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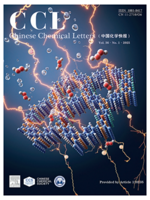

Metal-free construction of diverse 1,2,4-triazolo[1,5-*a*]pyridines on water

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ABSTRACT

A transition-metal- and oxidant-free amination/cyclization reaction to access 1,2,4-triazolo[1,5-*a*]pyridines was realized in water by using amino diphenylphosphinate as amino source. A broad array of readily accessible *N*-(pyridyl)amides could be converted into the products featuring a diverse set of functional groups. The sustainable methodology was successfully applied to the late-stage functionalization of natural products and drugs.

Sustainable synthetic practices, especially green solvents, transition-metal free, and strong oxidants-free strategies, are highly desired to medicinal chemistry and synthetic chemistry [1–4]. The sustainable construction of nitrogen-containing compounds is an enduring topic, owing to their value in drugs, bioactive compounds and functional materials [5–8]. As one of the most important triazole heterocycles, 1,2,4-trizaolo[1,5-*α*]pyridines are widely found in drug candidates and natural products (Fig. 1), such as glucose-lowering drug candidate LY3104607 [9], cancer immunotherapeutic/antifibrotic agent EW-7197 [10], *anti*-atopic dermatitis agent LEO 39652 [11], and prolylhydroxylase domain enzayme PHD-1 inhibitor Takeda-39 [12]. Hence, the construction of 1,2,4-trizaolo[1,5-*α*]pyridines in a sustainable fashion is highly desirable.

Several strategies have been developed to access this important heterocyclic moiety. In 2009, Nagasawa's group reported a CuBr catalyzed oxidative coupling approach of nitrile with 2-aminopyridine to yield the 1,2,4-triazoles in 1,2-dichlorobenzene DCB (Scheme 1a) [13]. Afterwards, this catalytic system was reformed to the solid-supported heterogeneous catalytic systems by Zhao's group and Cai's group, respectively [14,15]. However, these strategies rely on the use of transition-metal catalyst and carcinogenic solvent DCB. Alternatively, *N*-(2-pyridyl)amidines could be converted into 1,2,4-triazolo[1,5-*a*]pyridines in the presence of stoichiometric amounts of external oxidants, such as phenyliodine(III)bis(trifluoroacetate) PIFA [16], I_2 [17], isocyanuric chloride [18], in organic solvent (Scheme 1b). In 2019, Zhang's group disclosed an electrochemical protocol to deliver the scaffold with $^{n}Bu_4NBr$ as the redox mediator in CH_3CN (Scheme 1c) [19]. The use of organic solvent will bring the cost increasing, environmental threat, toxicity issues, and safety hazard. While, water is a low cost, environmentally benign, nontoxic, and non-flammable alternative. Therefore, developing the reactions conducted in water represent a vibrant area of investigation both in industry and academia [20–47].

The amino diphenylphosphinate (DPPH) as amino source was successfully applied in various nitrogen insertion reactions [48–52]. However, aminations using DPPH conducted in water are rarely reported, and construction of the hetero-aromatic ring with DPPH is underdeveloped. With our continued interest in developing sustainable strategy to the construction and derivatization of privileged scaffolds [53–60], we herein report an additive-free procedure to access 1,2,4-triazolo[1,5-*a*]pyridines from the readily available *N*-(pyridyl)amides and amino diphenylphosphinate in water (Scheme 1d).

