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A Straightforward, One-Pot Protocol for the Synthesis of Fused 3-Aminotriazoles

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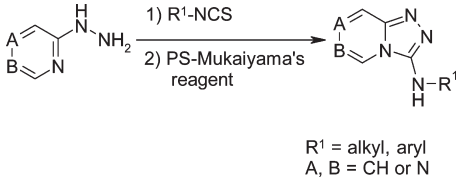

A simple protocol for the synthesis of 3-amino-[1,2,4]triazolo[4,3-*a*]pyridines is reported. The newly developed one-pot methodology involves the reaction of hydrazinopyridine with isothiocyanates to give the corresponding thiosemicarbazides, which are further desulfurized *in situ* using polymer-supported Mukaiyama's reagent to promote the final cyclization and formation of the central core. Aryl isothiocyanates bearing both electron-donating and electron-withdrawing groups are well tolerated, and the expected compounds were obtained in excellent purities and yields after removal of salts with a SPE-NH_2 column. This methodology proved to be robust in the extension to 3-amino-[1,2,4]triazolo[4,3-*a*]-pyrazines and 3-amino-[1,2,4]triazolo[4,3-*c*]-pyrimidines, and no significant differences were noticed in terms of purities and yields. The straightforward protocol developed, *mix*, *filter*, and *evaporate*, is appropriate for performing multiple reactions in parallel fashion without need of purification.

Introduction

Triazolopyridine derivatives are an important class of molecules in medicinal chemistry and can be found in many biologically active compounds.[1] However, the use of 3-amino-[1,2,4]triazolo[1,5-*a*]pyridines as central scaffolds in drug discovery is very limited due to the lack of generally applicable methodology for their synthesis starting from commercially readily available precursors. To the best of our knowledge, only three approaches have described the synthesis of *N*-unsubstituted 3-amino-[1,2,4]triazolo[1,5-*a*]-pyridines ($R^2 = H$) (Scheme 1).[2]

The first synthesis involves the reaction of 2-bromopyridine with thiosemicarbazide via an oxidative cyclization of the corresponding adduct under heating conditions, affording the product after purification in moderate yield.[2a] In the second approach, the expected product was obtained in good yield from 6-chloro-2-hydrazinopyridine and cyanogen bromide.[2b] Later, this highly toxic reagent was replaced by di-(imidazol-1-yl)methanimine but with a moderate yield in this case.[2c] Concerning the *N*-substituted 3-amino-[1,2,4]triazolo[4,3-*a*]pyridines ($R^2 \neq H$), their syntheses have not been extensively explored (Scheme 1).[3] The synthesis of the

(1) For recent examples of biologically active [1,2,4]triazolo[1,5-*a*]pyridines, see: (a) Samori, C.; Guerrini, A.; Varchi, G.; Fontana, G.; Bombardelli, E.; Tinelli, S.; Beretta, G. L.; Basili, S.; Moro, S.; Zunino, F.; Battaglia, A. *J. Med. Chem.* **2009**, *52*, 1029–1039. (b) Guan, L.-P.; Jin, Q.-H.; Wang, S.-F.; Li, F.-N; Quan, Z.-S. *Arch. Pharm. Chem. Life Sci.* **2008**, *341*, 774–779. (c) Roma, G.; Grossi, G.; Di Braccio, M.; Piras, D.; Ballabeni, V.; Tognolini, M.; Bertoni, S.; Barocelli, E. *Eur. J. Med. Chem.* **2008**, *43*, 1665–1680. (d) Cappelli, A.; Giuliani, G.; Anzini, M.; Riitano, D.; Giorgi, G.; Vomero, S. *Bioorg. Med. Chem.* **2008**, *16*, 6850–6859. (e) Pierce, A. C.; Jacobs, M.; Stuver-Moody, C. *J. Med. Chem.* **2008**, *51*, 1972–1975. (f) Nayana, M. R. S.; Sekhar, Y. N.; Kumari, N. S.; Mahmood, S. K.; Ravikumar, M. *Eur. J. Med. Chem.* **2008**, *43*, 1261–1269. (g) Edmondson, S. D.; Mastracchio, A.; Mathvink, R. J.; He, J.; Harper, B.; Park, Y.-J.; Beconi, M.; Di Salvo, J.; Eiermann, G. J.; He, H.; Leiting, B.; Leone, J. F.; Levorse, D. A.; Lyons, K.; Patel, R. A.; Patel, S. B.; Petrov, A.; Scapin, G.; Shang, J.; Roy, R. S.; Smith, A.; Wu, J. K.; Xu, S.; Zhu, B.; Thornberry, N. A.; Weber, A. E. *J. Med. Chem.* **2006**, *49*, 3614–3627. (h) Kenyon, V.; Chorny, I.; Carvajal, W. J.; Holman, T. R.; Jacobson, M. P. *J. Med. Chem.* **2006**, *49*, 1356–1363. (i) McClure, K. F.; Letavic, M. A.; Kalgutkar, A. S.; Gabel, C. A.; Audoly, L.; Barberia, J. T.; Braganza, J. F.; Carter, D.; Carty, T. J.; Cortina, S. R.; Dombroski, M. A.; Donahue, K. M.; Elliott, N. C.; Gibbons, C. P.; Jordan, C. K.; Kuperman, A. V.; Labasi, J. M.; LaLiberte, R. E.; McCoy, J. M.; Naiman, B. M.; Nelson, K. L.; Nguyen, H. T.; Peese, K. M.; Sweeney, F. J.; Taylor, T. J.; Trebino, C. E.; Abramov, Y. A.; Laird, E. R.; Volberg, W. A.; Zhou, J.; Bach, J.; Lombardo, F. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4339–4344.

