



One-pot synthesis of [1,2,4]Triazolo[1,5-*a*]pyridines from azines and benzylidenemalononitriles *via* copper-catalyzed tandem cyclization

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ABSTRACT

A simple and efficient copper-catalyzed tandem radical cyclization reaction has been discovered for the synthesis of triaryl [1,2,4]triazolo[1,5-*a*]pyridines from easily accessible azines and benzylidenemalononitriles. The new transformation involves multiple C–H/C–C bonds cleavage and C–C/C–N bonds formation, with extrusion of gaseous hydrogen and methane. A wide variety of substrates with different functional groups could be converted into the corresponding products in good yields. The fused heterocycles have strong blue fluorescence with large Stokes shifts and high quantum yields.

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1. Introduction

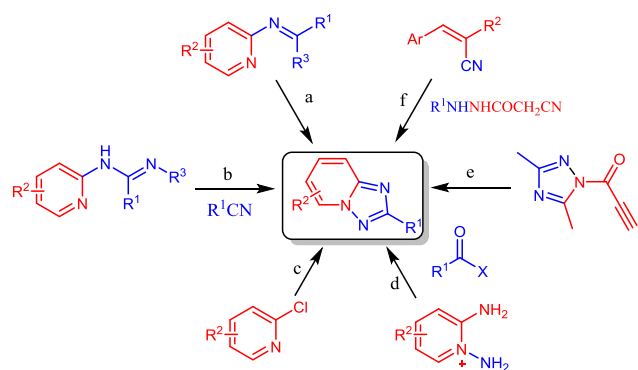
Triazolopyridines represent an important class of nitrogen-rich heterocyclic aromatic compounds. The 1,2,4-triazole unit can be found in numerous molecules with various biological activities, including kinase inhibitor,¹ antibacterial,² and antioxidative.³ Their applications in material chemistry and other fields have been also explored.⁴ During the past decades, a number of synthetic routes to construct [1,2,4]triazolo[1,5-*a*]pyridines had been revealed. Based on different available raw materials, the syntheses can be divided into three main strategies: 1) pyridines and their derivatives; 2) triazoles and their derivatives; 3) multiple components. Representative examples included oxidative cyclization of pyridylimidamides^{5a–j} or guanidyl pyridines (Scheme 1, route a),^{5k} tandem addition/cyclization of 2-aminopyridines with nitriles catalyzed by aluminium trichloride,^{6a} copper catalysts^{6b–d} (Scheme 1, route b), coupling reactions of 2-chloropyridines with thiadiazoles (Scheme 1, route c),⁷ cyclization of aliphatic and aromatic

acids or their derivatives with 1,2-diaminopyridinium salts generated by reacting 2-aminopyridines with hydroxylamine-*O*-sulfonic acid (Scheme 1, route d),⁸ pyrolysis/cyclization of triazole functionalized with an alkynyl group (Scheme 1, route e).⁹ A majority of conventional protocols chose easily available aminopyridines and their derivatives as the initial synthetic point to establish the adjacent triazole nucleus by forming one or two new bonds. Direct approaches to simultaneously construct both pyridine and triazole moieties within one channel had been rarely reported due to the complexity and efficiency of forming multiple bonds.¹⁰ For instance, condensation of arylmethylenemalononitriles with cyanoacetohydrazides led to a range of highly substituted triazolopyridines (Scheme 1, route f).¹¹ In 2013, Alizadeh and his co-workers studied on the one-pot synthesis of [1,2,4]triazolo[1,5-*a*]pyridines through the iodine-catalyzed multi-component reactions from four acyclic fragments, namely dimethyl acetylenedicarboxylate, benzylidenehydrazines, aryl aldehydes and malononitrile (Scheme 2, route g).^{11e} Whereas only alkynes with strong electron deficient groups can be applied in this method, the new strategy could directly introduce multi-functionalities into triazolopyridines *via* a sequential 1,4-dihydropyridine construction and C–N bond formation in the presence of molecular iodine.

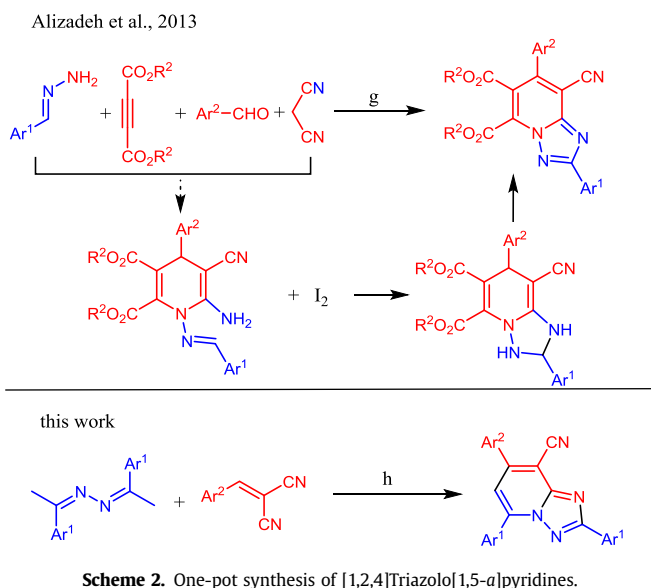
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Scheme 1. Typically traditional synthetic routes to [1,2,4]Triazolo[1,5-*a*]pyridines.



