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Oxidative Fluorocyclization of Vinyl Azides Leading to 5-Azido, 5-Fluoro-1,3-oxolan-2-one

Lin Li,[#] Shanshan Cao,[#] Fanyi Lin, Peiqiu Liao* and Yongquan Ning.*

Abstract: Vinyl azides have become versatile building blocks in organic synthesis. Most of their transformations usually undergo a fast release of molecular N_2 to generate 2H-aziridine and vinyl nitrene intermediates. However, retaining the azides group in the final product is quite rare and great challenging. Here we design and validate a new alkene difunctionalization strategy that involves an oxidative fluorocyclization of vinyl azides for the synthesis of a variety of 5-azido, 5-fluoro-1,3-oxolan-2-ones with broad substrate scope and good functional group tolerance in good to excellent yields. The in situ introduction of a removal leaving group in this difunctionalization reaction is a key to retain azide moiety in the final product.

Introduction

Since the vinyl azides are easily prepared via the hydroazidation of alkynes,[1] which are employed as versatile building blocks in organic synthesis as witnessed from the reported literature.[2,3] Most of the transformations based on vinyl azides usually undergo a fast release of molecular N_2 to generate 2H-aziridine and vinyl nitrene intermediates, providing diverse, structurally distinct molecular skeletons. Mechanistically, vinyl azide usually acts as an important C-C-N synthons for synthesis of various N-containing molecules. Although retaining the azides group in the final product is quite rare and a great challenge. To date only a few reports available in the literature. For example, in 2017, López et al. reported a Cu-catalysed [3+2] cycloaddition/allylic azide rearrangement of vinyl carbene precursors with vinyl azide to form azidocyclopentenes (Fig 1a).[4] Very recently, Xu group reported Cu-catalyzed asymmetric [4+2]-cycloaddition of vinyl azides with unsaturated ketone esters to build various chiral cyclic azides (Fig 1b).[5] Considering the widespread importance of azides group in organic synthesis, exploring new strategies of for the synthesis of organic azides from vinyl azides would be highly desirable.[6]

In this context, we targeted to develop a new strategy via alkene difunctionalization that enables the in situ introduction of a leaving group and intact the N_3 group in the transformations. The idea was inspired by recent works from the group of Jacobsen and others.[7] In their works, the interaction of the $PhIF_2$•HF (generated in situ from reaction of PIDA with Py•HF) with the double bond of styrenyl triggered a sequential fluoride addition and cyclization process, in which a hypervalent iodine moiety acts as an in situ formed leaving group. Building from our long understanding efforts in the chemistry of α-vinyl azides,[8] we here report an oxidative fluorocyclization of vinyl azides with in situ generated difluoroiodobenzene from PIDA and Py•HF.[7] It is the first example of intermolecular oxyfluorination of vinyl azides. Moreover, azides group retained in the final products as a useful handle. Furthermore, all of these 5-azido, 5-fluoro-1,3-oxolan-2-one are novel compounds, which may have potential application value in organic and medicinal chemistry research.

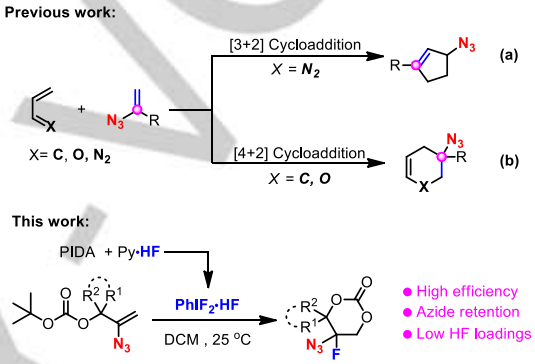
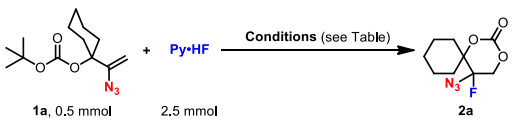


