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Direct Synthesis of CF₂H-Substituted 2-Amido-Furans via Copper-Catalyzed Addition of Difluorinated Diazoacetone to Ynamides.

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Supporting Information Placeholder

ABSTRACT: The significance of molecules containing difluoromethyl groups is driven by their potential applications in pharmaceutical and agrochemical science. Methods for the incorporation of lightly fluorinated groups such as –CF₂H are less well developed. Here we report the use of difluorinated diazoacetone as a practical reagent for the direct synthesis of CF₂H-substituted 2-amido-furans through addition to ynamides. These newly designed difluorinated amidofurans were elaborated to create new nitrogen-containing frameworks that would be challenging to obtain otherwise.

The incorporation of fluorine-containing moieties into organic molecules has become a powerful strategy in drug design.^[1] Special attention has been paid to the difluoromethyl group (CF₂H) because of its unique physicochemical properties.^[2] The CF₂H group can act as an unusual lipophilic hydrogen bond donor and can thereby be considered as a metabolically stable bioisostere of a hydroxyl group or a thiol group.^[3] As hydrogen bonding interactions play a crucial role in diverse chemical processes, this surrogate enjoys a special niche in the search for new drug candidates.

Furans represent a privileged structural motif found in myriad natural products, human pharmacopeia, as well as in phytochemistry.^[4] Among this family, 2-amino/amidofurans have been identified either as valuable pharmacophores exhibiting significant biological activities,^[5] or as building blocks, providing access to a higher degree of molecular complexity.^[6] Despite their extensive applicability, only limited protocols have been developed for the synthesis of aminofurans. Classical syntheses involve base-promoted reactions of α -hydroxy- and halo-ketones with malononitriles.^[7] Current methods include transition-metal-catalyzed reactions to construct 2-aminofurans with diversified substituents.^[8] In this context, Hsung's group investigated a Rh(II)-catalyzed cyclopropanation of ynamides using diazo compounds,

Scheme 1. Synthesis of CF₂H-containing furans.

providing an entry to substituted 2-amidofurans. In this process, monosubstituted diazo-carbonyl compounds such as ethyl diazoacetate proved to be ineffective; only dicarbonylated diazo- and iodonium ylides were beneficial.^[9]

Although the difluoromethylation of heterocycles is in vogue, the synthesis of CF₂H-substituted furans has been scarcely investigated (Scheme 1). Thus, difluoromethylated furans are currently exclusively generated through functionalization of pre-existent furans.

For example, decarboxylation of a CF₂CO₂Et moiety has been developed to access CF₂H-substituted furans (Scheme 1, a).^[10] However, this method requires harsh reaction conditions, which limits functional group compatibility. Among the metal-catalyzed, direct difluoromethylation reactions of heterocycles, only two examples, have been reported to produce CF₂H-substituted furans. Vicic *et al.* reported a base metal-catalyzed transformation of aryl halides, (Scheme 1, b),^[11] whereas Mikami *et al.* explored a palladium-catalyzed difluoromethylation of arylboronic acids (Scheme 1, c).^[12] Recently, an elegant direct CF₂H difluoromethylation of heterocycles via organic photoredox catalysis proved to be efficient on a furan derivative (Scheme 1, d).^[13]

In view of the limited methods for introduction of the CF₂H functional group onto the furan substructure, and given our involvement in ynamide chemistry,^[14] we envisioned the addition of difluoro-diazoacetone to ynamides (Table 1, e) to provide a convenient entrée to difluoromethylated furans. Among the toolbox of reagents currently utilized to introduce a CF₂H moiety, the conveniently available CF₂H-diazo-carbonyl compound is conspicuously missing. Taking into account Nikolaev's work,^[15] we prepared 3-diazo-1,1-difluoro-propan-2-one **3** in a one-step procedure by reacting commercially available 1,1,5,5-tetrafluoropentane-2,4-dione **1** in the presence of a diazo-transfer reagent [*p*-acetamidobenzenesulfonyl azide (*p*-ABSA)] and DBU. Spontaneous deacylation of the difluorinated diazodiketone **2** intermediate took place in the presence of the base, providing the desired difluoro-diazoacetone **3** in 58% yield (Scheme 2).

