}N NMR Spectrometry*; Diehl, P., Fluck, E., Kosfeld, R., Eds; Springer-Verlag: New York, 1981; p 4.

(15) Rykowski, A. *Synthesis* **1985**, 884.

(16) For the formation of the complex base, see Experimental Section.

TABLE 2. Influence of Substituent 1,2,4-Triazine Moiety in Position 3



1a-c 2a 3a S_NAr 4a, 5, 6 S_N^H

entry		R	M	yield of S_NAr[a] (%)		yield of S_N^H[b](%)	
1	**1a**	SMe	Na	**3a**	58	**4a**	20
2	**1a**	SMe	K	**3a**	5	**4a**	75
3	**1b**	OMe	Na	**3a**	32	**5**	–
4	**1b**	OMe	K	**3a**	30	**5**	8
5	**1c**	S*t*Bu	Na	**3a**	62	**6**	27
6	**1c**	S*t*Bu	K	**3a**	39	**6**	43

[a] Yield of pure, isolated product. [b] S_NAr compound **3a** and the starting 2-aminopyrimidine **2a** having the same polarity, we isolated the mixture **2a** + **3a** by silica gel column of chromatography. Thus, yields were assessed by ^{1}H NMR integration. Nevertheless, preparative HPLC conditions were optimized to isolate and fully characterize compound **3a**.

thoughthe actual superbasic metallating species is not yet known,[17] for simplification reasons, these mixtures will be abbreviated as NaTMP,[18] and KTMP,[19] respectively. It is noteworthy that a MTMP series was chosen instead of a MDA series (*N,N*-diisopropylamine/*t*BuONa or *t*BuOK/*n*BuLi) to avoid possible addition of amine on the triazine moiety.

First, it clearly appeared that the reaction conversion was greatly improved when the reaction was performed in the presence of potassium or sodium ion instead of lithium ion (Table 1, compare entries 5 and 6 to 7−10). In the HMDS system, the difference between the Li and Na salts is small at reflux and nonexistent at room temperature (Table 1, entry 11 vs 13 and 12 vs 14). Under heating, the amination was not favored, since degradation was observed in many of those cases (Table 1, entries 2, 4, 8, 10, and 14). Moreover, the S_NAr/S_N^H ratio was largely increased when a sodium series were used instead of a potassium series (Table 1, entries 7−10 and 13−16). It means that sodium favors the S_NAr pathway, whereas potassium gives the S_N^H compound as the major product. Finally, it is clear that the S_NAr/S_N^H ratio is also improved by using the TMPH series instead of a HMDSH series (Table 1, entries 5−16). In summary, we will use NaTMP to generate the S_NAr compound and KTMP to strongly favor the S_N^H mechanism.

This regioselectivity was particularly difficult to explain. Indeed, in the "simple" case of LiTMP, it was stipulated[20] that this base can form, in addition to monomers and dimers,[21,22] larger cyclic oligomers,[23] open dimers,[24,25] triple ions,[25] and assorted mixed aggregates.[22] The case of superbases such as NaTMP or KTMP is much more complicated because of the presence of several partners. In any case, owing to the size of the gegenions and their different complexation power, it seems evident that lithium, sodium, and potassium aggregates have distinct behavior. Furthermore, according to the literature,[26] it was mentioned that complications due to additional coligands preclude direct comparison of the gegenion influence. Consequently, interactions with the substrates in the amination reaction were modified and generated a difference of reactivity.

With the optimized bases (2,2′,6,6′-tetramethylpiperidine/*t*BuOM/*n*BuLi, with M = Na or K), we studied the influence of the leaving group at the 3-position of 1,2,4-triazine. According to the electronegativity of the oxygen compared to that of the sulfur, we chose the methoxy group,[13a,27] which was anticipated to be a better partner for the S_NAr than the methylsulfanyl group. On the other hand, we decided to evaluate the never described 3-*tert*-butylsulfanyl-1,2,4-triazine **1c** bearing a hindered substituent to avoid or, at least, reduce the S_NAr process. This compound was generated by performing the reaction between 3-methylsulfanyl-1,2,4-triazine **1a** and *t*BuSLi in tetrahydrofuran.[28]

By performing the amination reaction with 3-methoxy-1,2,4-triazine **1b** in the presence of NaTMP or KTMP, we observed a total conversion with a regioselectivity towards S_NAr. Unfortunately, significant degradation was observed, and we supposed that the S_N^H compound might degrade before rearomatization. Indeed, it is known[29] that in "spontaneous" oxidation a considerable part of the aromatic substrate used is decomposed as a result of the formation of byproducts. Curiously the S*t*Bu group did not induce the expected regioselectivity, and even if it seems obvious that steric effects could be considered, a sensible explanation seems difficult. Indeed, only 43% of the S_N^H product **6** was isolated from **1c** (Table 2, entry 6), whereas 75% of **4a** was obtained from **1a** (Table 2, entry 2). From those runs, we decided to work with R = SMe on the 3-position of the 1,2,4-triazine

