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Metal-free regioselective construction of 2-aryl-2*H*-tetrazol-5-yl difluoromethylene phosphonates

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ABSTRACT

Three bench-stable difluoromethylene phosphonate hydrazones were prepared from simple diethyl(difluoromethyl)phosphonate within two steps in good yields. The [3 + 2] cycloaddition reaction of these diazo precursors with aryl diazonium salts has been accomplished under metal-free conditions with exclusive regioselectivity. This transformation provides practical access to a broad panel of 2-aryl-2*H*-tetrazol-5-yl difluoromethylene phosphonates, including the corresponding derivatives of amino acid (phenylalanine) and drug cores (Pomalidomide and Lapatinib fragment).

Difluoromethylene phosphonates [DFMP, $CF_2PO(OR)_2$] could mimic the naturally occurring phosphates and phosphonates, thus having emerged as a frequently utilized structural motif in the study of various biochemical processes [1,2]. For example, phosphonodifluoromethyl phenylalanine (F_2Pmp) has been developed as one of the most powerful nonhydrolyzable phosphotyrosine mimetics to modulate the corresponding protein-protein interactions and used as protein tyrosine phosphatases (PTPs) inhibitors (Fig. 1) [3–5]. Furthermore, the difluoromethylene phosphonate moiety has been also utilized in the design and development of signal transducer and activator of transcription (STAT) antagonists, fructose-1,6-bisphosphatase (FBPase) inhibitors, $P2Y_1$ receptor antagonists, and cytidine triphosphate synthetase inhibitors (Fig. 1) [6–10]. Therefore, the design and development of new difluoromethylene phosphonate-containing molecular frameworks has emerged as an increasingly important task in synthetic organic chemistry. In this context, while simple aryl-substituted difluoromethylene phosphonates have been extensively studied in the past few decades [11–17], the construction of heterocyclic difluoromethylene phosphonates remains far less explored. More importantly, most previous studies have mainly focused on the use of metalated $CF_2PO(OR)_2$ derivatives to undergo cross-coupling-type transformations, while the development of new reactive DFMP-containing 1,3-dipoles to be used in convergent cycloadditions remains elusive. Very recently, Han, Röschenthaler, and co-workers reported the design of aryl-substituted difluoromethylene phosphonate-containing diazo reagents (DFMP-Diazo, Scheme 1a) [18,19]. The [3 + 2] cycloaddition reaction of DFMP-Diazo with vinyl sulfones enabled the synthesis of difluoromethylene phosphonate-containing pyrazolines with good efficiency. However, due to the instability of DFMP-containing diazo compounds, the utilization of unsubstituted DFMP-functionalized 1,3-dipolar species to produce aromatic cycloadducts is an unsolved problem. As part of our long interest in fluorinated diazoalkanes [20–28] and the construction of tetrazoles (Scheme 1b) [29–33], herein we report the preparation of three bench-stable DFMP-containing diazo precursors (DFMP-Hydrazones) and their application in the regioselective synthesis of DFMP-tetrazoles *via* [3 + 2] cycloaddition reactions with aryldiazonium salts (Scheme 1c). Note that this study represents the first example of introducing a difluoromethylene phosphonate motif onto the tetrazole scaffold. These two chemical entities are both metabolically stable to many of the biological transformations and have widespread implications in pharmaceuticals and bioconjugations [34–36].

At the outset, we synthesized three DFMP-hydrazones *via* the condensation of DFMP-aldehyde precursor **S-2** with the

