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[4 + 1] Cyclization of benzohydrazide and $ClCF_2COONa$ towards 1,3,4-oxadiazoles and 1,3,4-oxadiazoles-d_5

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ABSTRACT

A facile synthesis of 1,3,4-oxadiazoles and 1,3,4-oxadiazoles-d_5 *via* [4 + 1] cyclization of $ClCF_2COONa$ with non-amine compounds containing amino groups is developed. Of note, this is the first time that halofluorinated compounds are used as C1 synthon to construct deuterated nitrogen-heterocyclic compounds. The current protocol features simple operation, readily accessible raw materials, wide substrate scope and valuable products

Owing to the diverse beneficial effects brought by fluorine atoms, fluorine chemistry has drawn much attention from chemists over the past years [1–10]. Especially, halofluorinated compounds, which are recognized as versatile building blocks, have been emerging as one of the hottest research topic in fluorine chemistry [10–30]. Various reaction modes of XCF_2R have been established by our group [10–24] and others [25–30]. For example, besides the double cleavage of XCF_2R, several intriguing utilities of XCF_2R such as playing the role of difluorocarbene precursors [25–27], serving as C1 synthon *via* quadruple cleavage, and reacting with amines to construct nitrogen-containing compounds have been demonstrated [12–18]. Despite those achievements, the reaction between the amino groups in hydrazine compounds and XCF_2R has not yet been explored. Previously, our group reported the first example for synthesis of deuterated formamide from halofluorinated compounds and amines (Scheme 1A) [13]. However, the utilization of $ClCF_2COONa$ as C1 synthon and D_2O as deuterium sources to construct deuterated nitrogen-heterocyclic compounds has not been documented so far.

1,3,4-Oxadiazoles are a very important class of *N*-heterocyclic compounds, which are extensively found in pharmaceuticals and biologically active molecules [31–36]. In view of the importance of 1,3,4-oxadiazoles and deuterated compounds in pharmaceuticals, we reported an effective [4 + 1] cyclization of $ClCF_2COONa$ to synthesize 1,3,4-oxadiazoles and more importantly, 1,3,4-oxadiazoles-d_5 in decent yields and with excellent deuteration ratios under transition-metal-free conditions. To the best of our knowledge, the direct construction of 1,3,4-oxadiazole-d_5 has never been documented up to date. Thus our protocol provide a facile and straightforward route for divergent construction of 1,3,4-oxadiazoles and 1,3,4-oxadiazoles-d_5 *via* a transition-metal-free [4 + 1] cyclization, which represents the first example of efficient one-pot construction of 1,3,4-oxadiazoles-d_5 (Scheme 1B).

To explore the feasibility of our hypothesis, we selected benzohydrazide **(1a)** and $ClCF_2COONa$ **(2a)** as the model substrates for our proof-of-concept study (Table 1). To our delight, when the reaction was carried out in the presence of base Cs_2CO_3, the expected 2-phenyl-1,3,4-oxadiazole **(3a)** was obtained in 73% yield (Table 1, entry 1). Inspired by this result and in light of our previous researches, a range of bases were screened, which turned out that K_3PO_4 was the best choice to deliver the desired product **3a** (90% yield) (Table 1, entries 2–4). Next, we examined the reaction temperature. Nevertheless, elevating or lowering the temperature are both unfavorable for the reaction (Table 1, entries 5 and 6). In order to enhance the yield of **3a**, we also inspected a number of solvents (Table 1, entries 7–10). However, no superior results gained and it was found that CH_3CN was still the opti-

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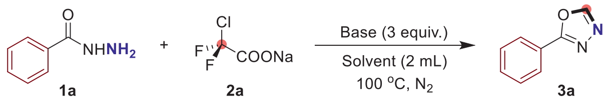
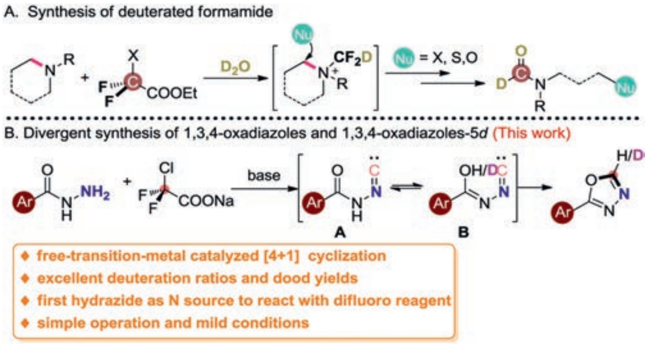
Table 1
Screening of optimized reaction conditions.



