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Letter

PIDA-Mediated Rearrangement for the Synthesis of Enantiopure Triazolopyridinones

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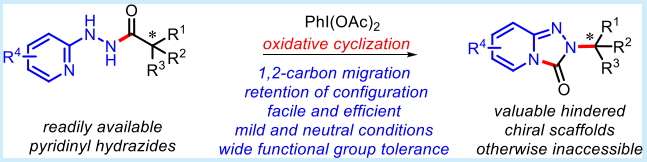
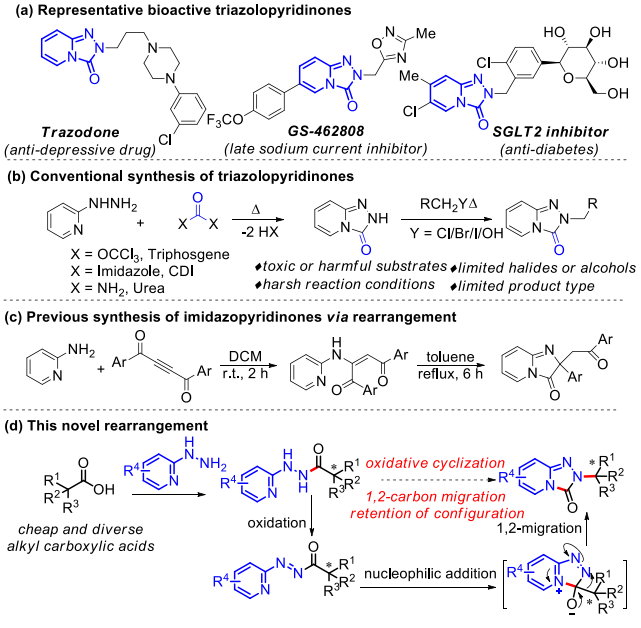
ABSTRACT: A tandem oxidative cyclization/1,2-carbon migration of hydrazides for the synthesis of otherwise inaccessible hindered or enantiopure triazolopyridinones has been developed. This protocol exhibits broad substrate scope and can be easily scaled up by continuous flow synthesis under mild conditions. Most importantly, this method demonstrates a rearrangement with retention of configuration and can be readily applied for the late-stage modification of carboxylic-acid-containing pharmaceuticals, amino acids, and natural products to access enantiopure triazolopyridinones.



Rearrangement reactions have been recognized as powerful chemical transformations for the construction of carbon−carbon (C−C) or carbon−heteroatom (C−X) bonds, and they were frequently employed for generating structural complexity in bioactive (un)natural product synthesis.[1] According to the nature of the migrating group, they can be classified into nucleophilic, electrophilic, radical, and sigmatropic rearrangements, and the migrating group can be shifted from C to C (such as Wagner−Meerwein,[2] pinacol,[3] and Favorskii[4] rearrangements), C to X (such as Beckmann,[5] Hofmann,[6] Curtius,[7] and Schmidt[8] rearrangements), or X to C (such as Stevens,[9] Sommelet−Hauser,[10] and Wittig[11] rearrangements). Among them, the 1,2-migration processes from C to X are particularly useful to introduce a heteroatom into the carbon framework or construct the heterocycles from carbocycles. However, these rearrangements generally require a leaving group attached on the heteroatom and proceed via the loss of either nitrogen (Schmidt and Curtius reactions), halogen (Hofmann reaction), or carboxylic acid (Baeyer−Villiger oxidation)[12] under relatively harsh acidic or basic conditions, which might limit their substrate scope and wide applications. Furthermore, few of them can be conducted with retention of stereochemistry.[13] Nevertheless, more novel enantioselective rearrangement reactions which can be conducted under mild conditions are highly demanded for efficient access of those otherwise inaccessible molecules to further explore their chemical space and synthetic applications.

The triazolopyridinone skeleton is widely found in materials, pharmaceuticals, and agrochemicals due to their special properties.[14] A wide range of biological activities have been reported with this skeleton,[15] such as antidepressive and antidiabetic activities (Scheme 1a).[16] The conventional synthesis of triazolopyridinone derivatives generally requires a two-step procedure: the formation of the triazolopyridinone skeleton from 2-hydrazinopyridine and carbonyl source followed by a nucleophilic substitution reaction with alkyl halide or alkyl alcohol (Scheme 1b).[17] This method normally requires toxic carbonylating agents such as triphosgene and harsh reaction conditions. Also, it was limited by the availability of alkyl halides or alcohols, and the tertiary substituted triazolopyridinone