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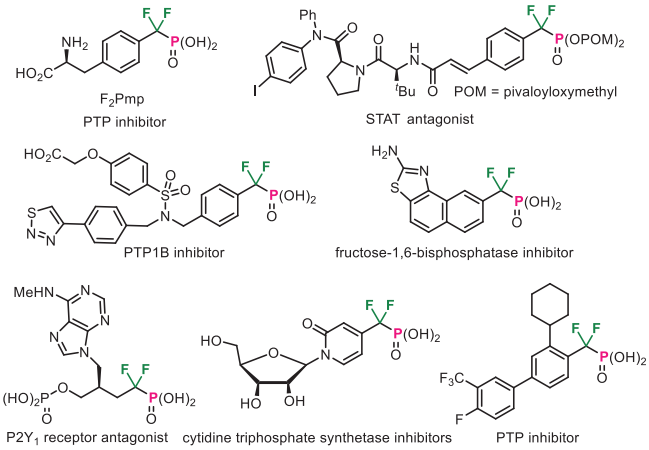
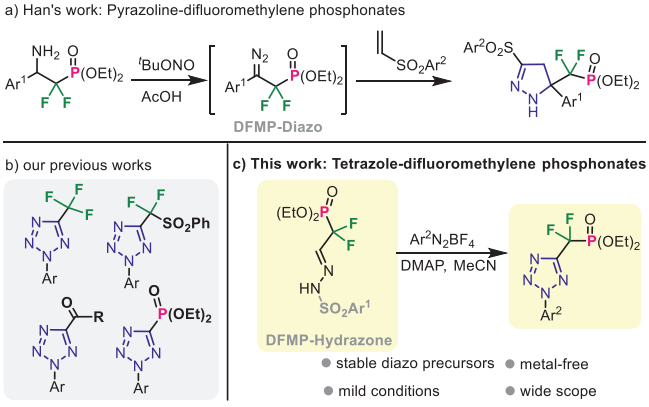


Fig. 1. Selected bio-active difluoromethylene phosphonates.

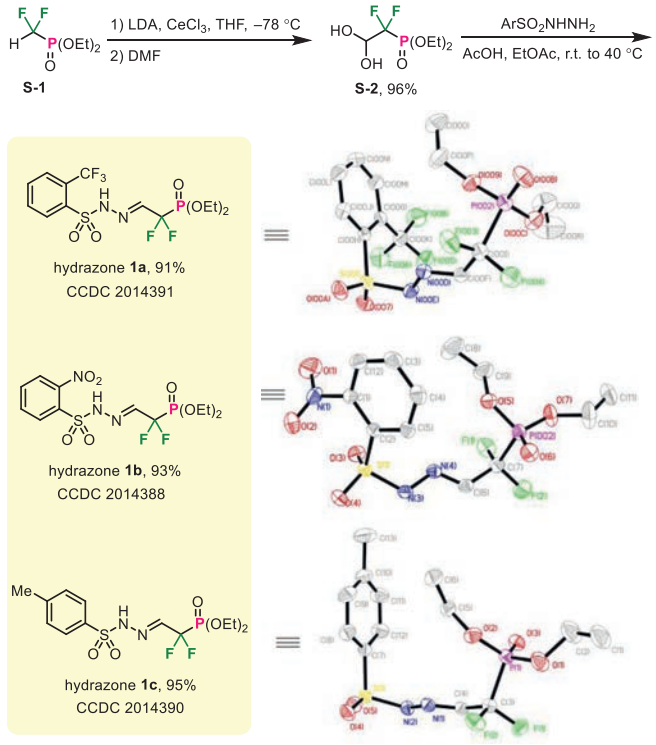


Scheme 1. Cycloaddition reactions for the preparation of difluoromethylene phosphonate heterocycles.

corresponding benzenesulfonyl hydrazides. As outlined in Scheme 2, treating commercially available diethyl (difluoromethyl)-phosphonate **S-1** with LDA in the presence of $CeCl_3$, followed by addition of *N,N*-dimethylformamide (DMF) in one-pot, the desired dihydrate **S-2** was smoothly obtained in 96% yield [37,38]. Subsequently, condensation of this masked aldehyde **S-2** with different hydrazides under acidic conditions proved to be viable, thus giving the target DFMP-hydrazones **1a**–**1c** in 91%–95% yields [39,40]. Importantly, these diazo precursors were found to be quite stable under bench conditions, and all of them have been successfully crystallized for X-ray diffraction analysis.