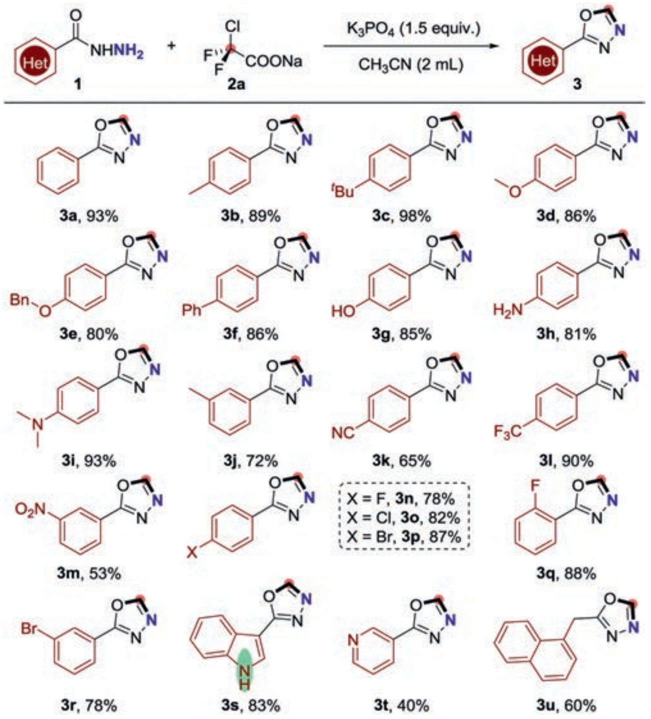
Entry	Base	Solvent	Yield (%)[a]
1	Cs_2CO_3	CH_3CN	73
2	Na_2CO_3	CH_3CN	78
3	$NaHCO_3$	CH_3CN	67
4	K_3PO_4	CH_3CN	90
5[b]	K_3PO_4	CH_3CN	50
6[c]	K_3PO_4	CH_3CN	70
7	K_3PO_4	THF	30
8	K_3PO_4	1,4-dioxane	trace
9	K_3PO_4	DCE	trace
10	K_3PO_4	EA	15
11[d]	K_3PO_4	CH_3CN	91
12[e]	K_3PO_4	CH_3CN	93

Reaction condition: **1a** (0.2 mmol), **2a** (0.6 mmol) and base (0.6 mmol) in slovent (2 mL) under N_2 atmosphere at 100 °C for 1 h.

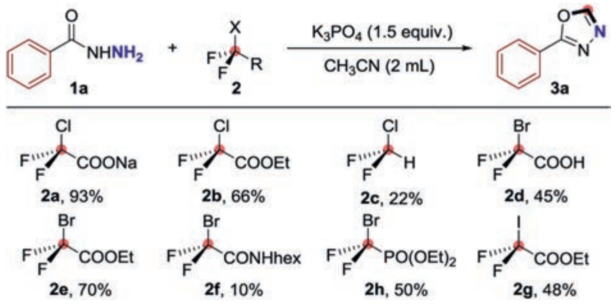
[a] Isolated yield.
[b] At 80 °C.
[c] At 120 °C.
[d] **2a** (0.3 mmol), base (0.5 mmol).
[e] **2a** (0.3 mmol), base (0.3 mmol).



Scheme 1. Transition-metal-free catalyzed synthesis of 1,3,4-oxadiazoles.



Scheme 2. Substrate scope for the synthesis of 1,3,4-oxadiazoles. Reaction condition: **1** (0.2 mmol), **2a** (0.3 mmol), K_3PO_4 (0.3 mmol), CH_3CN (2 mL), N_2, 100 °C, 1 h.



