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A Direct Approach to a 6-Hetarylamino[1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazine Library

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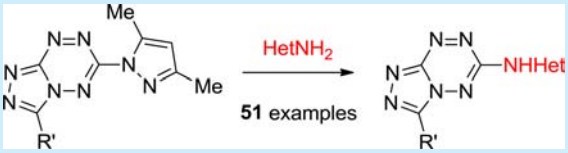
Supporting Information

ABSTRACT: The synthesis of 6-hetarylamino[1,2,4]triazolo[4,3-*b*]-[1,2,4,5]tetrazines is reported. The functionalized secondary amines were constructed via a K_2CO_3-mediated S_NAr reaction of weakly basic hetarylamines with 3-(3,5-dimethylpyrazol-1-yl)[1,2,4]triazolo[4,3-*b*]-[1,2,4,5]tetrazines, which allowed displacement 3,5-dimethylpyrazolyl leaving group. Significantly, the reaction exhibited a broad substrate scope and proceeded in good yields.



[1,2,4]Triazolo[4,3-*b*][1,2,4,5]tetrazines are molecules of wide interest and importance due to their utilization in synthetic chemistry[1] and as key scaffolds in energetic materials.[2] Some derivatives of the bicycle also possess a wide spectrum of the biological activities with antihemostatic,[3] antimicrobial,[4] and antitumor properties,[5] as inhibitors of a Bcl-2 protein,[6] and as antibacterial serine-threonine protein kinases.[7] On the other hand, in recent years, interest in secondary *s*-tetrazinamines with respect to their unique potential in high energetic materials[8] and pharmaceutical applications[9] has been followed by development of the new and useful methods for their synthesis. Typically, these compounds are synthesized by the nucleophilic aromatic substitution (S_NAr) reaction of *s*-tetrazines bearing a leaving group with amines; 3,5-dimethylpyrazolyl moiety has been used in place of a halogen as a leaving group in many reactions.[10] However, the reported successful S_NAr reactions at *s*-tetrazine ring are limited to some highly basic primary amines; even at elevated temperatures, anilines bearing electron-withdrawing groups remained unreactive.[11] No previous nucleophilic replacement of a leaving group of [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazines with a primary amine has been documented. Moreover, the electrophilic bicyclic heterocyclic system was usually destroyed by *O*-,[12] *N*-,[13] and *C*-nucleophiles.[1]

We recently reported an approach to *s*-tetrazines and [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazins bearing 3-R-furazan-4-ylamino substituents via the copper catalyzed cross-coupling of the corresponding tetrazinylamines with iodofurazans (3-iodo-1,2,5-oxadiazoles).[14] However, moderate yields (42−58%) and the application of hardly accessible iodofurazans[15] limit the scope of this reaction

Because of importance of the secondary [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazinamines, a straightforward protocol to prepare them using mild conditions and more readily available reagents would thus offer a valuable tool for the synthesis of these high-nitrogen molecules.

We recently reported an efficient procedure for the S_NAr reactions of 3,6-bis(3,5-dimethylpyrazol-1-yl)-*s*-tetrazine **1** with weakly basic hetarylamines on heating in MeCN in the presence of K_2CO_3 or Cs_2CO_3.[16] This methodology allows an efficient access to 3-hetarylamino-6-(3,5-dimethylpyrazol-1-yl)-*s*-tetrazines, as the result of a displacement 3,5-dimethylpyrazolyl group. Similar reaction with a related fused tetrazine has never been reported in the literature. However, this strategy would be of even greater appeal if it was applicable to the fused tetrazine derivatives, allowing the synthesis of corresponding secondary biheterocyclic amines.

The main concern in applying this strategy on 3-(3,5-dimethylpyrazol-1-yl)[1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazines **2** was the known instability of the bicyclic core under basic conditions. However, it was interesting to discover that under the same reaction conditions as developed for compound **1**, using K_2CO_3 as a base in MeCN at reflux, triazolotetrazine **2** underwent efficient couplings with 3-amino-4-*R*-furazans **3a−v** (Scheme 1).