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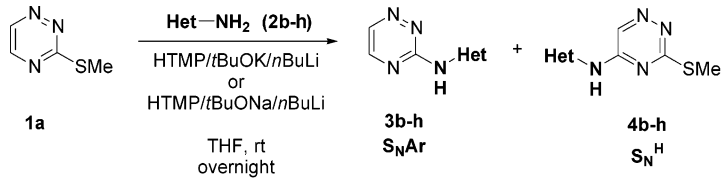
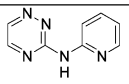
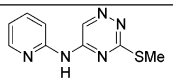
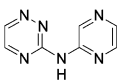
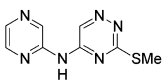
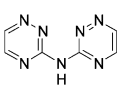
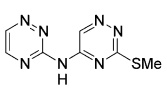
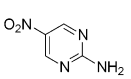
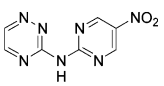
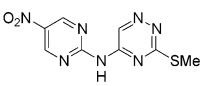
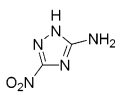
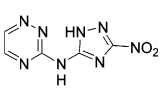
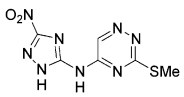
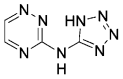
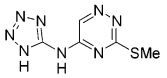
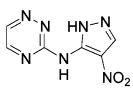
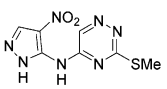
(27) (a) Paudler, W. W.; Chen, T.-K. *J. Heterocycl. Chem*. **1970**, *7*, 767. (b) Keen, B. T.; Krass, D. K.; Paudler, W. W. *J. Heterocycl. Chem*. **1976**, *13*, 807. (c) Neunhoeffer, H.; Lehman, B. *Chem. Ber*. **1976**, *109*, 1113.
(28) For preparation, see Experimental Section.
(29) Chupakhin, O. N.; Charushin, V. N.; van der Plas, H. C. Nucleophilic substitution of hydrogen in heteroaromatics. In *Nucleophilic Aromatic Substitution of Hydrogen*; Academic Press: San Diego, 1994; p 271.

TABLE 3. N-Arylations with Various Heteroaryl Amines and 3-Thiomethyl-1,2,4-triazine 1a



entry	Het-NH_2		base	S_NAr product		yield[a] (%)	S_N^H product		yield[a] (%)
1		**2b**	KTMP		**3b**	--		**4b**	71
			NaTMP			42			45
2		**2c**	KTMP		**3c**	21		**4c**	65
			NaTMP			49			41
3		**2d**	KTMP		**3d**	13		**4d**	59
			NaTMP			48			40
4		**2e**	KTMP		**3e**	--[b]		**4e**	--[b]
			NaTMP			--[b]			--[b]
5		**2f**	KTMP		**3f**	15		**4f**	48
			NaTMP			54			--
6		**2g**	KTMP		**3g**	--		**4g**	64
			NaTMP			45			--
7		**2h**	KTMP		**3h**	36		**4h**	--
			NaTMP			53			--

[a] Yield of pure, isolated compound. [b] Starting materials were recovered.

because of the highest regioselectivity and the better yields obtained.

Encouraged by these promising results, we examined, as a second part of this work, the possibility of introducing other heteroarylamines on the triazine skeleton. As illustrated in Table 3, various heterocyclic amines turned out to be valuable coupling partners. In all but one example (see entry 7), the amination with KTMP proceeded with high regioselectivity in the 5-position.

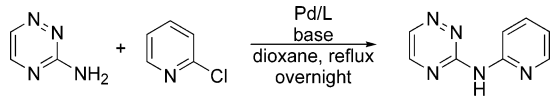
First, the pyridine and the 1,2,3,4-tetrazole adducts **4b** and **4g** (Table 3, entries 1 and 6) were selectively obtained by using KTMP, and corresponding S_NAr compounds **3b** and **3g** were isolated in moderate yield with NaTMP. In the same way, products **3c**, **3d** and **4c**, **4d** (Table 3, entries 2 and 3), resulting from the reaction with the aminopyrazine **2c** and the electron-poor 3-amino-1,2,4-triazine **2d**, were obtained in moderate (S_NAr compounds) to good yields (S_N^H compounds), respectively. 3-Amino-5-nitro-1,2,4-triazole (ANT)[30] **2f** (Table 3, entry 5) gave the corresponding S_N^H product **4f** in only 48% yield. This low yield could be explained by the sensitivity of the nitro group toward bases, which probably caused the degradation of the final compound, and the S_NAr compound was selectively obtained with 54% yield. Unfortunately, no reaction was observed with 2-amino-5-nitropyrimidine **2e** (Table 3, entry 4). Curiously, N-arylation reaction with 3(5)-amino-4-nitropyrazole[31] **2h** using either KTMP or NaTMP led only to the S_NAr compound **3h** with 36% and 53% yield, respectively (Table 3, entry 7). It is noteworthy that with heterocycles bearing both NH and NH_2 groups, we always isolated adducts resulting from the reaction of the exocyclic primary amines[32] (Table 3, entries 5−7). As a conclusion, by using 3-methylsulfanyl-1,2,4-triazine **1a** and potassium heteroaryl amides generated with 2,2′,6,6′-tetramethylpiperidine/*t*BuOK/*n*BuLi (KTMP) in tetrahydrofuran at room temperature, we have found conditions to obtain regioselectively S_N^H compounds **4a**−**h** in good yields. Unfortunately, 2,2′,6,6′-tetramethylpiperidine/*t*BuONa/*n*BuLi (NaTMP) in tetrahydrofuran at room temperature enabled isolation of only S_NAr compounds **3a**−**h** with moderate yields and regioselectivities. For this reason, we decided to study Pd-catalyzed N-arylation as an alternative way to the S_NAr process.