(2) (a) Heinisch, L. *Z. Chem. (Leipzig, Ger.)* **1970**, *10*, 188. (b) Schneller, S. W.; Bartholomew, D. G. *J. Heterocycl. Chem.* **1978**, *15*, 439–444. (c) Wu, Y.-Q.; Limburg, D. C.; Wilkinson, D. E.; Hamilton, G. S. *J. Heterocycl. Chem.* **2003**, *40*, 191–193.

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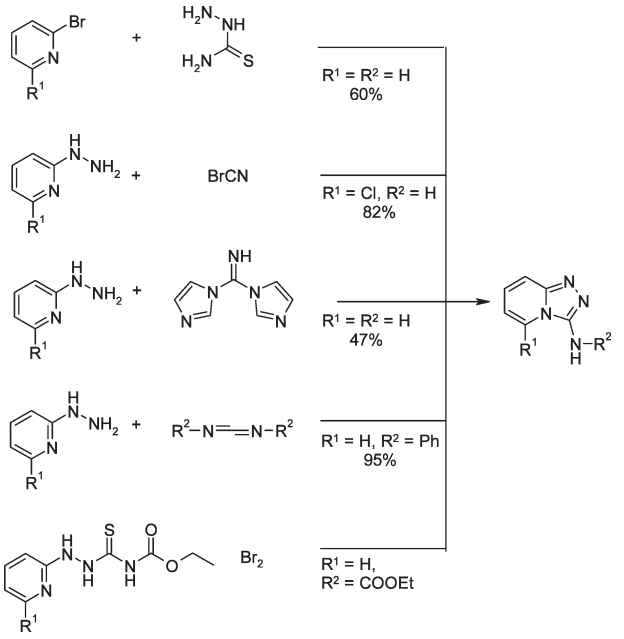
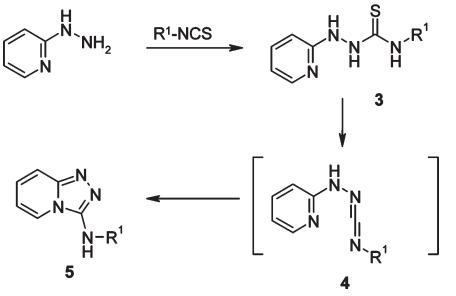
SCHEME 1. Synthesis of 3-Amino-[1,2,4]triazolo[1,5-*a*]pyridines



N-phenyl derivative was reported starting from 2-hydrazinopyridine and diphenylcarbodiimide.[3a] Hence, this approach is not general and is limited to specific symmetric carbodiimides. The *N*-ethoxycarbonyl derivative was obtained from the corresponding thiosemicarbazide.[3b] The limitation is the use of bromine to promote the cyclization, which might not be compatible with all heterocycles.

In the present work, the synthesis of 3-amino-[1,2,4]-triazolo[4,3-*a*]pyridines via the cyclodesulfurization of the corresponding thiosemicarbazide was chosen for further investigations (Scheme 2). This strategy, which has precedence in the synthesis of other heterocyclic amidines (e.g., 2-aminobenzimidazoles,[4] 2-aminobenzothiazoles,[5,6] 2-aminobenzoxazoles,[6] 2-amino-1,3,4-oxadiazoles[7] and imidazopyridines)[8] is based on the formation of a carbodiimide as reactive intermediate.

SCHEME 2. Proposed Synthetic Pathway for Synthesis of 3-Amino-[1,2,4]triazolo[4,3-*a*]pyridines



In our case, the precursor thiosemicarbazide **3** could be easily obtained from 2-hydrazinopyridine and the isothiocyanate, which in the presence of a desulfurizing agent could undergo intramolecular cyclization to form the triazole ring **5**. Following this pathway, we also envisaged to synthesize the *N*-unsubstituted derivative ($R^1 = H$) through the corresponding acid-labile *N*-*tert*-octyl derivative (R^1 = *tert*-octyl).