In a typical procedure, solid K_2CO_3 was added in one portion to a suspension of the triazolotetrazine **2** and a furazanamine in boiling acetonitrile. The solution became dark red, and after the disappearance of starting reagents the desired product was isolated by an aqueous acidic[17] workup, subsequently washed,

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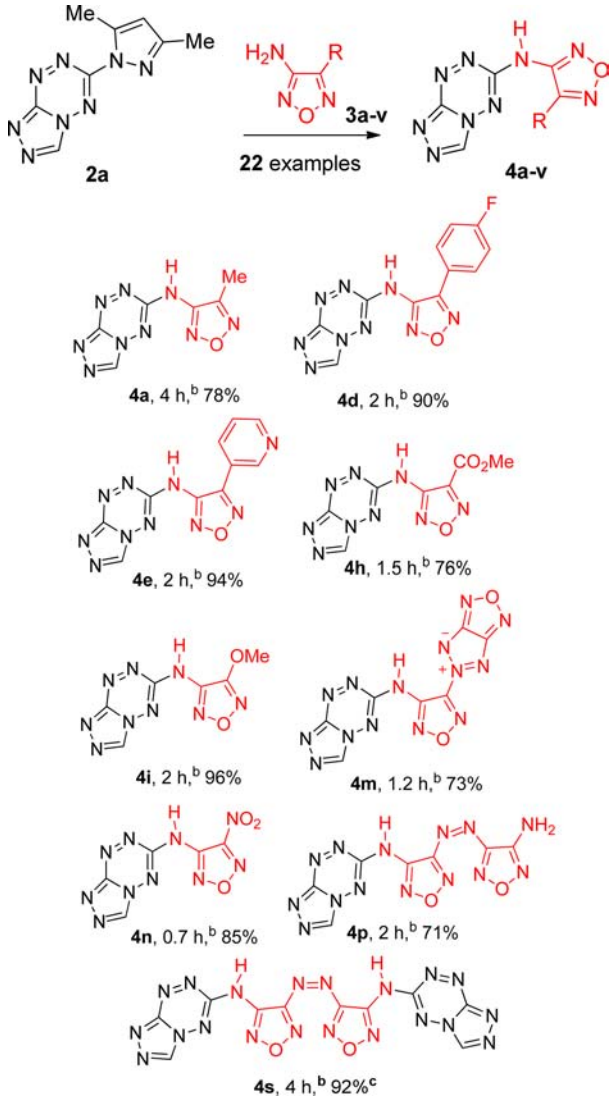
Scheme 1. Synthesis of Selected *N*-([1,2,4]Triazolo[4,3-*b*][1,2,4,5]tetrazin-3-yl)-4-*R*-furazan-3-amines[a]



[a]Reaction conditions: (i) triazolotetrazine **2a** (0.5 mmol), furazanamine **3a–v** (0.6 mmol), K_2CO_3 (0.6 mmol), MeCN (10 mL), reflux; (ii) aqueous HCl to pH 1. Isolated yields are for an average of at least two runs. A full list of products is given in the Supporting Information. [b]Time at which TLC (CCl_4/MeCN, 3:1) indicated complete disappearance of the starting reagents. [c]In this case: triazolotetrazine **2a** (1 mmol), diamine **3o–q,u,v** (0.5 mmol), K_2CO_3 (0.6 mmol), MeCN (10 mL), reflux.

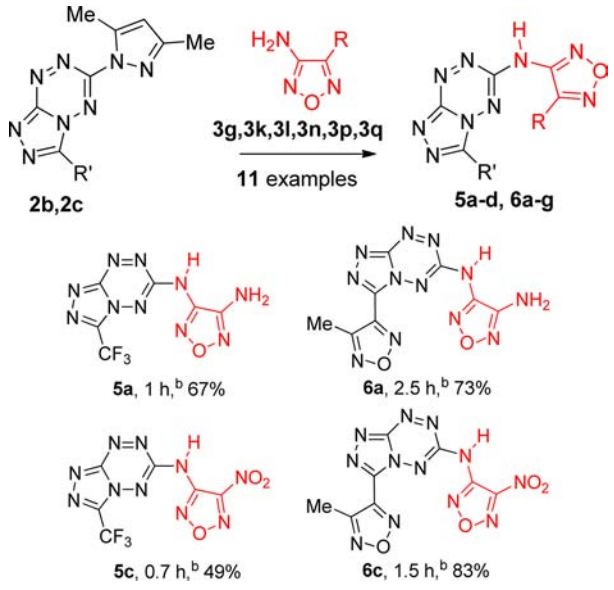
and dried. To our delight, a range of electron-donating and electron-withdrawing groups at the furazan ring are well tolerated, and the desired secondary amines **4** were formed in good to excellent yields. Our experiments clearly demonstrate that more electron-deficient furazanamines **3** show shorter reaction time. Thus, in the case of 3-amino-4-nitrofurazan **3j** the reaction was completed in less than 1 h, while for 3,4-diaminofurazan **3k** it took over 3 h to react completely. Notably, in cases if the triazolotetrazine **2a** was combined with 3-aminofurazan-4-carboxylic acid **3w** (not shown), the disappearance of the starting reagents resulted in an inseparable mixture from which the desired product **4w** could not be isolated.