(30) (a) Pevzner, M. S.; Kulibabina, T. N.; Povarova, N. A.; Kilina, L. V. *Khim. Geterotsikl. Soedin.* **1979**, *8*, 1132; *Chem. Abstr.* 92:6474. (b) Simpson, R. L.; Pagoria, P. F.; Mitchell, A. R.; Coon, C. L. *Propellants, Explosives, Pyrotechnics* **1994**, *19*, 174.

(31) Dorn, H.; Dilcher, H. *Liebigs Ann. Chem.* **1967**, *707*, 141.

(32) As we will see later, compound **3f** can be obtained either by the anionic or palladium method, and ^{13}C NMR and IR spectra are superimposable in both cases. As only one isomer can be isolated by Pd-catalyzed N-arylation, we can confirm that adducts came from the reaction with the exocyclic amino function.

TABLE 4. Amination of 2-Chloropyridine 7a with 3-Amino-1,2,4-triazine 2d

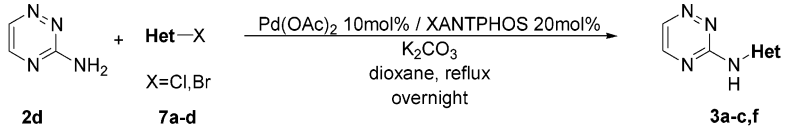


2d 7a 3b

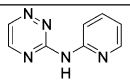
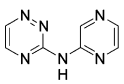
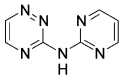
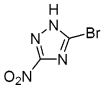
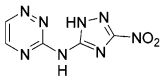
entry	Pd source	ligand	base (20 equiv)	reaction time (h)	yield[a] (%)
1	$Pd(OAc)_2$ 4 mol %	BINAP 8 mol %	K_2CO_3	24	–
2	$Pd(OAc)_2$ 4 mol %	BINAP 8 mol %	Cs_2CO_3	24	–
3	$Pd(OAc)_2$ 4 mol %	DCHPB 8 mol %	K_2CO_3	24[b]	–
4	$Pd(OAc)_2$ 10 mol %	DCHPB 20 mol %	K_2CO_3	24[b]	–
5	$Pd(OAc)_2$ 4 mol %	XANTPHOS 8 mol %	K_2CO_3	24	30
6	$Pd(OAc)_2$ 10 mol %	XANTPHOS 20 mol %	K_2CO_3	2	99
7	$Pd_2(dba)_3$ 4 mol %	XANTPHOS 8 mol %	K_2CO_3	2	89

[a] Yield of pure, isolated compound. [b] The same results were obtained in a sealed tube.

TABLE 5. Palladium-Catalyzed N-Arylations between Heteroaryl Halides 7a–d and 3-Amino-1,2,4-triazine 2d



2d 7a-d 3a-c,f

Entry	Het-X[a]		Product		Yield[b] (%)
1		**7a**		**3b**	99
2		**7b**		**3c**	76
3		**7c**		**3a**	82
4		**7d**		**3f**	68

[a] Commercially available compounds. [b] Yield of pure, isolated compound.

Palladium-catalyzed N-Arylations. Our initial experiments were focused on C–N bond formation between the 3-amino-1,2,4-triazine **2d** and heteroaryl halides **7a–d**. We therefore investigated such electron-poor partners using standard procedures. Indeed, the combination of Pd-catalysts with chelating bisphosphine ligands or bulky electron-rich biphenyl phosphine ligands have been shown to be effective for the amination of a variety of aryl and pyridinyl halides.[11] With the use of BINAP and K_2CO_3 or Cs_2CO_3 in refluxing dioxane, which were typically used in previous reports for this type of reaction, no coupling products were detected. In fact, only the use of the electron-rich DCHPB proved beneficial in some but not all described cases.[11a,b]

First, we decided to study cross-coupling reaction with the 3-amino-1,2,4-triazine **2d**. As we anticipated that we might run into trouble due to the unfavorable position of the amino group, we needed to find electron-poor halide nitrogen substrates such as the 2-chloropyridine **7a** as reference material to optimize cross-coupling conditions.

Amination with the 3-amino-1,2,4-triazine **2d** using the typically used $Pd(OAc)_2/K_2CO_3$ system and either BINAP or DCHPB ligands in dioxane at reflux was unsuccessful. No reaction occurred under these conditions, and starting materials were recovered. Even using large amounts of palladium catalyst and ligand (Pd/L 10/20 mol %, Table 4, entry 4) or using a sealed tube under inert atmosphere (Table 4, entry 3) did not give any expected result. Gratifyingly, by taking Yin's team work[11e] into account, we found that the use of xantphos resulted in the formation of small amount (30%) of the desired compound (Table 4, entry 5). Stimulated by this observation, we decided to optimize the other parameters. The use of 10 mol % $Pd(OAc)_2$ or 4 mol % tris(dibenzylidene acetone)-dipalladium $Pd_2(dba)_3$ with xantphos (Table 4, entries 6 and 7) gave the coupling product in high yield.[33] Using the above optimized conditions, i.e., xantphos as the ligand, K_2CO_3 as the base, and dioxane as the solvent, a variety of heteroaryl halides were reacted with the 3-amino-1,2,4-triazine **2d** (Table 5).