Several methods have been described for the desulfurization of thioureas that could be applied to thiosemicarbazides, which include the use of heavy metal salts and oxides (e.g., Pb_2O_4, $HgCl_2$, $Hg(OAc)_2$, HgO), methyl iodide, or highly reactive acid halides (e.g., phosgene, thionylchloride).[9] Mukaiyama's reagent in the presence of a weak base such as triethylamine[10] has been shown to be effective for this transformation under milder conditions, but the removal of the spent reagent (1-methyl-pyridine-2-thione) usually requires column chromatography. Since the use of resin-bound reagents can often accelerate purification,[11] the polymer-supported version of Mukaiyama's reagent was first considered to promote the desulfurization step.[12] In this case, the spent reagent can be easily removed by simple filtration since it is bound to the insoluble solid support.

To determine the scope of the reaction, five different aryl-isothiocyanates were chosen, bearing electron-donating and electron-withdrawing groups. One alkyl derivative was also included, the *tert*-octylisothiocyanate, as it provides the possibility of further derivation after acidic cleavage.[13]

Results and Discussion

To validate the proposed synthetic pathway, the stepwise approach was first investigated, and the thiosemicarbazides **3** were synthesized, isolated, and purified by recrystallization prior to the second step. The reactions proceeded smoothly at room temperature using equimolar amounts of 2-hydrazinopyridine and the corresponding isothiocyanates in THF as solvent, and no significant differences were observed among the six derivatives (Table 1).

With the thiosemicarbazides **3** in hands, we investigated the ability of polymer-supported Mukaiyama's reagent to

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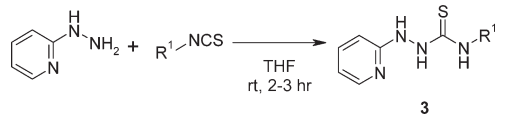
TABLE 1. Synthesis of Thiosemicarbazides 3

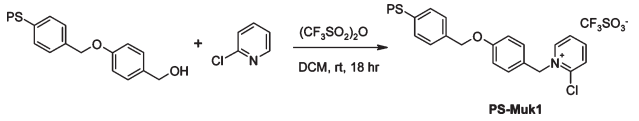


3

entry	R^1	compound	yield (%)[a]
1	phenyl	**3a**	71
2	3-F-phenyl	**3b**	69
3	4-MeO-phenyl	**3c**	85
4	2-Me-phenyl	**3d**	88
5	4-CF_3-phenyl	**3e**	58
6	*tert*-octyl	**3f**	77

[a]After recrystallization from ACN (not optimized).

SCHEME 3. Synthesis of PS-Muk1 from Wang Resin[12]



promote their desulfurization and subsequent spontaneous cyclization of the carbodiimides leading to the target heterocycles. We used polymer-supported Mukaiyama′s reagent previously developed in our laboratory (**PS-Muk1**) because it is easy to synthesize from relative cheap starting materials and stable under standard storage conditions (Scheme 3).[12]

The cyclization was carried out at room temperature using **PS-Muk1** (2.0 equiv) in the presence of TEA (5.0 equiv) in a mixture of DCM/DMF 9:1 to ensure the dissolution of the thiosemicarbazides **3**. After 1 h at room temperature, the desired heterocycles **5** were present in 50−77% (determined by HPLC), proving that **PS-Muk1** was effective to promote this transformation (Table 2, entries 1−5).[14] However, a major side product (**8**) was observed in each reaction, and decreasing the amount of **PS-Muk1** (from 2.0 to 1.25 equiv) and TEA (from 5.0 to 2.5 equiv) did not suppress the side reaction completely. There was a big improvement when performing the reaction at lower temperature (5 °C) for 21 h, and the 3-aryl-amino-[1,2,4]triazolo[4,3-*a*]pyridines **5a**−**e** were obtained as the main product (>82%, Table 2, entries 1−5).

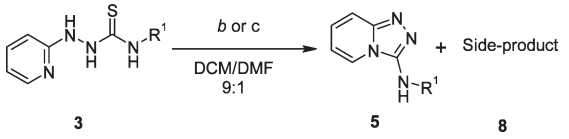
We then decided to focus our attention on the formation of the side product. Mass spectra analysis suggested that a pyridyl moiety was incorporated to the molecule.[15] To determine whether the polymer-supported reagent or the 2-hydrazinopyridine was responsible for the side reaction, the same transformation was carried out in solution with Mukaiyama's reagent (1.2 equiv) in the presence of TEA (2.4 equiv). In this case, a total conversion into the expected compounds was achieved after 2−3 h and no side products were observed (Table 3).

To further characterize the side product **8**, we chose to synthesize **8f** from the thiosemicarbazide **3f** (R^1 = *tert*-octyl) using a large excess of **PS-Muk1** (3.0 equiv) and TEA (5.0 equiv). Despite extensive analyses (^{1}H NMR, ^{13}C NMR, ^{19}F NMR, 2D NMR, MS, IR, elemental analysis),[16] the structural formula of **8f** could only be unambiguously determined by X-ray crystal structure analysis (Figure 1).[17]

(14) Compound **5c** was isolated and fully characterized.

(15) The measured mass/charge (*m*/*z*) ratio of the side product corresponded of the desired heterocycles **5** plus a mass of 77.