Scheme 1. Representative Triazolopyridinones and Their Synthetic Strategies



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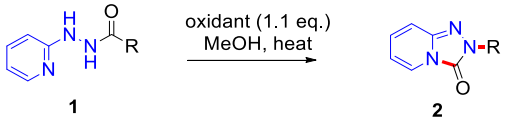
derivatives which have never been reported before cannot be prepared by this method. Furthermore, there is only one chiral triazolopyridinone derivative reported with 89% enantiometric excess (ee).[18] Therefore, a novel synthetic method is highly demanded for the efficient synthesis of enantiopure and sterically hindered triazolopyridinones, which remain an underexplored area of chemical space.

In 2007, the Adib group reported a synthetic method of imidazopyridiones via aryl migration to an adjacent α,β-unsaturated carbonyl group (Scheme 1c).[19] The inexpensive and ubiquitous alkyl carboxylic acid is one of the most common chemical building blocks on Earth.[20] Generally, it is employed for the preparation of ester or amide, and it was well-explored for decarboxylative coupling reactions by providing a reactive alkyl intermediate.[21] We envisaged that the hydrazides, readily made from diverse alkyl carboxylic acids and pyridinyl hydrazines, could be easily oxidized to the azo compounds due to their low oxidation potential.[22] The tandem nucleophilic addition of the pyridine to the carbonyl moiety followed by a 1,2-carbon migration would construct the triazolopyridinone skeletons (Scheme 1d). If the migrating group has a stereocenter, this oxidative cyclization/1,2-carbon migration process might take place with retention of stereochemistry to afford the enantiopure triazolopyridinones.

To verify our hypothesis, the initial efforts were focused on the condition optimization with pyridinyl hydrazide **1** as a model substrate. With primary (CH_2Ph) substituted hydrazide as the substrate, we first put special emphasis on screening the effects of various oxidants with methanol as the solvent at 40 °C (Table 1, entries 1−9). It was found that only a trace amount of

Table 1. Condition Optimization



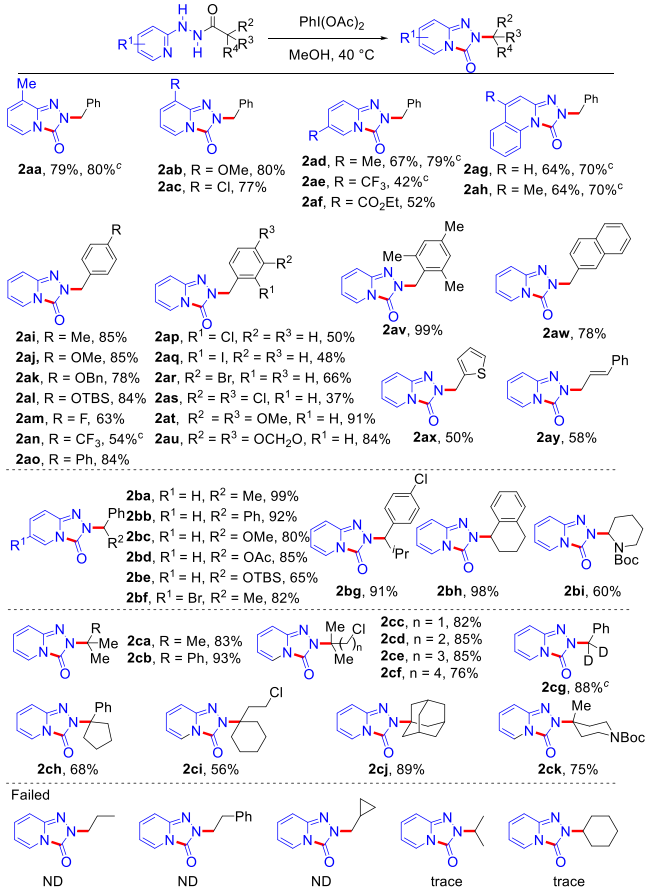
entry[a]	R	oxidant	temp (°C)	yield (%)[b]
1	CH_2Ph	$K_2S_2O_8$	40	trace
2	CH_2Ph	AgOAc	40	trace
3	CH_2Ph	$NaClO_2$	40	22
4	CH_2Ph	NaClO	40	25
5	CH_2Ph	*m*-CPBA	40	25
6	CH_2Ph	DDQ	40	44
7	CH_2Ph	DMP	40	44
8	CH_2Ph	PIFA	40	48
9	CH_2Ph	PIDA	40	65
10	CH_2Ph	PIDA	rt	41
11	CH_2Ph	PIDA	70	89
12	CHMePh	PIDA	40	99
13	^{t}Bu	PIDA	40	83