(33) When performing the reaction without base and/or without palladium, the coupling reaction did not occur.

The 3-amino-1,2,4-triazine was arylated with electron-poor heteroaryl chlorides such as 2-chloropyridine **7a**, chloropyrazine **7b**, and 2-chloropyrimidine **7c** (Table 5, entries 1−3) in good yields. Thus, even the electron-poor nitro-substituted derivative **7d** was coupled with 3-amino-1,2,4-triazine (Table 5, entry 4) in 68% yield.

Conclusion

We found conditions to generate selectively either 3- or 5-heteroaryl-1,2,4-triazines by investigating anionic processes or Pd-catalyzed N-arylations. By using palladium acetate as catalyst, xantphos as ligand, K_2CO_3, and dry dioxane, we isolated 3-heteroarylamino-1,2,4-triazines in very good yields. On the other hand, the use of bases such as 2,2′,6,6′-tetramethylpiperidide/*t*BuOK/*n*BuLi (KTMP) allowed us to generate potassium heteroaryl amides and to regioselectively isolate S_N^H derivatives with satisfactory yields. These methods were successfully applied to a wide variety of heteroarylamines. The optimization of these two methods represents a significant milestone toward the synthesis of fused polynitrogen compounds.

Experimental Section

General Methods. Melting points were determined on a Totolli apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in DMSO with a Bruker Avance 200 MHz NMR spectrometer. Chemical shifts (δ values) were reported in parts per million (ppm) and coupling constants (J values) in Hz. Multiplicity is indicated using the following abbreviations: s for a singlet, d for a doublet, t for a triplet, m for a multiplet, br s for a broad singulet, etc. Infrared spectra were recorded on a Perkin-Elmer Spectrum ON FT-IR spectrometer with a Perkin-Elmer Universal ATR sampling accessory. Elemental analyses were performed on a Flash EA 1112CHNS/O + MAS ThermoFinnigan apparatus. Mass spectra (MS) were recorded on a Perkin-Elmer mass spectrometer SCIEX API 300 by positive ion spray (IS), with samples dissolved in methanol containing 0.1% trifluoroacetic acid. Thin-layer chromatography (TLC) was performed with precoated Whatman SIL G/UV_{254} Kieselgel 60 0.25 mm TLC plates. The silica gel used for flash chromatography was Kieselgel of 0.070−0.200 mm particle size. Preparative HPLC was realized with a Merck column tube (diameter 50 mm, height 250 mm), packed with a LiChrospher 100 RP-18 silica gel, and the delivery of the pump was fixed to 20 mL/min. Compounds were detected with an UV Varian Prostar at λ = 300 nm. Reagent-grade THF and dioxane were first distilled from potassium hydroxide and then from sodium benzophenone ketyl and were stored over sodium until used. All reagents (metal hexamethyldisilazides MHMDS, 2,2′,6,6′-tetramethylpiperidine, palladium catalysts, ligands, etc.) were purchased from commercially available sources (Aldrich, Strem Chemicals) and were used as such.

As described in the literature,[12a] compound **1a** was prepared by condensation of *S*-methylthiosemicarbazide hydroiodide and 40% aqueous glyoxal. Compound **1b** was isolated in good yield[19] by reacting compound **1a** with sodium methoxide.

3-Methylsulfanyl-1,2,4-triazine (1a). Yield 75%; yellow needles; ^{1}H NMR δ (ppm) 2.60 (s, 3H, CH_3), 8.65 (d, J = 2.4 Hz, 1H, H_5), 9.15 (d, J = 2.4 Hz, 1H, H_6); mp 33 °C (lit.[12a] mp 31−33 °C).

3-Methoxy-1,2,4-triazine (1b). Yield 75%; ^{1}H NMR δ (ppm) 4.07 (s, 3H, CH_3), 8.67 (d, J = 2.3 Hz, 1H, H_5), 9.14 (d, J = 2.3 Hz, 1H, H_6); mp 48 °C (lit.[26] mp 44−46 °C).

3-*tert*-Butylsulfanyl-1,2,4-triazine (1c). At −20 °C, under inert atmosphere, *n*-BuLi (2.5 M in hexane, 30.8 mL, 77.1 mmol, 9.8 equiv) was added dropwise to a solution of 2-methyl-2-propanethiol (8.9 mL, 78.6 mmol, 10 equiv) in dry THF (25 mL). This solution was stirred during 30 min and allowed to warm to room temperature. The resulting anion was then transferred with a double syringe to a solution of 3-methylsulfanyl-1,2,4-triazine (1.00 g, 7.9 mmol) in THF (25 mL) at 0 °C. After stirring overnight at room temperature, the solution was hydrolyzed and extracted several times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in a vacuum. The crude product was purified by chromatography on silica gel column with heptane/ethyl acetate 5/1 to 2/1 v/v as eluent: yield 86%; yellow oil; IR ν (cm^{-1}) 2966, 1536, 1326; ^{1}H NMR δ (ppm) 1.57 (s, 9H, *t*Bu), 8.63 (d, J = 2.4 Hz, 1H, H_5), 9.12 (d, J = 2.4 Hz, 1H, H_6); ^{13}C NMR δ (ppm) 29.5 (*t*Bu), 47.7 (C_q), 146.1 (C_6), 149.4 (C_5), 173.2 (C_3); MS *m*/*z* 170 (M + 1). Anal. Calcd (found) for $C_7H_{11}N_3S$: C 49.68 (49.75), H 6.55 (6.58), N 24.83 (24.80).