Scheme 2. Synthesis of difluorodiazoacetone **3**.

The difluorodiazoacetone reagent was prepared on large scale and is perfectly stable for a few weeks at 4 °C without any decomposition. Inspired by Fu's work on copper-catalyzed coupling of terminal alkynes with α -diazocarbonyl compounds,^[16] we hypothesized that ynamides treated with difluoro-diazoacetone in the presence of a copper catalyst would generate amido(difluoromethyl)furans.

To test our hypothesis, we subjected ynamide **4a** to difluoro-diazoacetone in the presence of diverse copper catalysts. As illustrated in Table 1, only CuI and CuBr proved to be effective (Table 1, entries 1-4), albeit CuBr led to a huge erosion of the yield (37%). Using Cu(II) catalysts, the starting ynamide **4a** underwent degradation in almost all cases (Table 1, entries 5-7), albeit traces of difluoromethylated amidofuran **5a** were observed (Table 1, entry 5). The choice of the solvent is criti-

cal: use of tetrahydrofuran (THF), dichloroethane (DCE), dioxane, toluene, or ether did not lead to the target molecule (Table 1, entries 8-12), and the starting ynamide was recovered. The use of dimethylformamide led to a significantly lower yield of the desired product (Table 1, entry 13, 27%). A control experiment using difluoro-diazoacetone without any catalyst afforded none of the desired product (Table 1, entry 14).

Table 1. Screening of solvents and catalysts

entry	Solvent	Catalyst	yield (%) ^{a,b}
1	MeCN	CuI	71
2	MeCN	CuBr	37
3	MeCN	CuCl	— ^[d]
4	MeCN	Cu(MeCN) ₄ PF ₆	— ^[d]
5	MeCN	CuCl ₂	traces
6	MeCN	CuSO ₄	— ^[d]
7	MeCN	Cu(OTf) ₂	— ^[d]
8	THF	CuI	— ^[c]
9	DCE	CuI	— ^[c]
10	dioxane	CuI	— ^[c]
11	toluene	CuI	— ^[c]
12	Et ₂ O	CuI	— ^[c]
13	DMF	CuI	27
14	MeCN	—	— ^[c]

^aReaction conditions: to a solution of **4a** (0.2 mmol), catalyst (10 mol%), solvent (2 mL), **3** (1.5 equiv, 0.5 mol/L in Et₂O) was added dropwise at 23 °C. ^bIsolated yields. ^cStarting material **4a** was fully recovered. ^dDegradation was observed.

With the optimized reaction conditions in hand (Table 1, entry 1), we investigated the generality of this transformation. A diverse array of ynamides bearing a variety of functional groups were tested. Linear alkyl groups [e.g., methyl (**5b**), butyl (**5c**)] or cyclic alkyl groups [e.g., cyclopropyl (**5d**), cyclopentyl (**5e**), or cyclohexyl (**5f**)] were perfectly accommodated. The reaction is not restricted to saturated substituents; unsaturated side chains with diverse carbon linker chains (**5g-j**) as well as aryl groups (**5a**, **5k**, **5l**) were tolerated as well, albeit the yield of the furan **5j** bearing a terminal alkyne tether is moderate. X-Ray analyses of **5l** confirmed the structure of the amido-difluorinated furan **5l** obtained (CCDC 2071668 contains the supplementary crystallographic data for the structure).^[17] Notably, even halogens (**5m**), nitriles (**5n**), protected aldehydes (**5o**), ketones (**5p**), and amides (**5q**, **5r**) could be used, significantly broadening the substrate scope and providing the corresponding difluorinated furans with good yields.

Scheme 3. Scope of the synthesis of amido-difluorinated furans regarding the ynamide.