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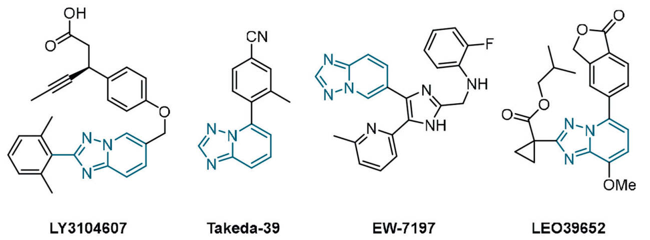
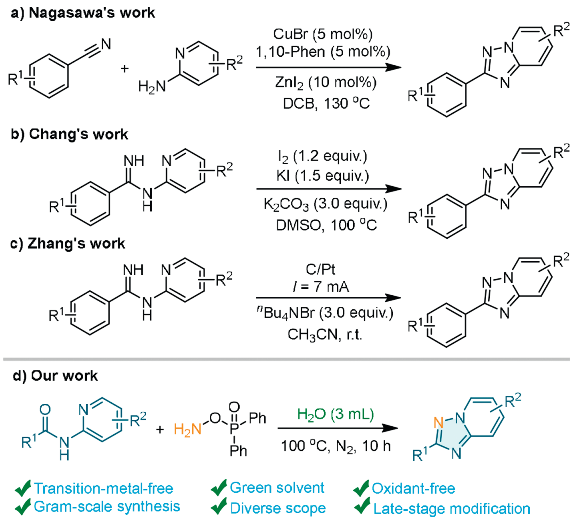
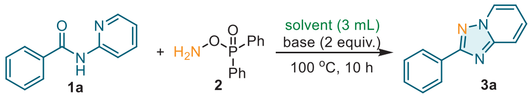


Fig. 1. The bioactive molecules bearing the 1,2,4-trizaolo[1,5-α]pyridines fragment.



Scheme 1. The synthesis of 1,2,4-triazolo[1,5-*a*]pyridines in water.

Table 1
Optimization of reaction conditions.[a]



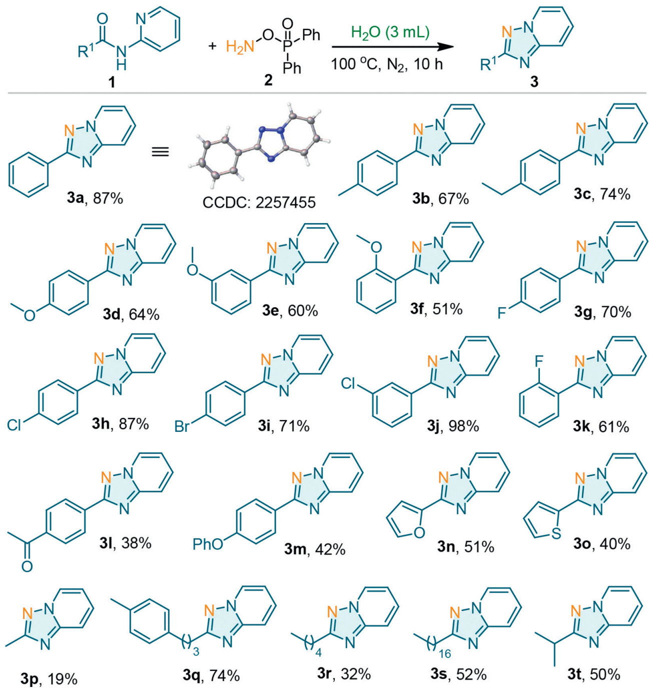
Entry	Solvent	Base	Yield (%)
1	DMF	–	74
2	DMF	Et_3N	N.R.
3	DMF	K_2CO_3	N.R.
4	DMF	NaH	34
5	DMF	NaOH	39
6	DMF	KOH	21
7	H_2O	–	87
8	PGE_{400}	–	63
9	EG	–	80
10	CPME	–	82
11	2-MeTHF	–	69
12	DMC	–	64
13[b]	H_2O	–	81
14[c]	H_2O	–	85

[a] Reaction conditions: **1a** (0.2 mmol), **2** (2 equiv.), base (2 or 0 equiv.), H_2O (3 mL), 100 °C, 10 h, N_2. Isolated yields were given.

[b] Under air atmosphere.

[c] Under O_2 atmosphere.