Typical Procedure for Preparation of Lithium 2,2,6,6-Tetramethylpiperidide (LiTMP). Under nitrogen, 2,2,6,6-tetramethylpiperidine (172 μL, 1.02 mmol, 1.3 equiv) was introduced in dry THF (2 mL) at −78 °C. Then *n*-BuLi (2.5M in hexane, 409 μL, 1.02 mmol, 1.3 equiv) was added dropwise, and the mixture was stirred at −78 °C during 10 min.

Typical Procedure for Preparation of Sodium and Potassium 2,2,6,6-Tetramethylpiperidides (2,2′,6,6′-Tetramethylpiperidine/*t*BuOM/*n*BuLi, M = Na or K). Under nitrogen, *t*-BuOM (1.02 mmol, 1.3 equiv) and 2,2,6,6-tetramethylpiperidine (172 μL, 1.02 mmol, 1.3 equiv) were introduced in dry THF (2 mL) at −78 °C. Then *n*-BuLi (2.5M in hexane, 409 μL, 1.02 mmol, 1.3 equiv) was added dropwise, and the mixture was stirred at −78 °C during 10 min.

Method A: Typical Procedure for Amination with 3-Methylsulfanyl-1,2,4-triazine (1a). Under an inert atmosphere, heteroarylamines **2a**−**h** (0.94 mmol, 1.2 equiv) were added by portions to the above prepared base in dry THF, and the mixture was stirred at −78 °C during 30 min (M = K) or 1 h (M = Na, Li) to generate the corresponding amides. In another round flask, 3-methylsulfanyl-1,2,4-triazine **1a** (0.100 g, 0.78 mmol) was dissolved in THF (2 mL) and added dropwise with a double syringe. The mixture was allowed to warm to room temperature and stirred overnight. It was poured into water and extracted several times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in a vacuum. The crude products were purified on silica gel column of chromatography with dichloromethane/methanol 99/1 v/v as eluent.

Method B: Typical Procedure for Pd-Catalyzed N-Arylations. A three-necked flask was flushed with nitrogen and charged with xantphos (20 mol %) and dry dioxane (5 mL). After degassing, $Pd(OAc)_2$ (10 mol %) was charged, and the mixture was stirred under nitrogen for 10 min. In another three-necked round-bottom flask, heteroaryl halide (0.100 g, 1 equiv), 3-amino-1,2,4-triazine (1.2 equiv), and K_2CO_3 (20 equiv) were poured into dry dioxane (7 mL). Then, the $Pd(OAc)_2$/xantphos solution was added with a double syringe. The resulting mixture was subsequently heated to reflux under N_2 with vigorous stirring until the starting heteroaryl halide has disappeared. After cooling, the solid material was filtered off and washed with CH_2Cl_2 and methanol. The solvent was evaporated, and the resulting crude product was purified by flash column chromatography using dichloromethane/methanol 99/1 v/v as eluent.

(2-Pyrimidinyl){3-(1,2,4-triazinyl)}amine (3a). Method B: 82%; yellow powder; mp 232−234 °C; IR ν (cm^{-1}) 2962, 1584, 1401, 1121; ^{1}H NMR δ (ppm) 7.12 (t, $J_{4'5'} = J_{5',6'} = 4.8$ Hz, 1H, $H_{5'}$), 8.60 (d, $J_{5,6} = 2.3$ Hz, 1H, H_5), 8.62 (d, $J_{4'5'} = J_{5',6'} = 4.8$ Hz, 2H, $H_{4'}$ et $H_{6'}$), 9.01 (d, $J_{5,6} = 2.3$ Hz, H_6), 10.99 (br s, 1H, NH); ^{13}C NMR δ (ppm) 110.2 ($C_{5'}$), 140.4 (C_6), 148.4 (C_5), 163.8 ($C_{2'}$), 164.5 ($C_{4'}$ et $C_{6'}$), 164.8 (C_3); MS *m*/*z* 175 (M + 1). Anal. Calcd (found) for $C_7H_6N_6$: C 48.27 (48.07), H 3.47 (3.42), N 48.25 (48.31).