It is important to note that the reaction of the diamine derivative using an identical protocol resulted in selective monohetarylation in good yields (e.g., compound **4p**, Scheme 1). Two-fold coupling of triazolotetrazine **2a** (2.2 equiv) with 4,4′-diaminoazofurazan **3p** at a more prolonged time provided the bis-product **4s** in 89% yield (Scheme 1). In order to further extend the utility of the cyclization protocol, several mono- and bis-secondary diamines were prepared from primary diamines in good to excellent yields (see the Supporting Information).

Compared with ones of triazolotetrazine **2a**, the ^1H, ^{13}C and ^{15}N NMR spectra of products **4a–v** displayed the disappearance of dimethylpyrazol moiety signals, and the appearance of signal characteristic of furazanic *C*-NH atom at δ ca. 154 ppm in ^{13}C NMR and signal for *N*H group at δ ca. −295 ppm in ^{15}N NMR. The spectral data of compounds **4a,b,i,k–n** are also consistent with those reported previously.[14,18]

It was next sought to extend the reaction scope to include triazolotetrazines bearing a substituent at the 3-position of the triazole ring. Both trifluoromethyl (**2b**) and 3-methylfurazan-4-yl derivatives (**2c**)[13] underwent coupling reactions efficiently when the standard procedure was used: K_2CO_3 in boiling MeCN (Scheme 2). Unfortunately, in the presence of the

Scheme 2. Synthesis of Selected 3-Substituted Secondary [1,2,4]Triazolo[4,3-*b*][1,2,4,5]tetrazinamines[a]



[a]Reaction conditions: (i) triazolotetrazine **2b** or **2c** (0.5 mmol), furazanamine **3g,k,l,n,p,q** (0.6 mmol), K_2CO_3 (0.6 mmol), MeCN (10 mL), reflux; (ii) aqueous HCl to pH 1. Isolated yields are for an average of at least two runs. A full list of products is given in the Supporting Information. [b]Time at which TLC ($CHCl_3$/MeCN, 3:1) indicated complete disappearance of the starting reagents.

amino group at the triazole ring of the bicycle, reactions of triazolotetrazine **2d** (R = NH_2, not shown) with aminofurazans substituted by both electron-withdrawing (e.g., nitro) and electron-donating groups (e.g., methoxy) failed; the disappearance of the starting 6-(3,5-dimethyl-1*H*-pyrazol-1-yl)[1,2,4]-triazolo[4,3-*b*][1,2,4,5]tetrazin-3-amine **2d** resulted in a complicated mixture.

The electron-deficient hetarylamine substrate scope for this reaction was next explored. As can be seen in Scheme 3, pyrazoles, triazoles, tetrazoles, pyridines, pyrazines, and

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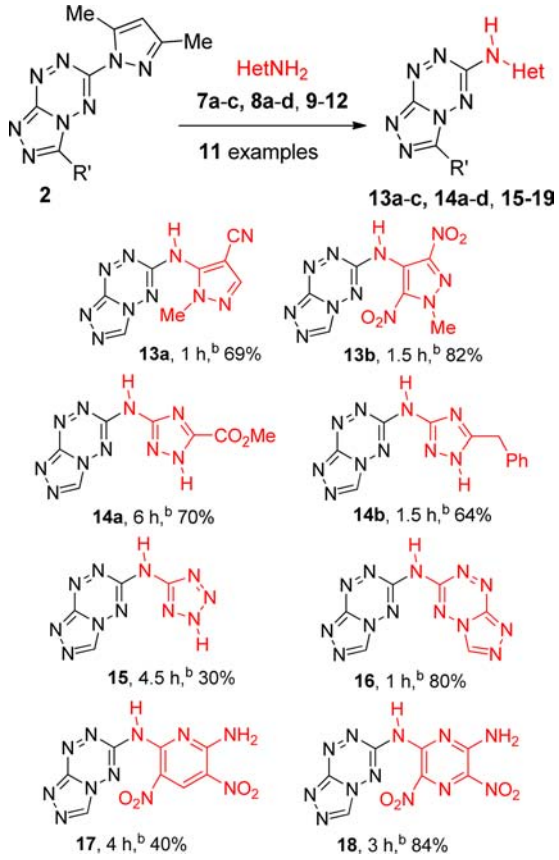
Scheme 3. Synthesis of Selected *N*-([1,2,4]Triazolo[4,3-*b*][1,2,4,5]tetrazin-6-yl)hetarylamines[a]



[a]Reaction conditions: (i) triazolotetrazine **2b**/**2c** (0.5 mmol), amine **7**−**12** (0.6 mmol), K_2CO_3 (0.6 mmol), MeCN (10 mL), reflux; (ii) aqueous HCl to pH 1. Isolated yields are for an average of at least two runs. A full list of products is given in the Supporting Information. [b]Time at which TLC (CCl_4/MeCN, 3:1) indicated complete disappearance of the starting reagents.