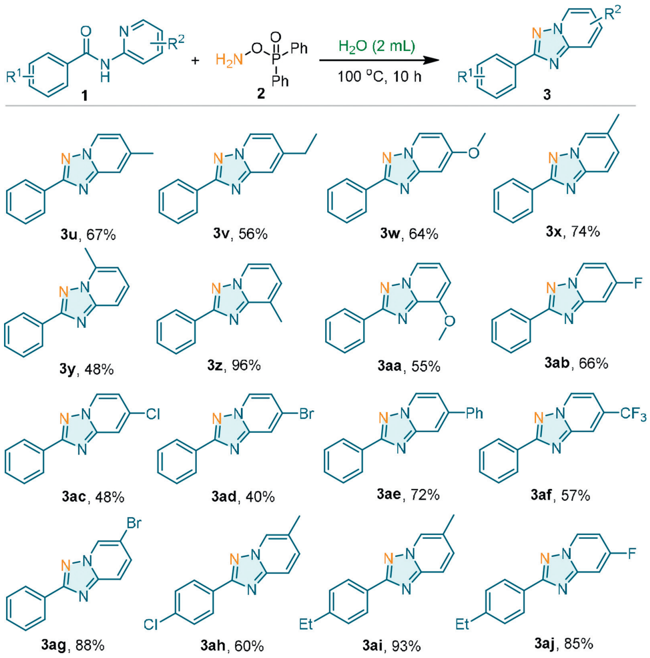
We carried out the study with *N*-(pyridin-2-yl)benzamide (**1a**) and amino diphenylphosphinate (**2**) as the substrates. The first model reaction was conducted in DMF at 100 °C under N_2 atmosphere, affording the desired product **3a** in 74% yield (Table 1, entry 1). Firstly, the effects of the base were investigated (entries 2–6). The use of Et_3N, K_2CO_3, NaH, NaOH, or KOH retarded the reaction. Green solvents H_2O, polyethyleneglycol (PEG400), ethylene glycol (EG), cyclopentyl methyl ether (CPME), 2-MeTHF, or dimethyl carbonate (DMC) were then evaluated (entries 7–12). It was found that H_2O (87%, entry 7) outperformed other green solvents (63%–82%, entries 8–12) in terms of the yield. Changing the reaction atmosphere from N_2 to air or O_2 has no adverse effect on the reaction efficiency (entries 13 and 14), indicating that the transformation is insensitive to O_2. Thus, the optimized conditions were identified as follows: **1a** (0.2 mmol), **2** (2 equiv.), H_2O (3 mL) as a solvent, at 100 °C under N_2 atmosphere.



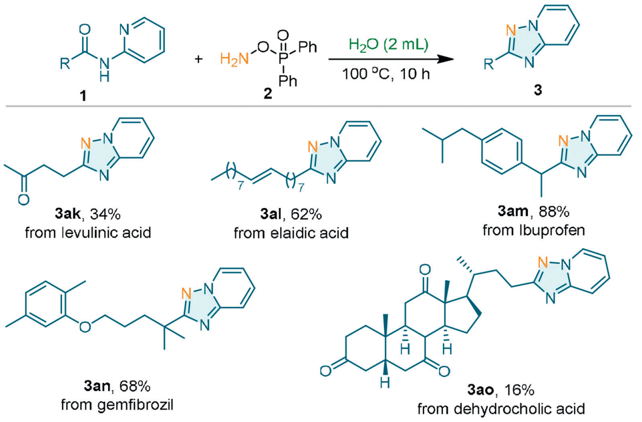
Scheme 2. Scope of the phenyl ring in *N*-(pyridyl)amide. Reaction conditions: **1** (0.2 mmol), **2** (2 equiv.), H_2O (3 mL), 100 °C, 10 h, N_2. Isolated yields were given.

With the optimal cyclization conditions at hand, the scope of the reaction was firstly investigated by variation of the R^1 group in *N*-(pyridyl)amide **1a** (Scheme 2). The result indicated that a variety of substitutions on the aromatic moiety were well tolerated regardless of their electronic properties or steric properties. For example, both electron-donating (Me, Et, OMe) and electron-withdrawing (F, Cl, Br) substitutions on *para*-, *meta*-, or *ortho*-positions of the phenyl group were well compatible, affording the desired products **3b**-**3k** in 51%–98% yields. Moreover, the *N*-(pyridyl)amides **1l** and **1m** bearing the valuable pharmacophores (acetyl and phenoxy group) reacted smoothly to give the desired products **3l** and **3m**. Unfortunately, *N*-(pyridyl)amide with nitro substitution was not compatible to the standard conditions. With R^1 being heteroaromatic rings (**1n**-**1o**), the reactions uneventfully afforded the corresponding products **3n**-**3o** in 51% and 40% yields. Importantly, the substrates **1p**-**1t**, with R^1 being an alkyl, also turned out competent, retrieving the cyclized products **3p**-**3t** in 19%–74% yields. Moreover, the structure of product **3a** was confirmed by the X-ray single crystal diffraction studies.