(2-Pyridinyl){3-(1,2,4-triazinyl)}amine (3b). Method B: 99%; yellow solid; mp 174−176 °C; IR ν (cm^{-1}) 3004, 1593, 1438, 1038; ^1H NMR δ (ppm) 7.79−7.89 (m, 2H, $H_{3'}$ et $H_{4'}$), 8.15 (ddd, $J_{4',5'}$ = 7.9 Hz, $J_{5',6'}$ = 5.3 Hz, $J_{3',5'}$ = 1.2 Hz, 1H, $H_{5'}$), 8.54 (d, $J_{5,6}$ = 2.3 Hz, 1H, H_6), 8.39 (ddd, $J_{3',6'}$ = 1.0 Hz, $J_{4',6'}$ = 1.2 Hz, $J_{5',6'}$ = 5.3 Hz, 1H, $H_{6'}$), 8.91 (d, $J_{5,6}$ = 2.3 Hz, 1H, H_5), 10.49 (br s, 1H, NH); ^{13}C NMR δ (ppm) 100.0 ($C_{3'}$), 117.3 ($C_{5'}$), 139.5 (C_6), 142.1 ($C_{4'}$), 149.4 (C_5), 153.4 ($C_{6'}$), 164.3 (C_3), 165.6 ($C_{2'}$); MS *m/z* 174 (M + 1). Anal. Calcd (found) for $C_8H_7N_5$: C 55.48 (55.29), H 4.07 (4.21), N 40.44 (40.25).

(2-Pyrazinyl){3-(1,2,4-triazinyl)}amine (3c). Method B: 76%; white solid; mp 256−261 °C; IR ν (cm^{-1}) 3029, 1556, 1418, 1040; ^1H NMR δ (ppm) 8.30 (d, $J_{5',6'}$ = 2.5 Hz, 1H, $H_{6'}$), 8.40 (dd, $J_{3',5'}$ = 1.6 Hz, $J_{5',6'}$ = 2.5 Hz, 1H, $H_{5'}$), 8.61 (d, $J_{5,6}$= 2.3 Hz, 1H, H_5), 8.99 (d, $J_{5,6}$ = 2.3 Hz, 1H, H_6), 9.38 (d, $J_{3',5'}$ = 1.6 Hz, 1H, $H_{3'}$), 10.88 (br s, 1H, NH); ^{13}C NMR δ (ppm) 136.4 ($C_{3'}$), 138.3 (C_6), 142.5 ($C_{5'}$), 144.0 ($C_{6'}$), 149.1 (C_5), 150.3 ($C_{2'}$), 159.2 (C_3); MS *m/z* 175 (M + 1). Anal. Calcd (found) for $C_7H_6N_6$: C 48.27 (48.11), H 3.47 (3.36), N 48.25 (47.99).

Di{3-(1,2,4-triazinyl)}amine (3d). Method A (NaTMP): 48%; yellow solid; mp 152−153 °C; IR ν (cm^{-1}) 3089, 1646, 1531, 1047; ^1H NMR δ (ppm) 8.20 (d, $J_{5',6'}$ = 2.3 Hz, 2H, H_5 and $H_{5'}$), 8.53 (d, $J_{5',6'}$ = 2.3 Hz, 2H, H_6 and $H_{6'}$), 10.47 (br s, 1H, NH); ^{13}C NMR δ (ppm) 140.6 (C_6 and $C_{6'}$), 149.9 (C_5 and $C_{5'}$), 163.3 (C_3 and $C_{3'}$); MS *m/z* 176 (M + 1). Anal. Calcd (found) for $C_6H_5N_7$: C 41.14 (41.24), H 2.88 (2.74), N 55.98 (56.11).

{3-(5-Nitro-2*H*-1,2,4-triazolyl)}{3-(1,2,4-triazinyl)}amine (3f). Method B: 68%; yellow powder; mp 216−218 °C; IR ν (cm^{-1}) 2961, 1501, 1314; ^1H NMR δ (ppm) 8.66 (d, $J_{5,6}$ = 2.4 Hz, 1H, H_5), 9.17 (d, $J_{5,6}$ = 2.4 Hz, 1H, H_6), 9.97 (br s, 1H, NH), 10.48 (br s, 1H, NH); ^{13}C NMR δ (ppm) 143.3 (C_6), 150.6 (C_5), 156.4 ($C_{3'}$), 157.2 (C_3), 172.0 ($C_{5'}$); MS *m/z* 209 (M + 1). Anal. Calcd (found) for $C_5H_4N_8O_2$: C 28.85 (28.76), H 1.94 (1.99), N 53.84 (54.01).

{5-(1*H*-1,2,4-Tetrazolyl)}{3-(1,2,4-triazinyl)}amine (3g). Method A (NaTMP): 45%; dark oil; IR ν (cm^{-1}) 3386, 2924, 1529, 1023; ^1H NMR δ (ppm) 8.65 (d, $J_{5,6}$ = 2.2 Hz, 1H, H_5), 9.15 (d, $J_{5,6}$ = 2.2 Hz, 1H, H_6), 9.95 (br s, 1H, NH), 10.47 (br s, 1H, NH); ^{13}C NMR δ (ppm) 141.6 (C_6), 142.2 (C_5), 148.1 ($C_{5'}$), 158.5 (C_3); MS *m/z* 165 (M + 1). Anal. Calcd (found) for $C_4H_4N_8$: C 29.27 (29.36), H 2.46 (2.49), N 68.27 (68.39).