TABLE 2. Synthesis of 5 using PS-Muk1

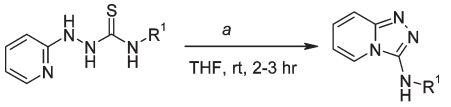


3 5 8

			composition (%)[a]			
entry	R	compound	1 h at rt[b]	1 h at 5 °C[c]	4 h at 5 °C[c]	21 h at 5 °C[c]
1	phenyl	**3a**	8	21	4	
		5a	55	76	87	82
		8a	37		8	13
2	3-F-phenyl	**3b**	11	37	3	
		5b	50	60	92	93
		8b	34		1	2
3	4-MeO-phenyl	**3c**	12	17	2	
		5c	67	82	94	96
		8c	21	0	2	3
4	2-Me-phenyl	**3d**	23	32	2	
		5d	57	67	87	85
		8d	20		8	12
5	4-CF_3-phenyl	**3e**				
		5e	77	97	94	92
		8e	23		2	2
6	*tert*-octyl	**3f**	15	57	27	19
		5f	64	29	45	41
		8f	18		23	37

[a]Determined by HPLC (254 nm). [b] PS-Muk1 (2.0 equiv), TEA (5.0 equiv), rt. [c]PS-Muk1 (1.25 equiv), TEA (2.5 equiv), 5 °C

TABLE 3. Synthesis of 5 using Mukaiyama's Reagent



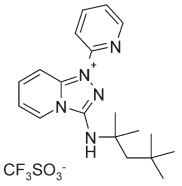
3 5

entry	R^1	compound	yield (%)[b]
1	phenyl	**5a**	78
2	3-F-phenyl	**5b**	63
3	4-MeO-phenyl	**5c**	69
4	2-Me-phenyl	**5d**	75
5	4-CF_3-phenyl	**5e**	72
6	*tert*-octyl	**5f**	68

[a]Mukaiyama's reagent (1.2 equiv), TEA (2.4 equiv). [b]After an acidic aqueous extraction followed by precipitation at pH 6.

(16) ^{1}H NMR (DMSO-d_6) clearly showed the signals corresponding to the *tert*-octyl, 2-pyridyl, and triazolopyridinyl moieties and one exchangeable proton (confirmed by adding MeOD-d_4) at 7.63 ppm. Moreover, ^{19}F NMR (DMSO-d_6, singlet at −78.2 ppm) and ^{13}C NMR (DMSO-d_6, quadruplet with $^1J_{C-F}$ = 322.4 Hz at 120 ppm) suggested the presence of trifluoromethanesulfonate group.

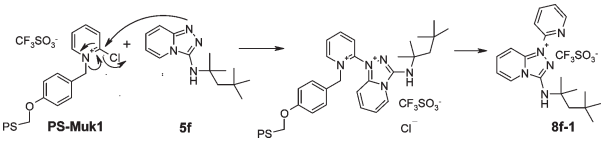
(17) In **8f** the pyridine-2-yl substituent is bound directly to the triazole ring giving a cationic compound with the trifluoromethanesuphonate present as a counterion. Hence, in the mass spectrometry (positive mode) the observed *m*/*z* corresponds to the MW and not to MW + 1 (observed *m*/*z* = 324). The ortep view of the crystal structure of **8f** is provided in Supporting Information and has been deposited in the Cambridge Data Centre (CCDC 730713).



8f

FIGURE 1. Structure of **8f**.

SCHEME 4. Plausible Mechanism for Formation of 8f

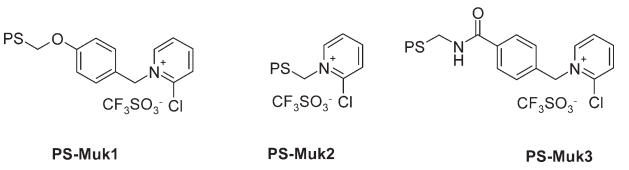


A plausible mechanism for the formation of **8f** is depicted in Scheme 4. Compound **5f** could further react with the excess of **PS-Muk1** (with loss of chloride) and a benzylic cleavage released the compound **8f** from the polymer support. This cleavage could be promoted by a nucleophilic addition (chloride or TEA) at the benzylic position (S_N2) or by a S_N1 mechanism involving the stabilized benzylic carbocation.[18]

The first step involved in the side-product formation appears to be a limitation of the methodology. However, the kinetic of the benzylic cleavage could be slowed down by choosing the appropriate solid support and hence increasing the purity of the desired heterocycle. For this purpose, hydroxymethyl polystyrene and 4-hydroxymethylbenzoic acid aminomethyl polystyrene were used for the synthesis of **PS-Muk2** and **PS-Muk3**, respectively (Figure 2), which would be more stable toward the benzylic cleavage than **PS-Muk1**. Their preparation was carried out following the same protocol as for **PS-Muk1**, achieving a quantitative attachment for both versions.

The results of the reactions of the new supported reagents **PS-Muk2** and **PS-Muk3** following the same conditions described before for **PS-Muk1** for the preparation of **5a** are summarized below (Table 4).