Fig 1. The reaction of vinyl azides with azide retention

We first investigated the reaction of vinyl azide 1a with in situ generated $PhIF_2$•HF (pyridine•HF as fluorine source, PIDA as oxidant) in DCM at 25 °C as a model reaction, affording the desired fluoroxidation product **2a** in 96% yield (Table 1, entry 1). When changing oxidant to PhIO and PIFA, a very low yield was obtained (entry 2, 3), and the reaction failed to provide the desired product when PIDA was replaced with $K_2S_2O_8$ or H_2O_2 (entry 4, 5). Switching to other potential fluorine sources (e.g. Et_3N•HF,[9] AgF,[10] CsF[11]), led to no reaction (entries 6-8). A brief survey of other solvents revealed poor or no conversion in DMF, DMSO and $CHCl_3$ (entries 9-11); similarly, lowering the reaction temperature to -40 or -20 °C led to reduced yields (entries 12-14)

Table 1. Optimization of the Reaction Conditions.[a,b]



Entry	oxidant	'F' source	solvent	T (°C)	yield (%)[b]
1	PIDA	Py·HF	DCM	25	96
2	PhIO	Py·HF	DCM	25	70
3	PIFA	Py·HF	DCM	25	86
4	$K_2S_2O_8$	Py·HF	DCM	25	0
5	H_2O_2	Py·HF	DCM	25	0
6	PIDA	Et_3N·HF	DCM	25	0
7	PIDA	AgF	DCM	25	0
8	PIDA	CsF	DCM	25	0
9	PIDA	Py·HF	DMSO	25	0
10	PIDA	Py·HF	DMF	25	0
11	PIDA	Py·HF	$CHCl_3$	25	57

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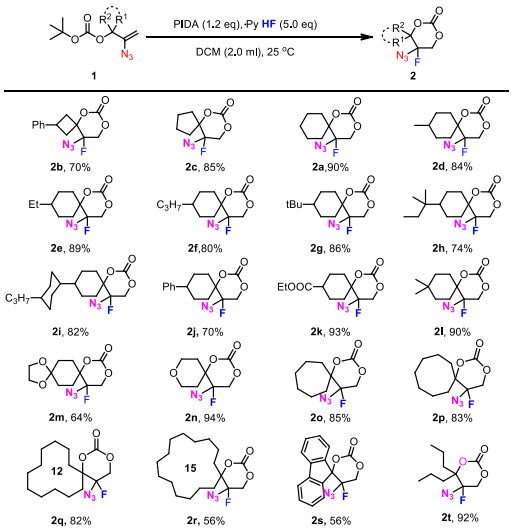
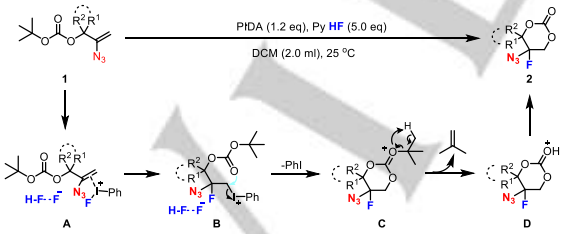
12	PIDA	Py·HF	DCM	-20	60
13	PIDA	Py·HF	DCM	0	84
14	PIDA	Py·HF	DCM	40	78

[a] Reaction conditions: 1 (0.5 mmol), PIDA (1.5 mmol), and Py·HF (5.0 mmol) in 3 mL of DCM at 25 °C for 1 min. Yields are of isolated products.



Scheme 1. Synthesis of 5-azido, 5-fluoro-1,3-oxolan-2-one

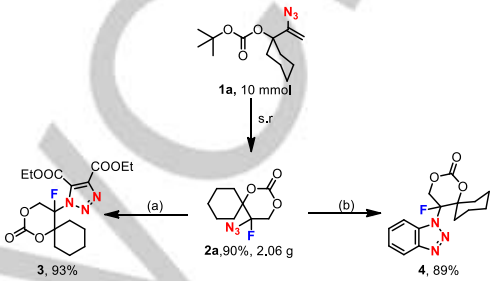
Next, the optimal reaction conditions were adopted on a variety of vinyl azides to investigate the generality of the protocol. As described in scheme 1, we first examined a variety of cyclic alcohols. 3-Phenylcyclobutanol and cyclopentyl alcohol were successfully subjected to this transformation with 70% and 85% yield (2b, 2d), respectively. Cyclohexyl alcohols tethered with different functional groups also suitable to give the desired fluorocyclization products (2, 4-11,) with good to excellent yields (80-93%). Also, the use of tetrahydropyran derivative leading to the desired product 2n in an 94% yield. Furthermore, 7-15 membered macrocyclic compounds were also efficiently converted into the corresponding 5-azido, 5-fluoro cyclic carbonate (2o-2r, 56%-85%). Remarkably, anthrone derivative also participated in this transformation to give the consistent cyclic carbonate in good yields (**2s**, 56% yield). Dialkyl alcohols was also smoothly transferred into cyclic carbonates (**2t**) with 67% yield.