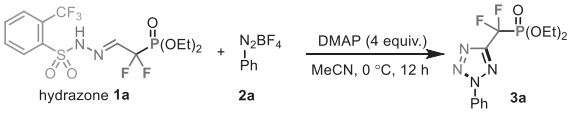
With the three difluoromethylene phosphonate hydrazones in hand, we then proceeded to optimize the [3 + 2] cycloaddition reaction with phenyldiazonium salt **2a** (Table 1) [41]. Pleasingly, by just using 4-dimethylaminopyridine (DMAP) as the base, acetonitrile as the solvent, the desired 2,5-disubstituted tetrazole **3a** was obtained in up to 90% yield from CF_3-hydrazone **1a** without the detection of any regioisomer (entry 1). Employing NO_2-hydrazone **1b** or Me-hydrazone **1c** could also permit the formation of tetrazole **3a**, albeit in decreased yields (entries 2 and 3). The significantly lower yield observed when using Me-hydrazone **1c** could be the result of a lower leaving-group ability of its benzenesulfonyl moiety with respect to **1a** and **1b**. Notably, this reaction does not require the use of an organometallic species and thus should not involve a carbenoid intermediate that is clearly indicative of a different mechanism compared with our previous studies on the silver-catalyzed synthesis of differently decorated tetrazoles (see Supporting Information for a proposed mechanism) [42]. Addition of silver acetate to the reaction mixture was not beneficial (entry 4). Changing DMAP to a series of organic and inorganic bases resulted in no obvious improvement (entries 5–10). This cycloaddition transformation was also found to be compatible with different solvents such as THF, CH_2Cl_2, and EtOAc (entries 11–13). Reducing the amount of diazonium salt **2a** to 1 equiv. could still generate **3a** at the expense of a relatively lower yield (entry 14). Using water as a co-solvent was found be viable, albeit in slightly decreased yield (entry 15).

This DMAP-promoted [3 + 2] cycloaddition protocol proved to be quite general with respect to the scope of aryldiazonium salts (Scheme 3). Electron-donating groups substituted at the ben-



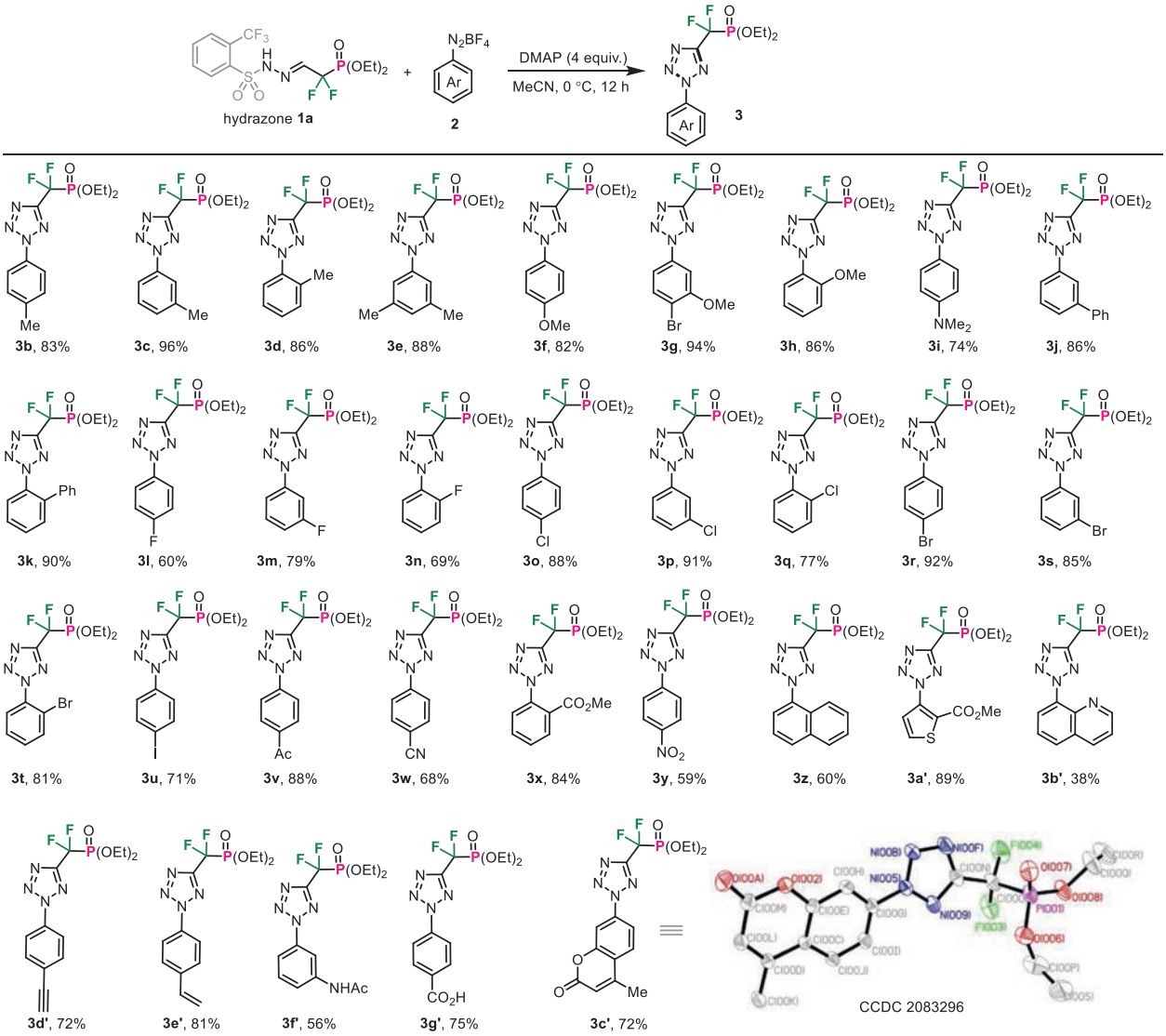
Scheme 2. Preparation of difluoromethylene phosphonate hydrazones.

