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SHORT COMMUNICATION

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A One-Pot Copper(II)-Catalyzed Tandem Synthesis of 2-Substituted Pyrrolo[1,2-*b*]pyridazin-4(1*H*)-ones

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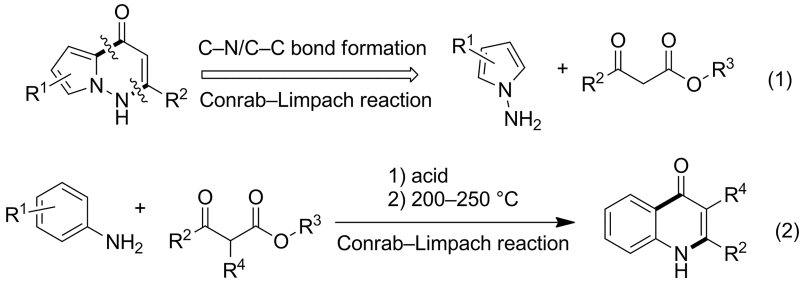
Keywords: Synthetic methods / Tandem reactions / Nitrogen heterocycles / Pyrroles / Pyridazines

A one-pot copper(II)-catalyzed tandem synthesis of 2-substituted pyrrolo[1,2-*b*]pyridazin-4(1*H*)-ones from *N*-aminopyrroles was developed. This tandem reaction involves a Conrad–Limpach-type reaction, including the thermal condensation of *N*-aminopyrroles with the carbonyl group of β-oxo esters followed by the cyclization of Schiff base intermediates. Compared to the traditional Conrad–Limpach quinoline synthesis, we herein successfully applied copper(II) as a catalyst in this transformation to furnish 2-substituted pyrrolo[1,2-*b*]pyridazin-4(1*H*)-ones for the first time. Most of the substrates bearing electron-donating (EDG) and electron-withdrawing (EWG) groups worked well with this procedure. The corresponding products could be converted directly into diverse pyrrolo[1,2-*b*]pyridazine for drug discovery and materials science.

Introduction

Pyrrolo[1,2-*b*]pyridazine and its derivatives, a considerably important class of heterocycles, have been intensively studied on account of their various bioactivities, including as JAK inhibitors,[1] HER-2 tyrosine kinase inhibitors,[2] DGAT1 inhibitors,[3] MEK inhibitors,[4] TRPV1 antagonists,[5] CRF1 receptor antagonists[6] etc. Meanwhile, numerous pyrrolo[1,2-*b*]pyridazines have been discovered to possess remarkable optical and electrochemical properties and are thus being broadly utilized in materials science, including as sensors and biosensors, electroluminescent materials, lasers, and other semiconductor devices.[7]

As a result, considerable efforts have been devoted to developing efficient synthetic approaches for this privileged structure.[7c,7e,8a,8b] One of the most used methods reported before for the assembly of pyrrolo[1,2-*b*]pyridazine moieties typically relied on condensation reactions, such as the condensation of cyanoacetic hydrazide with nitriles[9] and the condensation of oxazolo[3,2-*b*]pyridazinium perchlorates with malononitrile, ethyl cyanoacetate or ethyl malonate.[10] Additionally, cycloaddition reactions,[7a,11] such as the 1,3-dipolar cycloaddition of substituted pyridazines or mesoionic oxazolo[3,2-*b*]pyridazines to acetylenic esters,[7a,7b,12] were other versatile synthetic routes for obtaining pyrrolo[1,2-*b*]pyridazine. As an alternative, diversified pyrrolo[1,2-*b*]pyridazines could also be synthesized directly from pyrrolo[1,2-*b*]pyridazin-4(1*H*)-ones after modifying the 4-position of these precursors.[4,6] However, the methods reported for the synthesis of pyrrolo[1,2-*b*]pyridazin-4(1*H*)-ones are quite rare.[13] Recently, our group con-



Scheme 1. Conrad–Limpach reaction used in the synthesis of pyrrolo[1,2-*b*]pyridazin-4(1*H*)-ones.