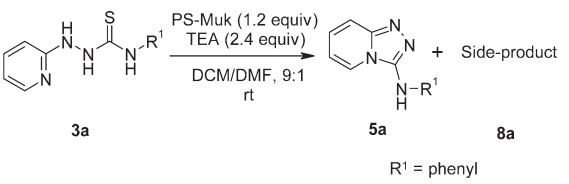
Gratifyingly, the two new linkers showed a better stability toward the benzylic cleavage and provided 99% of the desired heterocycles in the crude mixture after 1 h (determined by HPLC analysis of the supernatants). Only after 21 h were traces of the side product **8a** detected. Under these new conditions, it was the first time the starting thiosemicarbazide **3a** was totally consumed before the side product was released. The resin-bound pyridine-2-thione was removed by simple filtration, and the triethylammonium salts were removed using a SPE-NH_2 column followed by evaporation of the resulting TEA at the solvent removal stage.



PS-Muk1 **PS-Muk2** **PS-Muk3**

FIGURE 2. New polymer-supported Mukaiyama's reagent analogues.

TABLE 4. Comparison of PS-Muk1, PS-Muk2, and PS-Muk3



			composition (%)[a]	
entry	resin	compound	1 h	21 h
1	PS-Muk1	**3a**	8	7
		5a	55	56
		8a	37	37
2	PS-Muk2	**3a**		
		5a	99	98
		8a		2
3	PS-Muk3	**3a**		
		5a	99	95
		8a		3

[a]Determined by HPLC (254 nm).

Using this methodology, **5a** was isolated in good yield without any chromatographic separation.

PS-Muk2 was chosen as the best reagent candidate for further studies because its preparation is cheaper and easier to handle as compared to **PS-Muk3**.

The reactions of **3** with **PS-Muk2** (1.2 equiv) in DCM/DMF 9:1 at ambient temperature in the presence of TEA (2.4 equiv) gave complete conversion for the six derivatives after 1 h. Even the most problematic *tert*-octyl thiosemicarbazide **3f** gave the product in excellent purity.[19] The final heterocycles were easily isolated in good yields (71−85%) and excellent purities (>99%) without any chromatographic separation or any further purification, as shown by elemental analysis of the final heterocycles **5** (see Experimental Section).

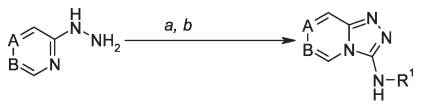
Our next goal was to develop a one-pot protocol from the previous results, which consisted of reacting 2-hydrazinopyridine with the isothiocyanate during 2 h before adding the TEA and **PS-Muk2** (Table 5). While attempting to simplify the one-pot protocol mixing all the reagents at once, we observed that 2-hydrazinopyridine was scavenged by **PS-Muk2**.[20] Consequently, the stepwise one-pot protocol was required to obtain the final compounds in good purities and

(18) Benzylic cleavages of *N*-benzyl pyridinium salts: (a) Katritzky, A. R. *Tetrahedron* **1980**, *36*, 679–699. (b) Katritzky, A. R.; Musumarra, G.; Sakizadeh, K. *Tetrahedron Lett*. **1980**, *21*, 2701–2703. (c) Katritzky, A. R.; Musumarra, G.; Sakizadeh, K.; Misic-Vukovic, M. *J. Org. Chem*. **1981**, *46*, 3820–3823. (d) Katritzky, A. R.; El-Mowafy, A. M.; Musumarra, G.; Sakizadeh, K.; Sana-Ullah, C.; El-Shafie, S. M. M.; Thind, S. S. *J. Org. Chem*. **1981**, *46*, 3823–3830. (e) Katritzky, A. R.; Musumarra, G.; Sakizadeh, K. *J. Org. Chem*. 1981, *46*, 3831−3835. Benzylic cleavages of quaternary ammonium salts: (f) Miller, M. W.; Vice, S. F.; McCombie, S. W. *Tetrahedron Lett*. **1998**, *39*, 3429–3432.

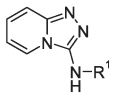
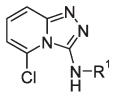
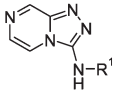
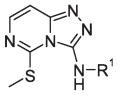
(19) The *tert*-octyl group of **5f** could be removed under acidic conditions, simply by reaction in a 1:1 mixture of aqueous 5 N HCl/methanol at rt for 16 h. After evaporation of the solvents, the residue was dissolved in MeOH and passed through a plug of basic alumina to give the NH_2-substituted derivative in 77% yield.

(20) It was confirmed later mixing both reagents under the same conditions of solvent, concentration, and temperature, where only 25% of the hydrazinopyridine was recovered after washing the resin and solvent removal.