Table 1
Optimization of reaction conditions.



Entry	Variation from the standard conditions[a]	Yield (%) [b]
1	none	90
2	**1b** instead of **1a**	80
3	**1c** instead of **1a**	54
4	AgOAc (5 mol%) was added	85
5	Pyridine instead of DMAP	91
6	DABCO instead of DMAP	80
7	DBU instead of DMAP	77
8	DIPEA instead of DMAP	66
9	Cs_2CO_3 instead of DMAP	80
10	K_3PO_4 instead of DMAP	65
11	THF instead of MeCN	82
12	CH_2Cl_2 instead of MeCN	73
13	EtOAc instead of MeCN	71
14	0.2 mmol of **2a** was employed	68
15	MeCN/H_2O = 1:1 was used as solvent	71

[a] Typical reaction conditions: Hydrazone **1** (0.2 mmol), phenyldiazonium tetrafluoroborate **2a** (0.4 mmol, 77 mg), and the base (0.8 mmol) were mixed in solvent (3 mL) and stirred at 0 °C for 12 h unless otherwise indicated.
[b] Isolated yield of tetrazole **3a**.

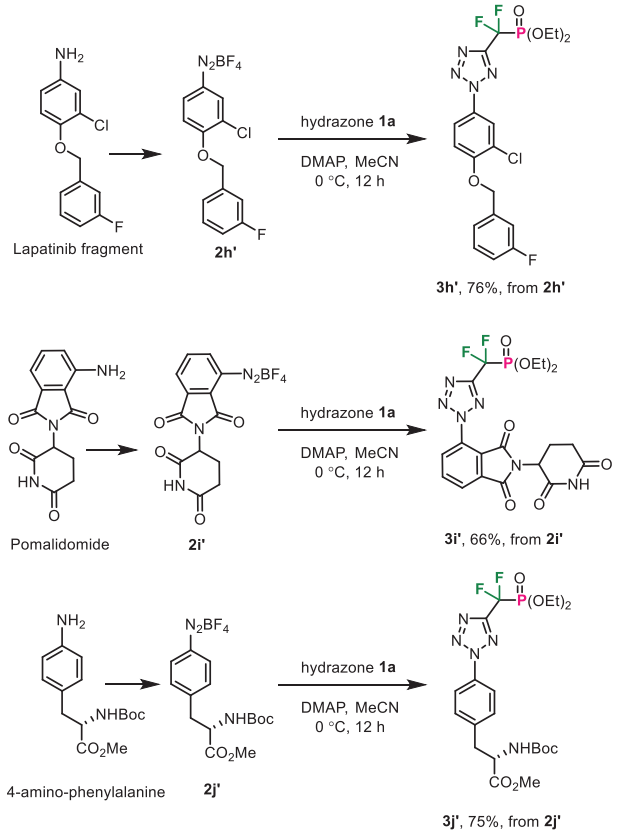


Scheme 3. Substrate scope of 2-aryl-2*H*-tetrazol-5-yl difluoromethylene phosphonates.

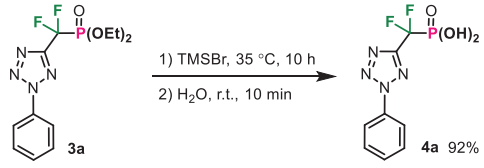
zene ring at different positions, including alkyl, alkoxyl, and amino groups, all reacted well with hydrazone **1a** under identical conditions (products **3b**–**3i**). Incorporation of another phenyl group turned out be no problem (products **3j**–**3k**). Fluorine, bromine, and iodine atoms substituted at the *para, ortho*, and *meta* locations on the phenyl ring were all well tolerated and afforded the corresponding tetrazoles **3l**–**3u** in up to 92% yield. Furthermore, strong electron-withdrawing substituents such as -Ac, -CN, -CO_2Me and -NO_2, had no obvious influence on the reaction performance (products **3v**–**3y**). 1-Naphthyl-, 3-thienyl-, and 8-quinolinyl-derived tetrazol-5-yl difluoromethylene phosphonates **3z**–**3b′** were also obtained with exclusive regioselectivity, albeit with low yield in the case of basic 8-quinolinyl product **3b′**. 