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Synthesis of fused 3-amino-1,2,4-triazoles via sequential addition of aryl hydrazines to isothiocyanates and I_2-mediated cyclodesulfurization

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ABSTRACT

A variety of fused 3-amino-1,2,4-triazole derivatives were synthesized via addition of aryl hydrazines to isothiocyanates followed by I_2-mediated oxidative cyclodesulfurization. This transition-metal-free synthetic process provides facile access to 1,2,4-triazolo[4,3-*a*]pyridines and related heterocyclic frameworks bearing a 3-amino substituent from readily accessible substrates in an efficient and scalable fashion.

1. Introduction

1,2,4-Triazolo[4,3-*a*]pyridine derivatives exhibit important biological and pharmaceutical properties including anti-inflammatory,[1] antiproliferative/anticancer,[2] antibacterial[3] and antiviral properties.[4] In addition, these compounds also have applications in agricultural chemistry[5] and material sciences.[6] To date, various synthetic methodologies have been developed to construct this heterocyclic skeleton.[7] However, few approaches provide efficient access to the biologically interesting 3-amino-1,2,4-triazolo[4,3-*a*]pyridines, and the existing methods suffer from the use of toxic reagents, low yields, and limited substrate scope/scalability.[8] In 2009, Swinnen et al.[9] disclosed a straightforward protocol for the synthesis of such fused 3-aminotriazoles via annulations of 2-hydrazinylpyridines and isothiocyanates promoted by a polymer-supported Mukaiyama reagent. Recently, Gunnlaugsson, Scanlan, and coworkers[10] reported a similar transformation using tetrabutylammonium fluoride (TBAF) under microwave conditions. These reactions can produce structurally diverse 1,2,4-triazolo[4,3-*a*]pyridine-3-amine derivatives from readily accessible substrates. As a continuation of our research on the synthesis of fused 1,2,4-triazoles,[11] herein we describe such a reaction employing molecular iodine as the sole oxidant.

2. Results and discussion

The addition of 2-hydrazinylpyridine (**2a**) to phenyl isothiocyanate (**3a**) finished within 10 min in most solvents at room temperature, generating a thiosemicarbazide intermediate **4a**. Then, I_2-mediated cyclodesulfurization of **4a** under basic conditions afforded the expected product **1a** (Table 1). Solvent screening indicated that the reaction proceeds faster in DMSO (entry 6), DMF (entry 7) and EtOH (entry 8), and gives better yields in 1,4-dioxane (entry 4) and EtOH (entry 8). Replacement of EtOH with MeOH or ^{i}PrOH affected the yield and/or the reaction rate (entries 9–10). Overall, EtOH is an optimal solvent for this transformation (entry 8), allowing for this synthetic process to be conducted on a gram scale. With a weaker base or no base, the cyclization still worked, but required longer reaction times and resulted in decreased yields (entries 11–12).

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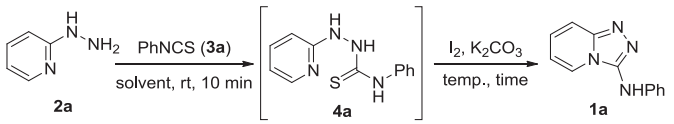
Table 1
Reaction conditions optimization for the synthesis of 3-amino-1,2,4-triazolo[4,3-*a*] pyridine **1a**[a].



Entry	Base	Solvent	Temp.	Time[b]	yield[c]
1	K_2CO_3	toluene	reflux	5 h	71%
2	K_2CO_3	THF	reflux	2 h	76%
3	K_2CO_3	CH_2Cl_2	reflux	1 h	79%
4	K_2CO_3	1,4-dioxane	80 °C	3 h	91%
5	K_2CO_3	MeCN	60 °C	2 h	80%
6	K_2CO_3	DMSO	rt	30 min	75%
7	K_2CO_3	DMF	rt	30 min	82%
8	K_2CO_3	EtOH	rt	15 min	91% (88%)[d]
9	K_2CO_3	MeOH	rt	15 min	80%
10	K_2CO_3	^{i}PrOH	rt	2 h	79%
11	$NaHCO_3$	EtOH	rt	2 h	85%
12	–	EtOH	rt	5 h	60%

[a] Reaction conditions: (1) **2a** (0.5 mmol), **3a** (0.6 mmol), EtOH (5 mL), rt, 10 min; (2) I_2 (0.55 mmol), base (1 mmol).
[b] Time for the second step.
[c] Isolated yields are given.
[d] Yield of gram-scale (6 mmol) reaction in parentheses.