TABLE 5. Synthesis of 3-Aminotriazoles Using a One-Pot Protocol



R1 = alkyl, aryl
A, B = CH or N

entry	scaffold	R^1	compound	yield (%)
1		phenyl	**5a**	67
		3-F-phenyl	**5b**	48
		4-MeO-phenyl	**5c**	56
		2-Me-phenyl	**5d**	69
		4-CF_3-phenyl	**5e**	43
		tert-octyl	**5f**	54
2		phenyl	**9a**	78
		3-F-phenyl	**9b**	63
		4-MeO-phenyl	**9c**	69
		2-Me-phenyl	**9d**	75
		4-CF_3-phenyl	**9e**	72
3		phenyl	**10a**	78
		3-F-phenyl	**10b**	79
		4-MeO-phenyl	**10c**	69
		2-Me-phenyl	**10d**	77
		4-CF_3-phenyl	**10e**	70
4		phenyl	**11a**	60
		3-F-phenyl	**11b**	51
		4-MeO-phenyl	**11c**	56
		2-Me-phenyl	**11d**	66
		4-CF_3-phenyl	**11e**	45

[a] R^1-NCS (1.0 equiv), hydrazino derivative (1.4 equiv) for 2 h. [b] PS-Muk2 (1.5 equiv), TEA (2.5 equiv) for 1 h.

yields but with the ability of using one reagent in excess that is often desirable in parallel synthesis.

Encouraged by these results, we were prompted to extend this methodology to the synthesis of related fused 3-aminotriazoles. A priori, any other hydrazine derivative bearing a nitrogen atom in the α position of an aromatic ring can replace the 2-hydrazinopyridine, leading to novel and interesting heterocycles. As examples we chose 6-chloro-2-hydrazinopyridine, 2-hydrazinopyrazine, and 2-methylsulfanyl-4-hydrazinopyrimidine, and we kept the 5 aryl isothiocyanates used before (Table 5). The reactions were carried out in a parallel fashion, using the optimized conditions (i.e., letting react at rt the isothiocyanate (1.0 equiv) with hydrazine derivative (1.4 equiv) in a mixture DMF/DCM for 2 h, before adding **PS-Muk2** (1.5 equiv) and TEA (2.5 equiv)). The isolation was carried out as mentioned before, affording analytically pure compounds **9**−**11** (Table 5). The moderate yields are explained by the partial scavenging of the formed heterocycles by the resin (step 1, Scheme 4).[21]

Conclusions

We have developed a convenient one-pot protocol for the synthesis of 3-amino-[1,2,4]triazolo[4,3-*a*]pyridines. The use of a new linker for the polymer-supported Mukaiyama′s reagent (**PS-Muk2**) is essential to achieve high purities of the products, since it was shown to be more stable than the previously reported analogue **PS-Muk1**. This protocol was shown to be robust in the extension to other related heterocycles, which broadens the scope of the presented methodology. The simplicity of the reaction and the purification step make this one-pot protocol an excellent choice for parallel synthesis.

Experimental Section

Polymer-supported Mukaiyama′s reagent 1 (PS-Muk1). In a 250 mL, 3-necked, round-bottom flask and under argon, Wang resin (15 g, 1.7 mmol/g, 25.5 mmol, 1.0 equiv) was swollen in dry DCM (150 mL), and 2-chloropyridine (12.0 mL, 127.5 mmol, 5.0 equiv) was added with stirring . The mixture was cooled in an ice−water bath before neat trifluoromethanesulfonic anhydride (6.0 mL, 35.7 mmol, 1.4 equiv) was added at such rate that the temperature did not rise above 20 °C (internal temp). The mixture was stirred gently overnight. The resin was filtered, washed with DCM, DMF, DCM (several times), and Et_2O, and dried under high vacuum at rt. Elemental analysis of the resin gave 3.38% Cl, 6.35% F, which corresponds to a loading of 1.1 mmol/g.

Polymer-supported Mukaiyama′s reagent (PS-Muk2). The same procedure as for **PS-Muk1** but using hydroxymethyl polystyrene (40 g, 0.98 mmol/g, 39.2 mmol, 1.0 equiv), DCM (400 mL), 2-chloropyridine (18.5 mL, 196 mmol, 5.0 equiv), and trifluoromethanesulfonic anhydride (9.27 mL, 54.9 mmol, 1.4 equiv). Elemental analysis of the resin gave 2.97% Cl, 4.92% F, which corresponds to a loading of 0.85 mmol/g.

Polymer-supported Mukaiyama′s reagent (PS-Muk3). The same procedure as for **PS-Muk1** but using 4-hydroxymethylbenzoic acid aminomethyl polystyrene (2.0 g, 0.85 mmol/g, 1.7 mmol, 1.0 equiv), DCM (20 mL), 2-chloropyridine (0.8 mL, 8.3 mmol, 5.0 equiv), and trifluoromethanesulfonic anhydride (0.4 mL, 2.3 mmol, 1.4 equiv). Elemental analysis of the resin gave 2.52% Cl, 4.46% F, which corresponds to a loading of 0.75 mmol/g.