Scheme 2. Proposed Mechanism

Based on the literature precedence, a plausible mechanism is proposed in Scheme 2. At first, the 1,2-iodofluorination of the vinyl azide with $PhIF_2$•2HF (generated in situ from reaction of PIDA with Py•HF),[7,13] occurs to form intermediate **B** through the activated intermediate **A**. Then the subsequent intermolecular nucleophilic attack of the carbonyl oxygen to the C-I bond in fluorinated intermediate **B** generates an intermediate **C**. After nucleophilic attack of the oxygen atom to hydrogen atom and electron transfers of hydrogen atom, intermediate **C** transfer to intermediate **D** with releasing 2-methylpropene. Finally, the products **2** are formed by losing hydrogen cation from intermediate **D**.

The practicality of the method was evaluated by the gram-scale synthesis of **2a** under identical reaction conditions, and produced in nearly similar yields in a 10 mmol scale reaction (Scheme 3). Next, the synthetic utility of the product was investigated. For example, the azide group in **2a** easily converted to 1,2,3-triazoles through base-mediated 1,3-dipolar cycloaddition with alkynes,[13] affording the corresponding triazole products **3** and **4** 93% and 89% yields, respectively.



Scheme 3. Gram-scale synthesis and further reactions of 2a. Reaction conditions: (a). **2a**. (0.5 mmol) and DMAD (0.6 mmol) in 8.0 mL of water at 70 °C for 8 h. (b). **2a**. (0.5 mmol), CsF (2 mmol) and 2-(trimethylsilyl)phenyl triflate (1.2 mmol) in 2.0 mL of MeCN at 25 °C for 24 h.

Conclusions

In conclusion, we have developed a general and practical strategy to synthesize 5-azido, 5-fluoro-1,3-oxolan-2-one via oxidative fluorocyclization of vinyl azides. The practicality of this method was highlighted by its mild reaction conditions, broad substrate scope, good functional group tolerance, and moderate to good yields. The azide group retained in the final product provides many synthetic opportunities for the preparation of valuable nitrogen-containing cyclic carbonate skeleton.

Experimental Section

Typical synthetic procedure (with 2a as an example): To a stirred solution of vinyl azides **1a** (0.5 mmol, 1.0 equiv), $PhI(OAc)_2$ (0.6 mmol, 1.2 equiv) in DCM (3.0 mL) in a 15 mL of Schlenk tube under air was added Py•HF (2.5 mmol, 5 equiv) in one portion. The reaction was allowed to stir at 25 °C until the complete consumption of vinyl azides as monitored by TLC analysis (typically 1 min). Then the resulting heterogeneous mixture was transferred carefully into a vigorously stirred suspension of silica (15 g per 1 mmol of the substrate) in ethyl acetate at -78 °C. The resulting suspension was allowed to warm to room temperature. Then the resulting suspension was filtered, extract with DCM (3×15 mL), washed with brine (3 ×40 mL). Then combined organic layer was dried over Na_2SO_4. After removal of the solvent under reducd pressure, rhe residue was separated by flash column chromatography to give 2a in 90% yield as a colorless oil.

Keywords: Vinyl azides • $PhIF_2$•HF • Azide retention • 5-azido, 5-fluoro-1,3-oxolan-2-one

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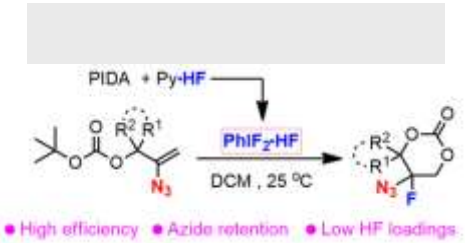
Here we design and validate a new strategy via alkene difunctionalization that enable the in situ introduction of a leaving group, keeping the N_3 group intact in the transformations, access to a variety of 5-azido, 5-fluoro- 1,3-oxolan-2-one derivatives with broad substrate scope and good functional group tolerance in good to excellent yields.



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