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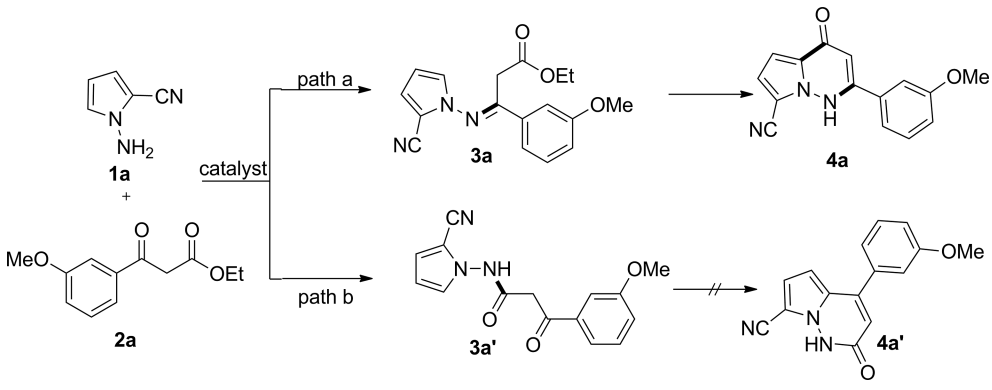
centrated on developing novel strategies for the synthesis of heterocyclic scaffolds from *N*-aminopyrroles, such as pyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-ones[14] and pyrrolo[1,2-*b*]pyridazines.[15] In a retrosynthetic analysis for the synthesis of pyrrolo[1,2-*b*]pyridazin-4(1*H*)-ones, we envisaged that this useful skeleton could be accessed from *N*-aminopyrroles through C–N/C–C bond formation by a Conrad–Limpach-type reaction as well [Scheme 1, Equation (1)]. The Conrad–Limpach reaction is a general approach to 4-hydroxyquinolines, but usually requires two steps and high temperatures over 200 °C [Scheme 1, Equation (2)].[16] Accordingly, there is still a high demand for facile one-pot synthetic methods for diverse pyrrolo[1,2-*b*]pyridazin-4(1*H*)-ones under mild conditions. Toward this goal, we herein first applied copper(II) as catalyst in the Conrad–Limpach reaction to furnish pyrrolo[1,2-*b*]pyridazin-4(1*H*)-ones in a one-pot procedure at a lower temperature of 140 °C [Scheme 1, Equation (1)].

Results and Discussion

At the outset of our study, the reaction of *N*-amino-1*H*-pyrrole-2-carbonitrile (**1a**) with ethyl 3-(3-methoxyphenyl)-3-oxopropanoate (**2a**) was used as a model reaction to optimize the reaction conditions (Table 1). Encouragingly, the desired product **4a** was obtained in a moderate yield by using toluenesulfonic acid monohydrate as the catalyst (Entry 1). Then, a range of Lewis acids as catalysts were examined (Entries 2–8), and the results indicated that the catalysts had a significant effect on this reaction. Interestingly, different pathways were observed when different Lewis acids were employed in this process. The screened trifluoromethanesulfonates (Entries 2–6), except $Zn(OTf)_2$, resulted in the formation of Schiff base intermediate **3a** by attacking the very reactive oxo group, leading to the desired pyrrolo[1,2-*b*]pyridazin-4(1*H*)-one **4a** by undergoing subsequent cyclization of **3a** in a one-pot reaction (path a). Among these Lewis acids, $Cu(OTf)_2$ proved to be the best catalyst for this kind of transformation (Entry 5), but the others resulted in lower yields (Entries 2–4). In contrast, no corresponding compound **4a** was detected when the reaction was carried out in the presence of other catalysts, such as $Cu(OAc)_2$, CuI and $Zn(OTf)_2$ (Entries 6–8). And in these cases, the amino group of **1a** actually first attacked the less reactive ester group rather than the oxo group, giving the thermodynamically preferred product amide **3a′** in a good yield. However, compound **3a′** failed to further convert into the corresponding product pyrrolo[1,2-*b*]pyridazin-2(1*H*)-one **4a′** (path b). After that we surveyed the effect of the solvents on the reaction, and this transformation performed