7-Coumarin-diazonium salt also underwent the cycloaddition with hydrazone **1a** under standard conditions, thus delivering the coumarin-tetrazole **3c′** in 72% yield (X-ray confirmed). Importantly, this cycloaddition reaction also tolerates alkynyl and alkenyl moieties as exemplified by the smooth generation of cycloadducts **3d′** and **3e′** in good yields. The presence of protected amino or free carboxylic group in aryldiazonium salts could be also tolerated, giving the corresponding tetrazoles **3f′** and **3g′** with good result.

To further illustrate the utility of this protocol, we conducted cycloaddition reactions with several pharmacophore-derived aryldiazonium salts (Scheme 4). Aniline derivative featuring the Lapatinib's substructure was easily converted to the diazonium salt and cyclized with hydrazone **1a** with good result (product **3h′**). Despite the presence of free amide group, Pomalidomide-derived diazonium salt was also a feasible substrate for this reaction and gave access to the corresponding difluoromethylene phosphonate **3i′** in 66% yield. More noteworthy is that phenylalanine-derived diazonium salt **2j′** smoothly participated in the cycloaddition process, thereby providing the noncanonical amino acid **3j′** in good yield with maintained complete regio-selectivity. Finally, the phosphonate group in **3a** was successfully hydrolyzed with the aid of TMSBr, affording the free phosphonic acid **4a** in 92% yield (Scheme 5).

In summary, we have developed a bench-stable difluoromethylene phosphonate hydrazone to serve as the corresponding diazo precursor and established a metal-free [3 + 2] cycloaddition transformation with aryldiazonium salts. A number of 2-aryl-2*H*-tetrazol-5-yl difluoromethylene phosphonates were obtained in good yields with single regioselectivity under mild conditions. Future studies will focus on the reaction mechanism and products applications.



Scheme 4. Preparation of pharmacophore-derived tetrazolyl difluoromethylene phosphonates.



Scheme 5. Hydrolysis of difluoromethylene phosphonate **3a**.

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.2021.08.007.

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