General Procedure for the Preparation of 1-(Pyridine-2-yl) thiosemicarbazides (3). 2-Hydrazinopyridine (2.73 g, 25 mmol, 1.00 equiv) was dissolved in THF (100 mL), and a solution of the corresponding isothiocyanate (25 mmol, 1.00 equiv) in THF (25 mL) was added over a period of 5 min using a dropping funnel. The reaction was stirred until completion (monitored by HPLC), and the solvent was evaporated under reduced pressure. The resulting solid was recrystallized from ACN and dried under vacuum at 40 °C.

N-Phenyl-2-pyridin-2-ylhydrazinecarbothioamide (**3a**). Yield 71%; mp 180.1−180.6 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.83 (s, 1H), 9.73 (s, 1H), 8.55 (s, 1H), 8.14 (dd, J = 4.9, 0.9 Hz, 1H), 7.68−7.58 (m, 1H), 7.54 (d, J = 7.5 Hz, 2H), 7.30 (t, J = 8.0 Hz, 2H), 7.12 (t, J = 7.3 Hz, 1H), 6.87−6.77 (m, 1H), 6.66 (d, J = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 181.2, 159.2,

(21) The fused 3-aminotriazole **5f** was reacted with **PS-Muk2** (1 equiv) and TEA (2 equiv) for 1 h. HPLC analysis of the supernatant using internal reference showed 66% of the initial amount of **5f**, suggesting it was partially scavenged by the resin (step 1, Scheme 4).

147.6, 139.2, 137.8, 127.9, 125.2, 124.7, 115.7, 107.2; IR 3149.3, 1545.7, 1434.8 cm^{-1}; MS (ESI) m/z 245 $(M + H)^+$; HPLC t_R = 1.62 min. Anal. Calcd for $C_{12}H_{12}N_4S$: C, 58.99; H, 4.95; N, 22.93. Found: C, 59.03; H, 4.95; N, 23.00.

The compound characterization data for **3b**−**f** are provided in Supporting Information.

General Protocol for 3-Amino-[1,2,4]triazolo[4,3-*a*]pyridines (5). Condition 1. From thiosemicarbazides **3** and using Mukaiyama's reagent. In a round-bottom flask, thiosemicarbazides **3** (2.0 mmol, 1.0 equiv) was dissolved in THF (10 mL), and a solution of triethylamine (0.66 mL, 4.8 mmol, 2.4 equiv) in THF (2 mL) was added followed by 2-chloro-1-methylpyridinium iodide (0.62 g, 2.4 mmol 1.2 equiv). The mixture was stirred at rt until completion (1−2 h, monitored by HPLC), and the solvent was evaporated under vacuum. The residue was taken up in EtOAc (50 mL) and washed with HCl 0.1 N (2 × 10 mL). The aqueous layers were combined, and NaOH (1 N) was added until pH 6. The resulting solid was filtered, washed with water, and dried under vacuum at 40 °C. (**5a**, 78%; **5b**, 63%; **5c**, 69%; **5d**, 75%; **5e**, 72%; **5f**, 68%)

Condition 2. From thiosemicarbazides **3** and using **PS-Muk2**. Thiosemicarbazide **3** (0.05 mmol, 1.0 equiv) was dissolved in DMF (0.1 mL), and a solution of TEA (2.4 equiv) in DCM (0.9 mL) was added followed by **PS-Muk2** (1.2 equiv). The capped vial was shaken at rt for 1 h, and MeOH (1 mL) was added. The crude was passed through a SPE-NH_2 column (500 mg, 0.56 mmol/g) and eluted with DCM (4.0 mL). Evaporation of the solvent under reduced pressure afforded the title compound. (**5a**, 79%; **5b**, 77%; **5c**, 85%; **5d**, 74%; **5e**, 71%; **5f**, 81%)

Condition 3. One-pot protocol from 2-hydrazinopyridine and using **PS-MUk2**. 2-Hydrazinopyridine (23 mg, 0.21 mmol, 1.4 equiv) was dissolved in DMF (0.3 mL), a solution of the corresponding isothiocyanate (0.15 mmol, 1.0 equiv) in DCM (1.0 mL) was added, and the mixture was shaken at rt for 2 h. Then, TEA (52 uL, 0.38 mmol, 2.5 equiv) was added followed by **PS-Muk2** (1.5 equiv), and the mixture was shaken at rt for 2 h. MeOH (1 mL) was added, and the crude was passed through a SPE-NH_2 column (500 mg, 0.56 mmol/g) and eluted with DCM (4.0 mL). Evaporation of the solvent under reduced pressure afforded the title compound. (**5a**, 67%; **5b**, 48%; **5c**, 56%; **5d**, 69%; **5e**, 43%; **5f**, 54%; **5g**, 72%)

N-Phenyl-3-amino-[1,2,4]triazolo[4,3-*a*]pyridine (**5a**). Mp 232.5−233.3 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.34 (dt, J = 6.9, 1.0 Hz, 1H), 7.61 (dt, J = 9.4, 1.0 Hz, 1H), 7.56 (dd, J = 8.6, 1.0 Hz, 2H), 7.35−7.27 (m, 2H), 7.24 (ddd, J = 9.3, 6.4, 1.0 Hz, 1H), 6.95−6.86 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.3, 144.3, 141.4, 129.0, 126.5, 122.6, 120.4, 116.2, 115.5, 112.3; IR 1606.2, 1556.7, 1498.4 cm−1; MS (ESI) m/z = 211 $(M + H)^+$; HPLC t_R = 1.77 min. Anal. Calcd for $C_{12}H_{10}N_4$: C, 68.56; H, 4.79; N, 26.65. Found: C, 68.21; H, 4.81; N, 26.45.