Table 1. Investigation of the reaction conditions.[a]



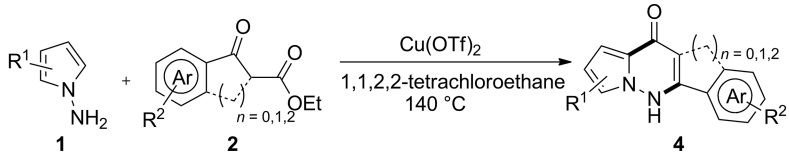
Entry	Catalyst	Solvent	Temp. [°C]	Yield [%][b]	
				3a′	**4a**
1	$TsOH·H_2O$	*o*-xylene	140	0	45
2	$Er(OTf)_3$	*o*-xylene	140	0	15
3	$Yt(OTf)_2$	*o*-xylene	140	0	25
4	AgOTf	*o*-xylene	140	0	58
5	$Cu(OTf)_2$	*o*-xylene	140	0	70
6	$Zn(OTf)_2$	*o*-xylene	140	70	0
7	CuI	*o*-xylene	140	85	0
8	$Cu(OAc)_2$	*o*-xylene	140	60	0
9	$Cu(OTf)_2$	PhCl	140	0	41
10	$Cu(OTf)_2$	DMF	140	0	0
11	$Cu(OTf)_2$	$Cl_2(CH)_2Cl_2$	140		76
12	$Cu(OTf)_2$	$Cl_2(CH)_2Cl_2$	140		66[c]
13	$Cu(OTf)_2$	$Cl_2(CH)_2Cl_2$	140		69[d]
14	$Cu(OTf)_2$	$Cl_2(CH)_2Cl_2$	120		22