We next turned our attention to study the effects of substitutions on the pyridine moiety (Scheme 3). Electron-donating groups on the different position of pyridine ring, such as 4-Me, 4-Et, 4-MeO-, 5-Me, 6-Me, 3-Me, and 3-MeO were amenable to the standard protocols, giving the desired products **3u**-**3aa** in 48%–96% yields. Furthermore, the substrates **1ab**-**1ag** with electron-withdrawing substituents (4-F, 4-Cl, 4-Br, 4-pH, 4-CF_3, 5-Br) also proceeded smoothly and afforded the anticipated products **3ab**-**3ag** in moderate to good yields. To our delight, the products **3ah**-**3aj** were also delivered in 60%–93% yields when there were substituents both on the pyridine ring and aryl ring.



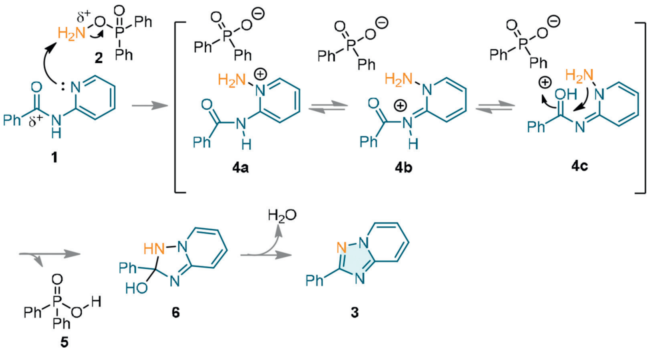
Scheme 3. Scope of the pyridine ring in *N*-(pyridyl)amide. Reaction conditions: **1** (0.2 mmol), **2** (2 equiv.), H_2O (3 mL), 100 °C, 10 h, N_2. Isolated yields were given.



Scheme 4. The late-stage modification of natural products and drugs. Reaction conditions: 1 (0.2 mmol), 2 (2 equiv.), H_2O (3 mL), 100 °C, 10 h, N_2. Isolated yields were given.

To highlight the usefulness of this sustainable strategy in medicinal chemistry, we conducted the late-stage modification of valuable natural products and pharmaceuticals (Scheme 4). The *N*-(pyridyl)amides derived from levulinic acid (**1ak**) and elaidic acid (**1al**) reacted efficiently to produce the products **3ak**-**3al** in 34% and 62% yields, respectively. Furthermore, the method could also be successfully applied in the functionalization of nonsteroidal anti-inflammatory drug (Ibuprofen, **1am**), lipid regulators (gemfibrozil, **1an**), and cholagogues (dehydrocholic acid, **1ao**). The value of these current methods was further displayed by a scale-up synthesis which afforded the desired product in 70% yield (see Supporting information for details).

Considering that amino diphenylphosphinate is a typical electrophilic amination reagent widely used in the regioselectivity N–N coupling reaction [61–65], a plausible mechanism for the amination/cyclization reaction is depicted in Scheme 5. Initially, the pyridine in **1** attacks amino diphenylphosphinate **2**, generating the *N*-aminopyridinium phospate salt **4**, which exists in three resonance forms **4a-4c**. The amino group attacks the carbonyl group intramolecularly to afford diphenylphosphinic acid **5** (detected by HRMS) and **6**. Then, intermediate **6** underwent dehydration with the aid of acid **5** to give the final product **3** [66,67].



Scheme 5. The proposed mechanism.

In summary, we have developed a green and high yielding strategy for the amination/cyclization of *N*-(pyridyl)amides to access the 1,2,4-triazolo[1,5-*a*]pyridines in water. The transition metal- and oxidant-free protocol demonstrates broad substrate scope and exceptional functional group tolerance. The utility of this protocol is also highlighted in late-stage modification of several natural products and drugs. Accordingly, we anticipate that this sustainable protocol will be of great utility to the pharmaceutical chemistry as well as many other fields.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.109755.

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