{3-(4-Nitro-2*H*-pyrazolyl)}{3-(1,2,4-triazinyl)}amine (3h). Method A (NaTMP): 53%; brown oil; IR ν (cm^{-1}) 3033, 2931, 1532, 1345, 1024; ^1H NMR δ (ppm) 8.38 (s, 1H, $H_{5'}$), 8.63 (br s, 1H, NH), 9.00 (d, $J_{5,6}$ = 2.4 Hz, 1H, H_5), 9.46 (d, $J_{5,6}$ = 2.4 Hz, 1H, H_6), 10.15 (br s, 1H, NH); ^{13}C NMR δ (ppm) 94.8 ($C_{4'}$), 124.5 ($C_{5'}$), 145.4 (C_6), 153.6 (C_5), 152.7 ($C_{3'}$), 164.9 (C_3); MS *m/z* 208 (M + 1). Anal. Calcd (found) for $C_6H_5N_7O_2$: C 34.79 (34.65), H 2.43 (2.44), N 47.33 (47.20).

5-(3-Methylsulfanyl-1,2,4-triazinyl)(2-pyrimidinyl)amine (4a). Method A (KTMP): 75%; off white powder; mp >260 °C; IR ν (cm^{-1}) 2920, 1610, 1527, 1013, 795; ^1H NMR δ (ppm) 2.58 (s, 3H, CH_3), 7.21 (t, $J_{4',5'} = J_{5',6'}$ = 4.9 Hz, 1H, $H_{5'}$), 8.71 (d, $J_{4',5'} = J_{5',6'}$ = 4.9 Hz, 2H, $H_{4'}$ and $H_{6'}$), 9.92 (s, 1H, H_6), 11.16 (br s, 1H, NH); ^{13}C NMR δ (ppm) 13.0 (CH_3), 116.2 ($C_{5'}$), 137.4 (C_6), 151.1 (C_5), 157.8 ($C_{2'}$), 158.6 ($C_{4'}$ et $C_{6'}$), 170.5 (C_3); ^{15}N NMR δ (ppm) −256.7 (NH), −133.4 (N_4), −117.1 ($N_{1'}$ and $N_{3'}$), −52.2 (N_2), 33.3 (N_1); MS *m/z* 221 (M + 1). Anal. Calcd (found) for $C_8H_8N_6S$: C 43.62 (43.63), H 3.66 (3.63), N 38.16 (38.22).

5-(3-Methylsulfanyl-1,2,4-triazinyl)(2-pyridinyl)amine (4b). Method A (KTMP): 71%; yellow oil; IR ν (cm^{-1}) 2922, 1643, 1023; ^1H NMR δ (ppm) 2.57 (s, 3H, CH_3), 6.41 (ddd, $J_{3',4'}$ = 7.7 Hz, $J_{3',5'}$ = 1.1 Hz, $J_{3',6'}$ = 0.9 Hz, 1H, $H_{3'}$), 6.44 (ddd, $J_{3',5'}$ = 1.1 Hz, $J_{4',5'}$ = 5.5 Hz, $J_{5',6'}$ = 5.2 Hz, 1H, $H_{5'}$), 7,14 (ddd, $J_{3',4'}$ = 7.7 Hz, $J_{4',5'}$ = 5.5 Hz, $J_{4',6'}$ = 1.4 Hz, 1H, $H_{4'}$), 8.38 (ddd, $J_{3',6'}$ = 1.1 Hz, $J_{4',6'}$ = 1.4 Hz, $J_{5',6'}$ = 5.2 Hz, 2H, $H_{6'}$ and H_6), 9.13 (br s, 1H, NH); ^{13}C NMR δ (ppm) 13.1 (CH_3), 107.9 ($C_{3'}$), 114.0 ($C_{5'}$), 119.4 (C_6), 138.4 ($C_{4'}$), 150.9 ($C_{6'}$), 151.6 (C_5), 159.7 ($C_{2'}$), 170.2 (C_3); MS *m/z* 220 (M + 1). Anal. Calcd (found) for $C_9H_9N_5S$: C 49.30 (49.43), H 4.14 (4.08), N 31.94 (31.78).

5-(3-Methylsulfanyl-1,2,4-triazinyl)(2-pyrazinyl)amine (4c). Method A (KTMP): 65%; orange solid; mp 182−185 °C; IR ν (cm^{-1}) 2911, 1556, 1407, 1011; ^1H NMR δ (ppm) 2.60 (s, 3H, CH_3), 8.38 (d, $J_{5',6'}$ = 2.5 Hz, 1H, $H_{6'}$), 8.45 (dd, $J_{5',6'}$ = 2.5 Hz, $J_{3',5'}$ = 1.3 Hz, 1H, $H_{5'}$), 9.09 (s, 1H, H_6), 9.25 (d, $J_{3',5'}$ = 1.3 Hz, 1H, $H_{3'}$), 11.11 (br s, 1H, NH); ^{13}C NMR δ (ppm) 13.1 (CH_3), 131.6 ($C_{3'}$), 132.4 (C_6), 136.7 ($C_{5'}$), 141.9 ($C_{6'}$), 150.8 ($C_{2'}$), 156.1 (C_5), 170.4 (C_3); MS *m/z* 221 (M + 1). Anal. Calcd (found) for $C_8H_8N_6S$: C 43.62 (43.55), H 3.66 (3.61), N 38.16 (38.21).