2. Results and discussion

Based on our previous experiences in radical synthesis of heterocycles,¹² herein we report on an efficient copper-catalyzed one-pot elaboration of multi-substituted [1,2,4]triazolo[1,5-*a*]pyridines from readily accessible azines and benzyldenemalononitriles (Scheme 2, route h).

We chose (1*E*, 2*E*)-1,2-bis(1-phenylethylidene)hydrazine (**1a**, 0.5 mmol) and 2-benzyldenemalononitrile (**2a**, 1.0 mmol) as starting materials in our initial reaction optimization (Table 1). Various azines and benzyldenemalononitriles can be easily obtained from arylketones with hydrazines, and arylaldehydes with malononitrile respectively (see in supporting information). In the presence of CuCl (0.1 mmol) using dry DMSO (10 mL) as solvent under air atmosphere, 2,5,7-triphenyl-[1,2,4]-triazolo[1,5-*a*]pyridine-8-carbonitrile (**3aa**) was obtained in 66% isolated yield at 100 °C after 8 h (Table 1, entry 1). The structure of **3aa** was unambiguously confirmed by single crystal X-ray diffraction analysis (Fig. 1).¹³ Notably, the reaction hardly took place without the copper catalyst (Table 1, entry 2). While other copper catalysts were also applicable, copper powder was found to be the best for the reaction, affording **3aa** in 74% yield (Table 1, entries 3–5). Other common solvents such as NMP, toluene, DMF, 1,4-dioxane, acetic acid or pyridine could not achieve comparable results as DMSO (Table 1, entries 6–11). The reaction was not further improved by adding

Table 1
Screening of the reaction conditions^a.

Entry	Catalyst (mmol)	Additive	Solvent	Yield ^b (%)
1	CuCl (0.1)	—	DMSO	66
2	—	—	DMSO	Trace
3	Cu (0.1)	—	DMSO	74
4	CuI (0.1)	—	DMSO	47
5	Cu ₂ O (0.1)	—	DMSO	66
6	Cu (0.1)	—	NMP	17
7	Cu (0.1)	—	Toluene	Trace
8	Cu (0.1)	—	DMF	50
9	Cu (0.1)	—	Dioxane	10
10	Cu (0.1)	—	HOAc	10
11	Cu (0.1)	—	Pyridine	Trace
12	Cu (0.1)	<i>m</i> -CPBA	DMSO	62
13	Cu (0.1)	4 Å-MS	DMSO	73
14	Cu (0.1)	Phen	DMSO	53
15	Cu (0.1)	K ₂ CO ₃	DMSO	Trace
16	Cu (0.1)	H ₂ O	DMSO	30
17	Cu (0.05)	—	DMSO	52
18	Cu (0.15)	—	DMSO	71
19 ^c	Cu (0.1)	O ₂	DMSO	61
20 ^d	Cu (0.1)	N ₂	DMSO	22

^a Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), solvent (10 mL), 100 °C, 8 h, under air atmosphere.

^b Isolated yields of **3aa** based on **1a**.

^c Under oxygen atmosphere.

^d Under nitrogen atmosphere.

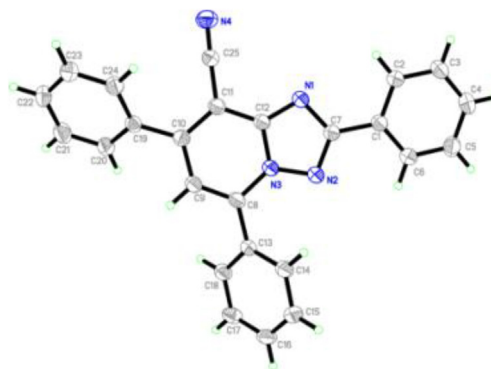


Fig. 1. X-ray crystallographic structure of **3aa**.

molecular sieves, but the yield was slightly decreased by other additives such as *m*-CPBA and 1,10-phenanthroline (Table 1, entries 12–14). Water and even mild base K₂CO₃ dramatically affected the reaction (Table 1, entries 15–16). Reducing catalyst loadings lowered the yield, but the increase could not further improve the conversion (Table 1, entries 17–18). Oxygen was important to this catalytic system, by contrast, the desired product was obtained in only 22% yield under N₂ atmosphere (Table 1, entries 19–20). The optimal condition for this multi-component reaction was therefore established as follows: **1a** (0.5 mmol), **2a** (1.0 mmol), Cu (0.1 mmol) in dry DMSO (10 mL) at 100 °C for 8 h under air (Table 1, entry 3).

With the optimized reaction conditions in hand, we further investigated the applicability of this new catalytic reaction with a broad spectrum of substrates (Table 2). In general, azines bearing electron-donating groups on the *para* positions of the phenyl rings led to higher yields than those bearing electron-withdrawing

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