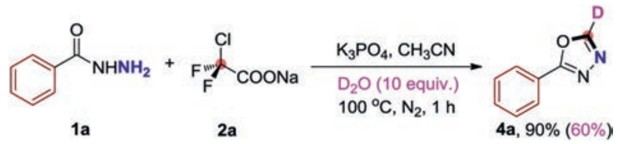
Scheme 3. Substrate scope of halodifluoromethyl compounds. Reaction condition: **1a** (0.2 mmol), **2** (0.3 mmol), K_3PO_4 (0.3 mmol), CH_3CN (2 mL), N_2, 100 °C, 1 h.

mized solvent. Gratifyingly, when we reduced the amount of both $ClCF_2COONa$ and the base to 1.5 equiv., the targeted 2-phenyl-1,3,4-oxadiazole **(3a)** could be isolated in 93% yield (Table 1, entry 12).

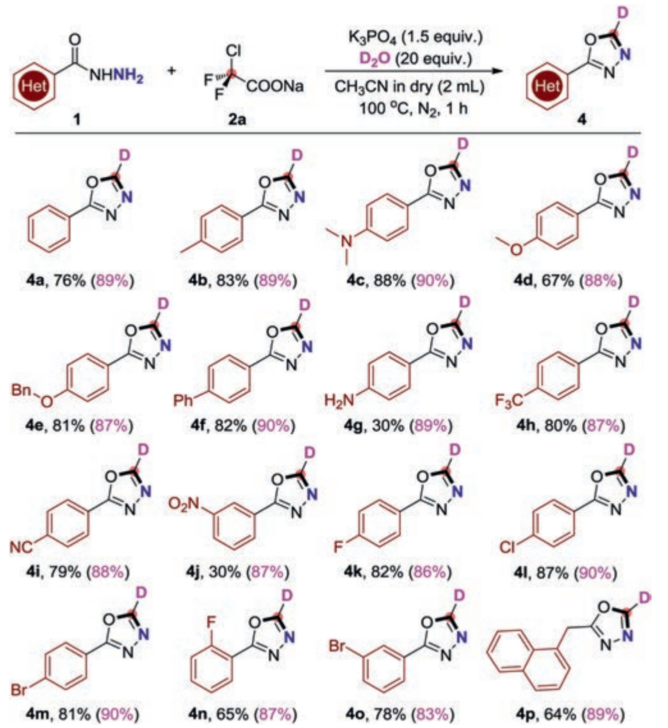
With the optimized conditions in hand, we next investigated the substrate generality of this [4 + 1] cyclization (Scheme 2). To our delight, a wide range of easily accessible benzohydrazides **(1a–1u)** could react smoothly with $ClCF_2COONa$ **(2)** to provide the desired products 2-substituted-1,3,4-oxadiazoles **(3a–3u)** in good yields by using CH_3CN as solvent and K_3PO_4 as base. The structure of **3a** was unambiguously confirmed by X-ray single crystal analysis. As showcased in Scheme 2, a variety of benzohydrazides bearing both electron-donating and electron-withdrawing groups were good candidates in this transformation, affording the desired 2-substituted-1,3,4-oxadiazole products **(3a–3m)** in 53% to 98% yields. Moreover, halo-substituted benzohydrazides **(1n–1r)** were also proven to be good candidates in this cyclization reaction, enabling to formation of the desired 2-substituted-1,3,4-oxadiazole products **3n**–**3r** in 78% to 88% yields. In addition to *para*-substituted benzohydrazides, *ortho*- and *meta*-substituted benzohydrazides could also work well in this reaction, providing the corresponding 1,3,4-oxadiazoles **3q** and **3r** in good yields. To our delight, heterocyclic benzohydrazides and alkyl hydrazide demonstrated decent reactivity in this cyclization reaction as well, finishing the targeted products **3s**–**3u** in moderate to good yields. Of note, the indole was well-tolerated under the standard conditions without the difluoromethylation of the free N-H in indole.