5-(3-Methylsulfanyl-1,2,4-triazinyl)(2-triazinyl)amine (4d). Method A (KTMP): 59%; yellow powder; mp 222−224 °C; IR ν (cm^{-1}) 2827, 1600, 1515, 1048; ^1H NMR δ (ppm) 2.60 (s, 3H, CH_3), 8.74 (d, $J_{5',6'}$ = 2.4 Hz, 1H, $H_{5'}$), 9.16 (d, $J_{5',6'}$ = 2.4 Hz, 1H, $H_{6'}$), 9.78 (s, 1H, H_6), 11.67 (br s, 1H, NH); ^{13}C NMR δ (ppm) 13,1 (CH_3), 137,6 (C_6), 145,6 ($C_{6'}$), 150,6 ($C_{5'}$), 150,9 (C_5), 159,1 ($C_{3'}$), 170,7 (C_3); MS *m/z* 222 (M + 1). Anal. Calcd (found) for $C_7H_7N_7S$: C 38.00 (37.89), H 3.19 (3.12), N 44.32 (44.29).

5-(3-Methylsulfanyl-1,2,4-triazinyl){3-(5-nitro-2*H*-1,2,4-triazolyl)}amine (4f). Method A (KTMP): 48%; dark oil; IR ν (cm^{-1}) 3253, 2927, 1602, 1516, 1329, 1043; ^1H NMR δ (ppm) 2.30 (s, 3H, CH_3), 7.53 (s, 1H, H_6), 9.97 (s, 1H, NH), 10.48 (br s, 1H, NH); ^{13}C NMR δ (ppm) 15.4 (CH_3), 145.6 (C_6), 156.2 (C_5), 159.3 ($C_{3'}$), 171.1 ($C_{5'}$), 175.2 (C_3); MS *m/z* 255 (M + 1). Anal. Calcd (found) for $C_6H_6N_8O_2S$: C 28.35 (28.28), H 2.38 (2.45), N 44.08 (44.13).

5-(3-Methylsulfanyl-1,2,4-triazinyl){5-(1*H*-tetrazolyl)}amine (4g). Method A (KTMP): 64%; dark oil; IR ν (cm^{-1}) 3393, 2925, 1653, 1023; ^1H NMR δ (ppm) 2.75 (s, 3H, CH_3), 7.49 (s, 1H, H_6), 9.96 (br s, 1H, NH), 10.47 (br s, 1H, NH); ^{13}C NMR δ (ppm) 13.2 (CH_3), 142.3 (C_6), 149.0 ($C_{5'}$), 153.3 (C_5), 173.1 (C_3); MS *m/z* 211 (M + 1). Anal. Calcd (found) for $C_5H_6N_8S$: C 28.57 (28.45), H 2.88 (2.80), N 53.30 (53.21).

5-(3-Methoxy-1,2,4-triazinyl)(2-pyrimidinyl)amine (5). Method A (KTMP): 8%; brown oil; IR ν (cm^{-1}) 3012, 1614, 1545, 1232, 1090; ^1H NMR δ (ppm) 3.87 (s, 3H, CH_3), 6.95 (t, $J_{4',5'} = J_{5',6'}$ = 4.7 Hz, 1H, $H_{5'}$), 8.15 (d, $J_{4',5'} = J_{5',6'}$ = 4.7 Hz, 2H, $H_{4'}$ and $H_{6'}$), 8.89 (s, 1H, H_6), 10.11 (br s, 1H, NH); ^{13}C NMR δ (ppm) 54.3 (CH_3), 113.4 ($C_{5'}$), 128.0 (C_6), 161.5 (C_5), 161.8 ($C_{4'}$ and $C_{6'}$), 164.3 ($C_{2'}$), 171.5 (C_3); MS *m/z* 205 (M + 1). Anal. Calcd (found) for $C_8H_8N_6O$: C 46.07 (45.91), H 3.95 (3.98), N 41.16 (41.27).

5-(3-*tert*-Butylsulfanyl-1,2,4-triazinyl)(2-pyrimidinyl)amine (6). Method A (KTMP): 43%; yellow oil; IR ν (cm^{-1}): 3005, 1623, 1514, 1003; ^1H NMR δ (ppm) 1.97 (s, 9H, *t*Bu), 7.19 (t, $J_{4',5'} = J_{5',6'}$ = 4.8 Hz, 1H, $H_{5'}$), 8.70 (d, $J_{4',5'} = J_{5',6'}$ = 4.8 Hz, 2H, $H_{4'}$ and $H_{6'}$), 9.82 (s, 1H, H_6), 10.51 (br s, 1H, NH); ^{13}C NMR δ (ppm) 26.2 (*t*Bu), 55.7 (C_q), 114.8 ($C_{5'}$), 130.2, (C_6), 151.0 (C_5), 156.3 ($C_{2'}$), 162.8 ($C_{4'}$ and $C_{6'}$), 178.9 (C_3); MS *m/z* 263 (M + 1). Anal. Calcd (found) for $C_{11}H_{14}N_6S$: C 50.36 (50.28), H 5.38 (5.37), N 32.04 (31.99).

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