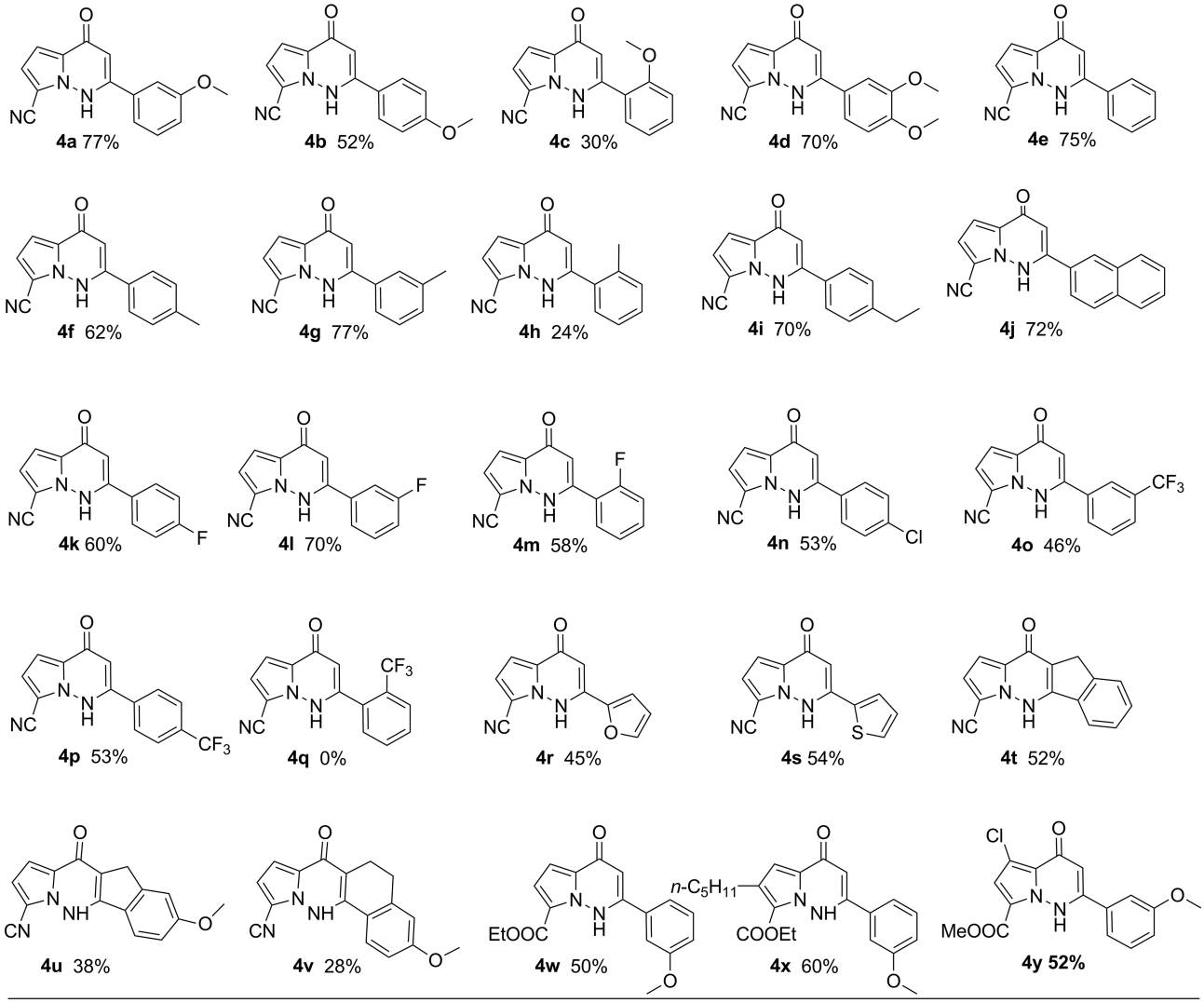
[a] Reaction conditions: **1a** (0.25 mmol, 1.0 equiv.), **2a** (0.275 mmol, 1.1 equiv.), catalyst (0.05, mmol, 0.2 equiv.), solvent (5.0 mL), 140 °C, 3 h. [b] Isolated yields. [c] 0.1 equiv. of $Cu(OTf)_2$ was used. [d] 0.5 equiv. of $Cu(OTf)_2$ was used.

best in 1,1,2,2-tetrachloroethane, giving the desired product **4a** in 76% yield. A moderate yield was obtained when chlorobenzene was used, but no desired product **4a** or by-product **3a′** were observed when DMF was used as the solvent (Entry 10). Then the amount of $Cu(OTf)_2$ was taken into consideration, suggesting that both increasing and decreasing the amount of the catalysts decreased the yield slightly (Entries 12–13). Finally, the reaction temperature was lowered to 120 °C, leading to an inferior yield of the corresponding product **4a** (Entry 14).

Under the optimized reaction condtions [1.0 equiv. of *N*-aminopyrrole, 1.1 equiv. of β-oxo ester, 0.2 equiv. of catalyst $Cu(OTf)_2$, 5.0 mL of 1,1,2,2-tetrachloroethane at 140 °C], the scope of this tandem reaction was explored, and the results are summarized in Table 2. In general, a series of functional groups on the phenyl ring of compound **2** including methyl, ethyl, methoxy, chloro, fluoro and trifluoromethyl were well tolerated, and the desired products were obtained in moderate to good yields (**4a**–**b**, **4d**–**g** and **4i**–**p**). The position of the substituents on the phenyl ring of the

Table 2. Exploration of the substrate scope.[a,b]





[a] Reaction conditions: **1** (0.25 mmol, 1.0 equiv.), **2** (0.275 mmol, 1.1 equiv.), catalyst (0.05, mmol, 0.2 equiv.), solvent (5.0 mL), 140 °C, 0.5–5 h. [b] Isolated yields.