As summarized in Scheme 3, we also investigated other halodifluoromethyl compounds and it was found that all of them could serve as carbon sources to forge 2-phenyl-1,3,4-oxadiazole under the same conditions by using benzohydrazides **1a** as the model substrates. In addition to sodium chlorodifluoroacetate **2a**, ethyl chlorodifluoroacetate **2b**, ethyl bromodifluoroacetate **2e** and ethyl iodifluoroacetate **2g** were proved to be good C1 source in this transformation, enabling to deliver **3a** in 48% to 70% yields, respectively. When difluorobromoacetic acid **2d** was used as C1 source, the yield of **3a** could be isolated in 45% yield. Diethyl(bromodifluoromethyl)phosphonate **2h** provided the corresponding 2-phenyl-1,3,4-oxadiazole **3a** in a comparable 50% yields. Compared to other halodifluoromethyl compounds, chlorodifluoromethane **2c** and 2-bromo-2,2-difluoro-*N*-hexylacetamide **2f** displayed lower reactivity, resulting in the target product **3a** with 22% and 10% yields, respectively.

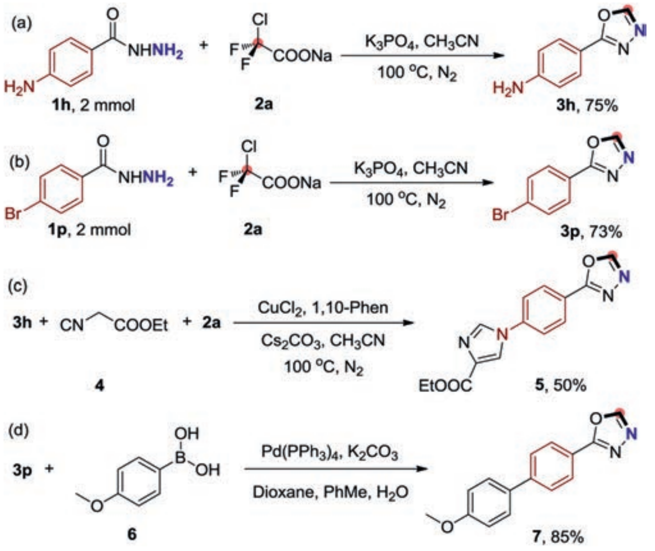
Deuterium incorporation plays an important role in isotope labelling, which can be used in the investigation of reaction mechanism, as well as in nuclear magnetic resonance spectroscopy



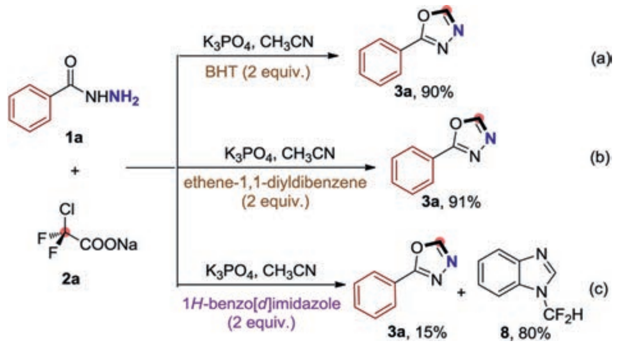
Scheme 4. Isotope-labelling experiments.



Scheme 5. Deuteration with D_2O as the deuterium source. Reaction condition: **1** (0.2 mmol), **2a** (0.3 mmol), K_3PO_4 (0.3 mmol), D_2O (20 equiv.), anhydrous CH_3CN (2 mL), N_2, 100 °C, 1 h. All yields are the isolated yields, and the numbers in parentheses are the deuteration ratios of the corresponding deuterated products.



Scheme 6. Scale-ups and synthetic transformations.



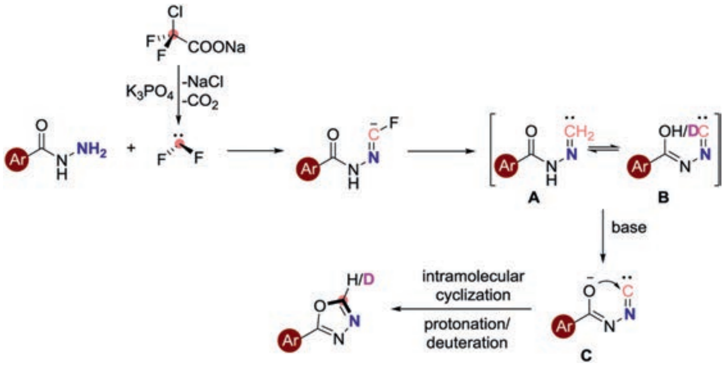
Scheme 7. Control experiments.

