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A Scalable and Regioselective Synthesis of 2-Difluoromethyl Pyridines from Commodity Chemicals

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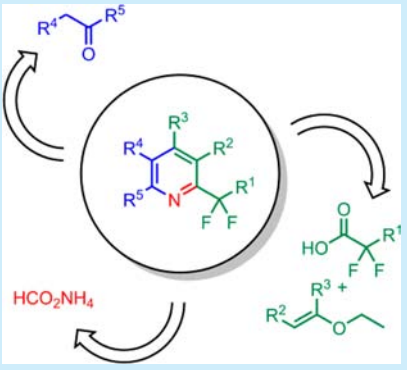
Supporting Information

ABSTRACT: A scalable *de novo* synthesis of difluoromethyl pyridines from inexpensive materials is reported. The pyridyl subunit is built around the difluoromethyl group rather than a late stage introduction of this moiety. This user-friendly approach allows access to a diverse range of substitution patterns on all positions on the ring system and on the difluoromethyl group.



Incorporation of the difluoromethyl group ($-CF_2H$) into organic molecules is highly attractive because of its unique chemical and physical properties. The CF_2H motif acts as a hydrogen bond donor with enhanced lipophilicity and can also serve as a bioisostere for thiol or hydroxyl groups while possessing improved metabolic stability.[1,2] Similarly, the difluoroalkyl ($-CF_2R$) subunit can be employed as a surrogate for ether linkages.[1] Insertion of the difluoromethyl moiety into pyridines is of particular interest to both agroscience and medicinal chemistry.[3] By modulating pyridines with this functionality at the 2-position, optimal herbicidal activity was obtained leading to the discovery of the widely commercialized Thiazopyr[4] (Visor) and Dithiopyr[5] (Dimension) agricultural products. By capitalizing on their attributes, 2-difluoromethyl pyridines (2-DFMPs) were also found to be potential inhibitors of prostaglandin synthases[6] and thrombin.[7]

The current routes for 2-DFMP synthesis rely on the difluoromethylation[8] of an existing functionalized pyridyl system (Figure 1). Several innovative strategies utilizing this approach are known including: deoxofluorination of pyridyl aldehydes with dialkylaminosulfur trifluorides (DAST, Deoxofluor)[9] or SF_4,[10] Cu-mediated difluoromethylation of pyridyl iodides using Bu_3SnCF_2H,[11] direct radical difluoromethylation utilizing $Zn(SO_2CF_2H)_2$,[12] and Cu-mediated coupling of activated difluoroacetate derivatives followed by a hydrolysis/decarboxylation sequence.[13] Methods to introduce higher order difluoroalkyl groups ($-CF_2R$) are far sparser. This transformation can be accomplished by treatment of a pyridyl ketone with DAST[14]/SF_4[10] or using difluoroalkylsulfinate salts and unactivated pyridines.[15]

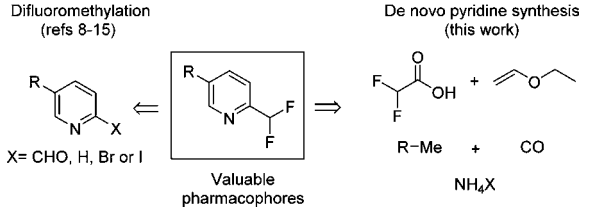


Figure 1. Comparison of strategies to access CF_2H pyridines.

Of the known approaches for 2-DFMP preparation, deoxofluorination *via* the use of dialkylaminosulfur trifluorides is most commonly utilized. However, these trifluorides can be thermally unstable and generate corrosive HF when in contact with moisture, and extensive purification is required to separate the byproduct from the desired pyridine.[16] Seeking an alternative approach to difluoromethyl and other difluoroalkyl pyridine preparation, we envisioned that construction of the pyridyl scaffold around the difluoromethyl group might offer us a selective, scalable, and cost-effective methodology (Figure 1). Moreover, it might enable us to start from one of the least expensive difluoromethyl building blocks, difluoroacetic acid (DFA). The latter is synthesized from either tetrafluoro- or tetrachloro-ethylene, which are both produced on a millions of metric ton scale per year.[17]

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We therefore attempted a *de novo* 2-DFMP synthesis using a Bohlmann−Rahtz-like approach.[18] From a bond disconnection standpoint, the desired pyridine can be built by a dehydroannulation of intermediate **3** with an ammonia equivalent (Figure 2). Retrosynthetically, this intermediate can be broken down into the butenone **1** and nucleophile **2**. Finally, to access very practical and inexpensive starting materials, the butenone **1** is prepared from DFA derivatives and vinyl ethers.

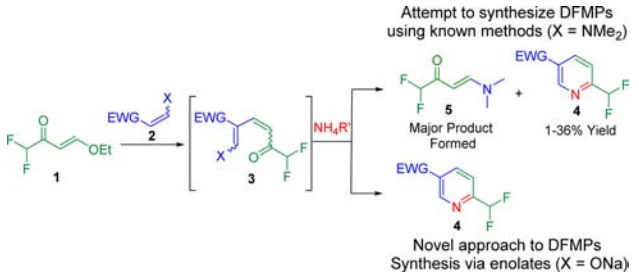


Figure 2. Attempts to exploit established routes to construct 2-DFMPs and novel enolate-based approach.