β-oxo ester affected the reaction yields significantly. Compared to substituents at other positions, *ortho* substituents provided lower yields due to steric hindrance (**4c** vs. **4a**–**b**, **4h** vs. **4f**–**g** and **4m** vs. **4k**–**l**), whereas substrates with the bulkier *ortho*-substituted trifluoromethyl group failed to give the corresponding products (**4q** vs. **4o**–**p**). Heterocyclic β-oxo esters such as thiophene- and furan-substituted substrates also gave moderate yields under the reaction conditions (**4r**–**s**). Notably, cyclic β-oxo esters were found to be suitable substrates as well, providing fused polycyclic pyrrolo[1,2-*b*]pyridazin-4(1*H*)-ones **4t**–**v** in acceptable yields. Further studies illustrated that compounds **1** with ester, electron-donating pentyl, and electron-withdrawing chloro groups are also compatible with the reaction process (**4w**–**y**). For the synthesis of product **4y**, the chloro group of the substrate was also a sterically encumbering group. Additionally, the structure of **4d** was further confirmed by X-ray crystallographic analysis (Figure 1).

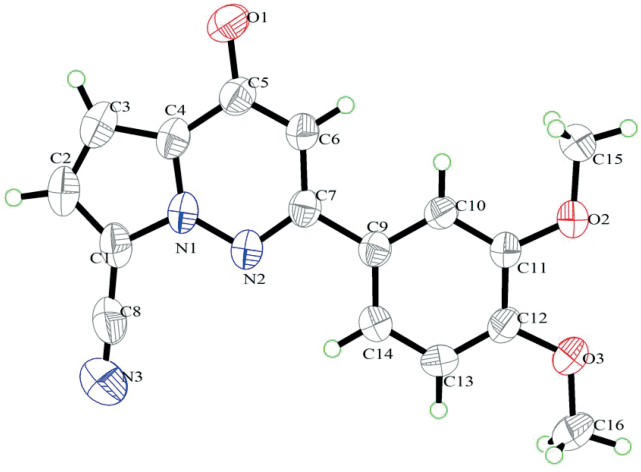


Figure 1. X-ray crystal structure of **4d**.[17]

Conclusions

We have developed the first copper(II)-catalyzed tandem synthesis of 2-substituted pyrrolo[1,2-*b*]pyridazin-4(1*H*)-ones by a Conrad–Limpach-type reaction. Compared to the traditional Conrad–Limpach quinoline synthesis, this reaction is the first example to apply Lewis acidic copper salts, which was further used to construct pyrrolo[1,2-*b*]pyridazin-4(1*H*)-ones. Moreover, the desired pyrrolo[1,2-*b*]pyridazin-4(1*H*)-ones could be converted into diverse pyrrolo[1,2-*b*]pyridazines for drug discovery and materials science.

Experimental Section

General Procedure for Compounds 4: To a mixture of *N*-aminopyrroles **1** (0.5 mmol) and β-aryl-β-oxo esters **2** (0.6 mmol) in dry 1,1,2,2-tetrachloroethane (10.0 mL) was added $Cu(OTf)_2$ (0.1 mmol). Then the mixture was stirred vigorously at 140 °C. When the reaction was complete, the solvent was removed in vacuo, and the crude product was eluted on silica gel with petroleum ether/ethyl acetate (10:1 to 2:1, v/v) to give target compounds **4**.

Acknowledgments

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[17] CCDC-1044805 (for **4d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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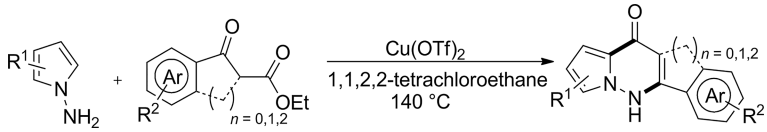
Nitrogen Heterocycles



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