(NMR) and mass spectrometry (MS) [37]. In addition, more and more deuterated drugs are reported [38], which has created an urgent need for synthetic methods to effectively generate deuterated building blocks. Grounded in our current successful 1,3,4-oxadiazoles formation *via* the base promoted [4 + 1] cyclization reaction, we also invented a mild and generic method for the deuteration of 1,3,4-oxadiazoles using D_2O as an inexpensive deuterium source (Scheme 4). Delightfully, when we replaced CH_3CN with anhydrous CH_3CN and add 20 equiv. of D_2O for this cyclization reaction, and the yields were barely affected along with excellent deuteration ratios (Scheme 5). Both aryl and alkyl benzohydrazides were inspected under the corresponding reaction conditions, the corresponding target products **(4a-4p)** were procured in up to 88% yields accompanied with excellent deuteration ratios.

We also studied the scalability of this [4 + 1] cyclization reaction. When current protocol was scaled up ten times, the desired 1,3,4-oxadiazoles **3h** and **3p** could be readily obtained in 75% and 73% yields without the loss of efficiency, respectively (Schemes 6a and b). Further transformations of the 1,3,4-oxadiazoles were executed. The ethyl 1-(4-(1,3,4-oxadiazol-2-yl)phenyl)-1*H*-imidazole-4-carboxylate **5** could be obtained in moderate yield *via* a Cu-catalyzed [3 + 1 + 1] type cyclization of $ClCF_2COONa$ for the assembly of imidazoles *via* the *in-situ* generated isocyanides (Scheme 6c) [12]. The synthetic utility of this approach was also showcased by the assembly of 2-(4′-methoxy-[1,1′-biphenyl]-4-yl)-1,3,4-oxadiazole **7** *via* a Pd-catalyzed Suzuki-coupling (Scheme 6d) [39].

We then turned our attention to shed light on the mechanism of this [4 + 1] cyclization reaction. Radical trapping experiments were investigated firstly (Scheme 7). When 2,6-di-*tert*-butyl-4-methylphenol (BHT) and ethene-1,1-diyldibenzene were served as radical scavengers under the standard conditions, this cyclization reaction has no significant influence (Schemes 7a and b, and Scheme S7b in Supporting information), indicating that a radical-type process might not be involved in this [4 + 1] cyclization. Based on our previous quadruple cleavage of halogenated difluoro compounds, difluorocarbenes (:CF_2) was generated in-situ. To verify the production of difluorocarbene in this reaction, the difluorocarbene trapping experiment was conducted. When benzimidazole was added as difluorocarbene trapper, the 1-(difluoromethyl)-1*H*-benzo[d]imidazole **(8)** was obtained in 80% yield (Scheme 7c).

Based on the above experimental results and previous literatures [40,41], a possible reaction mechanism for this cyclization reaction of benzohydrazides and $ClCF_2COONa$ is depicted in Scheme 8. Firstly, difluorocarbene is formed *via* the dechlorination and decarboxylation of $ClCF_2COONa$. The *in-situ* generated difluorocarbene is immediately captured by the benzohydrazides **1** with the assistance of a base to afford the Intermediate **A**, which rapidly undergoes the tautomerism to obtain Intermediate **B**. Simultaneously, the Intermediate **B** to give the intermediate **C** in



Scheme 8. Proposed reaction mechanism for the synthesis of 1,3,4-oxadiazole derivatives.

the presence of base. The intermediate **C** further goes through the intramolecular cyclization and protonation or deuterate to affords the target product **3**.

In conclusion, we have disclosed a novel transition-metal-free [4 + 1] cyclization of $ClCF_2COONa$ for the assembly of 1,3,4-oxadiazoles and 1,3,4-oxadiazoles-d_5 under mild conditions. The desired products were obtained in decent yields and excellent deuteration ratios with a wide substrate scope by using $ClCF_2COONa$ as C1 synthon. When D_2O was employed as deuterium sources, a sequence of 1,3,4-oxadiazoles-5d were obtained in good yields and excellent deuteration ratios. The current protocol also represents the first example of construction of deuterated *N*-heterocyclic compounds using $ClCF_2COONa$ and hydrazine compounds as starting materials.

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.

Acknowledgments

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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.2021.08.089.

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