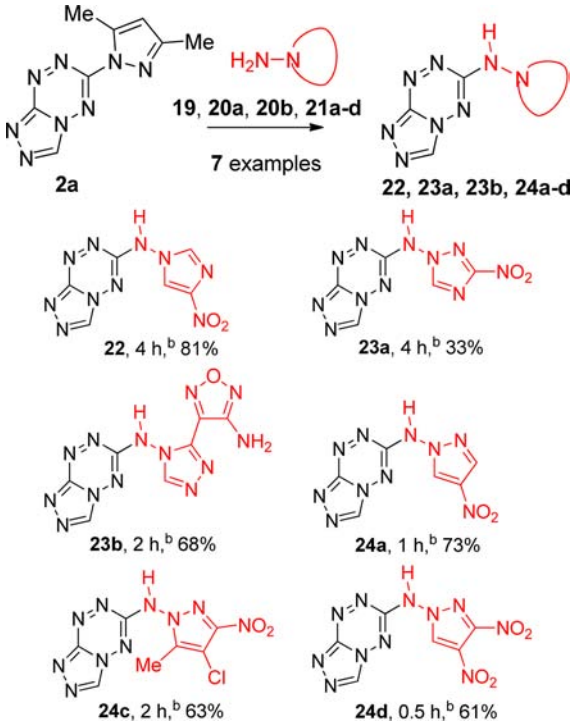
tetrazines reacted in moderate to good yields. However, when using parent aminopyridines, no reaction was observed after 12 h at reflux. Similarly, the reaction with 2,6-diamino-3,5-dinitropyrazine *N*-oxide was also unsuccessful.

A range of *N*-aminohetarenes were well tolerated. In particular, diamine, such as 3-amino-4-(4-amino-4*H*-1,2,4-triazol-3-yl)furazan, underwent this transformation in a good yield and with excellent chemoselectivity. In this case, only single product **23b** was obtained from the reaction. As can be seen from Scheme 4, both mono- and dinitroazoles were also converted by this method in good yields to the corresponding products. Notably, in the cases where the triazolotetrazine **2a** was combined with an *N*-amine containing activated chlorine atom, such as 1-amino-4-chloro-3,5-dinitropyrazole (not shown), all attempts to establish reaction conditions which would give separable product were unsuccessful.

The characteristic resonance by ^{15}N NMR at ca. −256 ppm indicated the presence of the Het(N)-*NH*- atom attached to the 6-positions of the triazolotetrazine core (Scheme 4).

The structures of compounds **4k**, **4o**, **5d**, **23a**, and **23b** were confirmed by single-crystal X-ray study. In all of the molecules, hydrogen atom was localized at the bridged nitrogen atom (see Figure 1 for **23b** as an example). In the case of products when the NH bridge was attached to the nitrogen atom of the azole

Scheme 4. Synthesis of Selected Secondary *N*-Amines[a,b]



[a]Reaction conditions: (i) triazolotetrazine **2a** (0.5 mmol), *N*-amine **19**−**21** (0.6 mmol), K_2CO_3 (0.6 mmol), MeCN (10 mL), reflux; (ii) aqueous HCl to pH 1. Isolated yields are for an average of at least two runs. A full list of products is given in the Supporting Information. [b]Time at which TLC (CCl_4/MeCN, 3:1) indicated complete disappearance of the starting reagents.

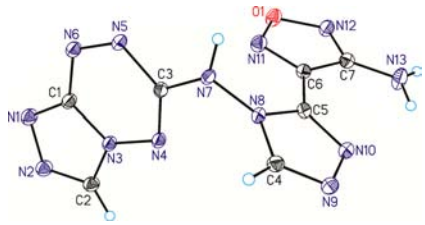


Figure 1. General view of **23b** in a representation of atoms by thermal displacements ellipsoids with 50% probability.

(**23a** and **23b**), the molecules were nonplanar. On the contrary, for compounds bearing C-NH-C bridge, nearly planar molecular structures were observed (**4k**, **4o**, and **5d**). The details of the X-ray study are given in the Supporting Information.

In conclusion, we have developed a general and straightforward protocol for the synthesis of high nitrogen secondary dihetarylamines from various weakly basic primary azolyl- and azinylamines. To the best of our knowledge, the present approach is the first combinatorial synthesis of the energetic compound library.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and copies of ^{1}H and ^{13}C, ^{15}N, ^{14}N, ^{19}F NMR spectra corresponding to all isolated and purified compounds. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.

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