The compound characterization data for **5b**−**f** are provided in Supporting Information.

General Protocol for 3-Amino-5-chloro[1,2,4]triazolo[4,3-*a*]-pyridines (9). The same protocol as for **5** (condition 3) but using 6-chloro-2-hydrazinopyridine (30 mg, 0.21 mmol, 1.4 equiv) instead of 2-hydrazinopyridine. (**9a**, 78%; **9b**, 63%; **9c**, 69%; **9d**, 75%; **9e**, 72%)

N-Phenyl-3-amino-5-chloro[1,2,4]triazolo[4,3-*a*]pyridine (**9a**). Mp 200 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 (s, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.29 (dd, J = 9.4, 7.2 Hz, 1H), 7.20 (t, J = 7.9 Hz, 2H), 7.06 (d, J = 6.8 Hz, 1H), 6.86−6.77 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.1, 144.9, 143.6, 129.1, 128.1, 124.2, 119.6, 115.1, 115.0, 114.9; IR 1624.8, 1534.8, 1480.7, 788.0 cm^{-1}; MS (ESI) m/z = 247 $(M + H)^+$; HPLC t_R = 2.57 min. Anal. Calcd for $C_{12}H_9ClN_4$: C, 58.91; H, 3.71; N, 22.90. Found: C, 58.53; H, 3.65; N, 22.77.

The compound characterization data for **9b**−**e** are provided in Supporting Information.

General Protocol for 3-Amino-[1,2,4]triazolo[4,3-*a*]pyrazines (10). The same protocol as for **5** (condition 3) but using 2-hydrazinopyrazine (23 mg, 0.21 mmol, 1.4 equiv) instead of 2-hydrazinopyridine. (**10a**, 78%; **10b**, 79%; **10c**, 69%; **10d**, 77%; **10e**, 70%)

N-Phenyl-3-amino-[1,2,4]triazolo[4,3-*a*]pyrazine (**10a**). Mp 262 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.54 (s, 1H), 9.21 (d, J = 1.6 Hz, 1H), 8.39 (dd, J = 5.1, 1.6 Hz, 1H), 7.81 (d, J = 4.9 Hz, 1H), 7.68 (dd, J = 8.7, 0.8 Hz, 2H), 7.35 (dd, J = 8.6, 7.3 Hz, 2H), 6.97 (t, J = 7.3 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.2, 144.1, 142.0, 140.5, 129.0, 127.6, 121.1, 116.7, 115.5; IR 1614.0, 1564.7, 1377.8 cm^{-1}; MS (ESI) m/z = 212 $(M + H)^+$; HPLC t_R 1.83 min. Anal. Calcd for $C_{11}H_9N_5$ + (0.06% DMF) C_3H_7NO: C, 62.28; H, 4.40; N, 32.87. Found: C, 62.01; H, 5.00; N, 33.15.

The compound characterization data for **10b**−**e** are provided in Supporting Information.

General Protocol for 3-Amino-5-methylsulfanyl[1,2,4]triazolo [4,3-*a*]pyrimidines (11). The same protocol as for **3** (condition 3) but using 4-hydrazino-2-(methylthio)pyrimidine (33 mg, 0.21 mmol, 1.40 equiv) instead of 2-hydrazinopyridine. (**11a**, 60%; **11b**, 51%; **11c**, 56%; **11d**, 66%; **11e**, 45%)

N-Phenyl-3-amino-5-methylsulfanyl[1,2,4]triazolo[4,3-*a*]pyrimidine (**11a**). Mp 197.6−198.2 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.65 (s, 1H), 7.83 (d, J = 6.6 Hz, 1H), 7.43 (d, J = 6.6 Hz, 1H), 7.20 (t, J = 7.7 Hz, 2H), 6.83 (t, J = 7.3 Hz, 1H), 6.76 (d, J = 7.5 Hz, 2H), 2.55 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 151.1, 148.3, 145.1, 143.0, 140.4, 129.1, 119.8, 115.1, 105.9, 13.5; IR 1536.9, 1645.5, 1307.6 cm^{-1}; MS (ESI) - m/z = 258 $(M + H)^+$; HPLC t_R = 2.62 min. Anal. Calcd for $C_{12}H_{11}N_5S$: C, 56.1; H, 4.31; N, 27.22; S, 12.46. Found: C, 56.12; H, 4.46; N, 27.26; S, 12.32.

The compound characterization data for **11b**−**e** are provided in Supporting Information.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.