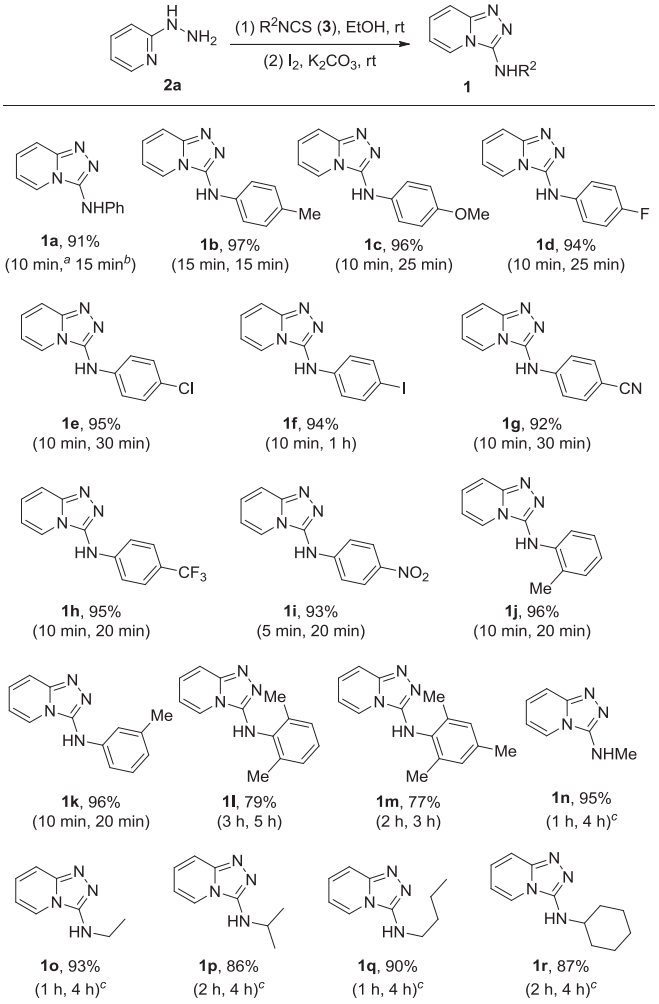
With the optimal reaction conditions (Table 1, entry 8) in hand, we examined the scope and generality of this methodology. Addition of 2-hydrazinylpyridine (**2a**) with isothiocyanates (**3**), followed by I_2-mediated cyclization, afforded a range of 3-amino-1,2,4-triazolo[4,3-*a*]pyridines (**1**) in good to excellent yields (Scheme 1). The present synthetic method works well with both aryl and alkyl isothiocyanates. For monosubstituted phenyl isothiocyanate substrates, the reaction was not affected by either electron-donating or electron-withdrawing groups (EDGs and EWGs) at *para*-, *meta*-, or *ortho*-positions (**1b**–**k**). The steric effect of the 2,6-dimethyl groups could be responsible for the lower yield of **1l** and **1m**, thus possibly attributing to the longer reaction times required in both the addition and cyclization steps. It is worth noting that the reactions with aliphatic isothiocyanates gave better yields of the desired products (**1n**–**r**) in 1,4-dioxane than in EtOH.

In light of these encouraging results, the scope of the hydrazine substrates was also explored (Scheme 2). 2-Hydrazinylpyridines bearing alkyl and halo groups (**2**) were all smoothly converted into the expected triazolopyridine products (**1s–u**) when reacted with phenyl isothiocyanate (**3a**) under the optimal cyclization conditions. The presence of stronger EWGs on the pyridine ring affected both the conversion rates and the yields (**1v–w**). Moreover, quinolino- (**1x**) and diazino-fused (**1y–aa**) 3-aminotriazoles were also synthesized in satisfactory yields.

Based on the experimental results, a plausible reaction mechanism is proposed (Scheme 3). Using the formation of **1a** as an example, addition of 2-hydrazinylpyridine (**2a**) to phenyl isothiocyanate (**3a**) yields a thiosemicarbazide **4a**. Oxidative desulfurization of compound **4a** by molecular iodine[12] in the presence of base generates intermediate **B**. Then, the nucleophilic addition of the pyridine nitrogen to the carbodiimide group and subsequent proton translocation form the 1,2,4-triazolo[4,3-*a*]pyridine-3-amine framework **1a**.

3. Conclusion

In summary, we have developed a practical methodology for the synthesis of fused 3-amino-1,2,4-triazoles under transition-metal-free conditions. Under the optimal reaction conditions, addition of aryl hydrazines to isothiocyanates followed by I_2-mediated oxidative desulfurization/cyclization produced a wide-range of 1,2,4-triazolo[4,3-*a*]pyridine-3-amines and related heterocyclic frameworks. This synthetic approach is operationally simple and can be conveniently conducted on a gram-scale.



Scheme 1. Scope of isothiocyanates. Reaction conditions: (1) **2a** (0.5 mmol), **3** (0.6 mmol), EtOH (5 mL), rt; (2) I_2 (0.55 mmol), K_2CO_3 (1 mmol), rt (isolated yields). [a]Time for the first step. [b]Time for the second step. [c]The reaction was performed in 1,4-dioxane with the second step at 80 °C.

4. Experimental section

4.1. General information

^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz (100 MHz for ^{13}C NMR spectroscopy) spectrometer. Chemical shift values are given in ppm with tetramethylsilane (TMS) as an internal standard. The resonance patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets. The coupling constants (*J*) are reported in Hz. Melting points were determined on a micromelting point apparatus without corrections. High-resolution mass spectra were obtained on a Q-TOF mass spectrometer equipped with an ESI source operated in positive mode. Flash column chromatography was performed over silica gel 200–300 mesh. EtOH, 1,4-dioxane and