[a]Reaction conditions: **1a** (0.2 mmol), oxidant (0.22 mmol, 1.1 equiv), solvent (2 mL), air, 5−30 min. [b]Isolated yield of product. DMP = Dess−Martin periodinane. PIFA = $PhI(OCOCF_3)_2$.

triazolopyridinone **2** was formed with either $K_2S_2O_8$ or AgOAc as the oxidant (Table 1, entries 1 and 2). By switching to the other oxidants, the desired product **2** was isolated in 22−48% yields (Table 1, entries 3−8). The yield could be improved to 65% with PIDA as the oxidant (Table 1, entry 9). The yield decreased significantly when the reaction was conducted at rt (Table 1, entry 10). To our delight, the yield was improved to 89% when the temperature was increased to 70 °C (Table 1, entry 11). Interestingly, the secondary (CHMePh) and tertiary (^{t}Bu) substituted hydrazides reacted more efficiently at 40 °C within 30 min and gave the corresponding products in 99 and 83% yields, respectively (Table 1, entries 12 and 13).

With the optimized conditions in hand, the scope of this reaction was evaluated, as shown in Scheme 2. Various

Scheme 2. Substrate Scope[a,b]



[a]Reaction conditions: hydrazide (0.2 mmol), $PhI(OAc)_2$ (0.22 mmol, 1.1 equiv), MeOH (2 mL), air, 40 °C, 5−30 min. [b]Isolated yields. [c]70 °C.

hydrazides were prepared readily from the corresponding pyridinyl hydrazines and alkyl carboxylic acids. First, the primary benzyl-substituted hydrazides were tested (**2aa**−**2ay**), and pleasingly, this reaction exhibits broad functional group tolerance and substrate scope. Generally, the substrates with electron-rich benzyl substituents (**2ai**−**2al**, **2at**−**2av**) gave corresponding products in yields much higher than those with electron-deficient ones (**2am** and **2an**). The quinolinyl (**2ag** and **2ah**), naphthyl (**2aw**), thienyl (**2ax**), or allylic (**2ay**) substituted substrates are also effective. It is worth mentioning that most of the substrates reacted well at 40 °C except for substrates with CF_3 substituents (**2ae** and **2an**). Next, the secondary substituted hydrazides with substituents at the α position, including ether, ester, amide, and cyclic systems, were tested, and all gave the corresponding products (**2ba**−**2bd**, **2bf**−**2bh**) in 80−99% yields except **2be** and **2bi**. Finally, the tertiary substituted hydrazides, such as simple alkyl substituted (**2ca**−**2cf**), deuterated (**2cg**), and cyclic systems (**2ch**−**2ck**), were tested and afforded the corresponding novel hindered triazolopyridinone derivatives effectively, which cannot be prepared by the

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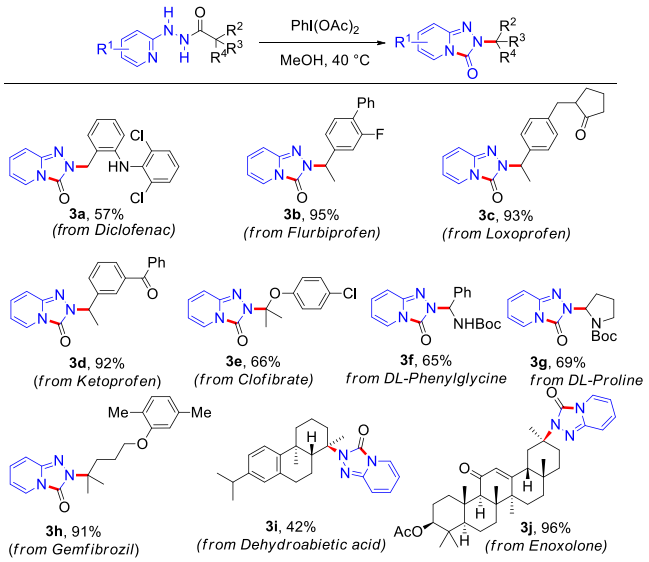
conventional nucleophilic substitution from the corresponding triazolopyridinone and alkyl halides or alcohols. However, when the migrating group was a primary aliphatic group, the corresponding diazo compound was detected during the reaction and decomposed after heating, and the secondary aliphatic migrating group would afford a trace amount of the desired product.