^a Performed on 0.4 mmole scale; ^b See [17] for CCDC deposition number; ^c yield of the two-step process: deprotection of the ynamide and cyclization

The influence of the electron-withdrawing group on the nitrogen atom was also explored (Scheme 4). Furans bearing an oxazolidinone (**7a**, **7b**) and amide moiety (**7c**) were obtained in modest yields. Sulfonyl groups such as mesyl (**7d**), nosyl (**7e**), and trimethyl-/triisopropyl-/trifluoromethyl-benzenesulfonamides (**7g**, **7h**, **7i**) were revealed to be accommodated in this transformation. More hindered cyclic sulfonamides were notably effective, providing the corresponding furans (**7j**, **7k**, **7l**) in good yields. A sulfamoyl derivative was also incorporated, providing furan **7f** in 70% yield.

To demonstrate the diversification potential of these difluorinated furans, we used them as building blocks to prepare various relevant heterocycles. Nitration⁽¹⁸⁾ of amido-difluorinated furan **7l** under controlled temperature led exclusively to C-4 nitrofurans **8** (Scheme 5, a). Further, we involved the amidofurans as platforms in intramolecular oxidative coupling reactions⁽¹⁹⁾ as well as in intramolecular Diels-Alder cycloadditions (IMDAF).⁽²⁰⁾ The oxidation process on compound **5i** took place in the presence of a catalytic amount of PdCl₂(MeCN)₂, CuCl₂, and the environmentally sustainable reoxidant O₂ to provide difluorinated furo[2,3-b]pyrrole **9** in a yield of 83% (Scheme 5, b). Whereas direct difluorination will only provide 2-substituted indolines,^[13] intramolecular Diels-Alder reaction of amido-furans **5h** led to difluorinated indoline **10** bearing a CF₂H group at position 5 that would be challenging to obtain otherwise (Scheme 5, c).

Scheme 4. Modification of the electron-withdrawing group on the nitrogen

^c yield of the two-step process: deprotection of the ynamide and cyclization.

Scheme 5. Synthetic applications of difluorinated furans

Based on deuterium incorporation experiments, literature data and on DFT calculations (see supporting information for more details), we propose the following mechanism (Scheme 6). In the presence of copper(I) salt, ynamide **A** leads to copper-ynamidyl **B**. The reaction of the latter with difluorodiazooacetone forms copper specie **C**. Rearrangement and loss of N_2 leads to copper intermediate **D**.⁽²¹⁾ At this point, two reactions pathways were envisioned: Protonation α to the carbonyl moiety leading to a Fu type compound **E**⁽¹⁶⁾ or protonation γ to the carbonyl moiety providing intermediate **G**. Both pathways were examined by DFT based calculations and have been found to be kinetically and thermodynamically possible (see Supporting Information for detailed description). *O*-alkylation on ynamide **E** or allenamide **G** followed by rearomatization of **F** and **H** and decupration of **I** regenerates the copper iodide and forms the difluoromethylated amidofuran **J**. These proposed reaction mechanisms are in agreement with the deuterium incorporation experiments. D-incorporation α to the carbonyl moiety (D position 4 of the furan) followed by decupration (D-position 3) (pathway D-E-F) or D-incorporation α to difluoroacetone (D position 4) followed by decupration (D-position 3) will lead to equal incorporation of deuterium at position 3 and 4 as observed experimentally.

Scheme 6. Plausible Mechanism

In conclusion, we have developed a copper-catalyzed synthesis of difluoromethylated amidofurans through addition of difluorodiazooacetone to ynamides. Difluorodiazooacetone was prepared for the first time, and proved to be the ideal candidate to perform this transformation. The method exhibits broad functional group tolerance and led to a number of highly diverse, high-value scaffolds. Finally, it was demonstrated that these newly designed difluoromethylated amidofurans could serve as platforms to construct a diverse set of more complex difluorinated heterocyclic molecules valuable for drug design.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Supporting information (PDF)

CCDC 2071668 contain 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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