To further demonstrate the utility of this novel rearrangement, we applied it for the late-stage modification of commercially available and acid-containing anti-inflammatory drugs (such as diclofenac **3a**, flurbiprofen **3b**, loxoprofen **3c**, and ketoprofen **3d**), anti-hyperlipidemic agent (such as clofibrate **3e** and gemfibrozil **3h**), amino acids (**3f** and **3g**), and natural products (dehydroabietic acid **3i** and enoxolone **3j**), and the corresponding triazolopyridinone derivatives were prepared in good to excellent yields (Scheme 3), which demonstrated an efficient and fast way to access their analogues for structure–activity relationship studies in medicinal chemistry.

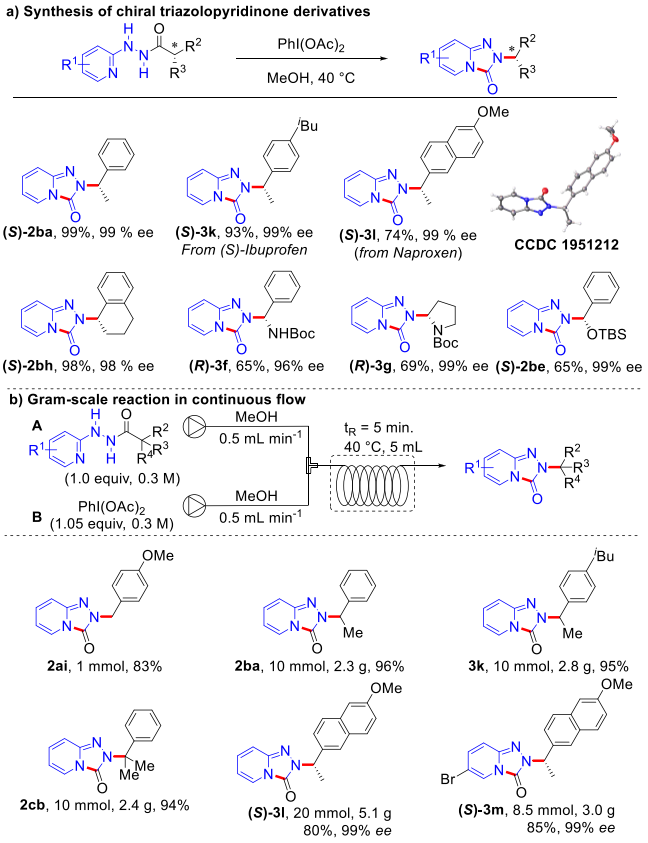
Scheme 3. Late-Stage Modification of Pharmaceuticals, Amino Acids, and Natural Products[a,b]



[a]Reaction conditions: hydrazide (0.2 mmol), $PhI(OAc)_2$ (0.22 mmol, 1.1 equiv), MeOH (2 mL), air, 40 °C, 5–30 min. [b]Isolated yields.

To verify whether the configuration could be retained in this tandem oxidative cyclization/1,2-carbon migration if the migrating terminus has a stereocenter, various optically pure hydrazides were synthesized from chiral acids including best-selling drugs (ibuprofen (*S*)-**3k**, naproxen (*S*)-**3l**) and amino acids ((*R*)-**3f**, (*R*)-**3g**) (Scheme 4a). Under the standard conditions, the corresponding novel triazolopyridinone products were obtained in excellent yields and ee. The X-ray crystallographic analysis of (*S*)-**3l** was conducted, and it was confirmed that the products were obtained with retention of configuration. To demonstrate the scalability of this reaction, we further conducted the gram-scale reaction by employing continuous flow chemistry (Scheme 4b). Various (enantiopure) triazolopyridinones can be prepared efficiently on a larger scale, which shows the potential applications in industry. It demonstrated that this novel rearrangement provides an efficient strategy for the synthesis of those valuable (enantiopure) triazolopyridinone derivatives, which are difficult to prepare by previous methods.

Scheme 4. Synthesis of Enantiopure Triazolopyridinone Derivatives and Gram-Scale Continuous Flow Synthesis



In conclusion, we have presented a novel and facile rearrangement involving a tandem oxidative cyclization/1,2-carbon migration. By employing this method, the previous inaccessible enantiopure triazolopyridinone derivatives can be prepared efficiently with diverse and cheap alkyl carboxylic acids as starting materials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02278.

Experimental procedures and spectroscopic characterization data (PDF)

Accession Codes

CCDC 1951212 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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