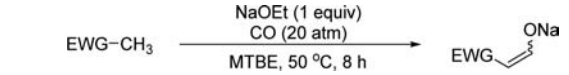
The synthesis of CF_3 pyridines through a condensation of aminocrotonates/aminoacrylonitriles and trifluorobutenones has been reported.[19] Inspired by this strategy, the synthesis of 2-DFMPs was attempted by condensing dimethylamino acrylates onto ethoxy-difluorobutenone (Figure 2, X = NMe_2). It was soon realized that the established methodologies are not applicable to the synthesis of 2-DFMPs. Competitive formation of **5** lead to an unacceptably low yield of 2-DFMPs.[20] To avoid concomitant amine transfer and gain better control over the regiochemical outcome of the cyclization, construction of the pyridine using the more nucleophilic sodium enolate (Figure 2, X = ONa) was explored. Such sodium formyl enolates have been used for more than 30 years[21] for the synthesis of heterocycles such as pyrimidines, but analogous pyridine syntheses have not been reported.[22]

Despite the encouraging promise of a scalable and economical route, several challenges remained: (1) preparation of the sodium enolates; (2) establishing optimal conditions for the initial condensation reaction; (3) determining the optimal ammonium source for the final pyridine formation.

To address the first challenge, we initially attempted to prepare model enolate **2a** by treatment of EtOAc with ethyl formate.[23] In our hands, this route gave inconsistent results, low yields, and significant CO evolution throughout the reaction. An alternative Claisen condensation was then attempted, drawing on work done by American Cyanamid in 1946.[24] Treatment of EtOAc in the presence of NaOEt under 20 atm of CO in MTBE afforded, after simple filtration, highly pure **2a** as a solid. Using this modified protocol, a range of sodium formyl enolates were prepared in high purity and in modest to excellent yield (Table 1). This not only provided a repertoire of solid reagents on hand for pyridine construction but also greatly improved the scope of the reported methodologies. While these enolates are stable to both oxygen and moisture, they are somewhat deliquescent and are recommended to be stored in a sealed container to minimize water absorption.

The other component to our putative cyclization reaction is the butenone **1**. The model butenone, **1a**, can easily be prepared from difluoroacetic anhydride or difluoroacetyl chloride and ethyl vinyl ether in excellent yield and purity.[25] **1a** is not stable for extended periods of time if stored neat, but storage with 1 wt % BHT at 0 °C greatly improved shelf life (see Supporting Information for stability studies).

Table 1. Synthesis of Sodium Enolates *via* α-Carbonylation



entry	EWG	yield (%)[a]	entry	EWG	yield (%)[a]
1	EtO, **2a**	82	6	**2f**	61
2	MeO, **2b**	86	7	**2g**	84
3	3-MeO-C_6H_4, **2c**	61	8	Me, **2h**	76
4	Me, **2d**	36	9	*t*-Bu, **2i**	61
5	Me_2N, **2e**	81			

[a]Yield determined by NMR weight percent analysis using triethanolamine as a standard.

With the requisite materials in hand, a brief solubility screen of our sodium enolates revealed DMSO to have the best solubilizing power for these species. Using DMSO as a reaction medium, treatment of **1a** with **2a** gave complete conversion to the desired intermediate enolate **3a** after 1 h at rt. When the same reaction was conducted in MeCN, precipitation and isolation of **3a** were possible, permitting us to characterize it. To complete the pyridine synthesis, addition of an appropriate ammonium salt was required. A range of salts were screened (see Supporting Information for details), and ultimately HCO_2NH_4 was selected as the optimal ammonium species. Using this nitrogen source, **4a** was prepared in 91% yield in a two-step one-pot method (Table 2, entry 1). The reaction could be scaled up significantly to a 3.31 mol scale to give 0.6 kg of **4a** while still maintaining the high yield and purity observed on smaller scales.

With the optimal conditions established, the remaining enolates were screened under similar conditions to probe the scope of the new protocol. It was found that a range of 2-DFMPs could be constructed *via* this route (Table 2). Enolates derived from esters (entries 1,2), sulfones (entries 3,4), amides (entries 4,5), and ketones (entries 7−9) fare equally well, giving good yields of their corresponding pyridines. The amide **4f** (entry 6) is of particular interest as morpholine-based amides can be used as Weinreb amide surrogates with enhanced thermal stability.[26]

We next explored whether difluoroalkyl pyridines could be obtained by using commercially available difluoroalkyl acids (Table 3). For this series, **2a** was used as the enolate coupling partner. Because of the inherent instability and in some cases volatility of requisite butenones required, the decision was made to use a crude solution, rather than trying to isolate these materials. A range of difluoroalkyl pyridines were successfully prepared using this strategy (Table 3). Alkyl groups (entries 1−3) were well-tolerated under the reaction conditions as was a representative olefinic moiety (entry 4). Both an aryl group (entry 5) and a perfluoropropyl group (entry 6) were equally successful for the alkyl systems. Substitution with additional halogens (F, Cl) enabled us to prepare $-CF_3$ and $-CF_2Cl$

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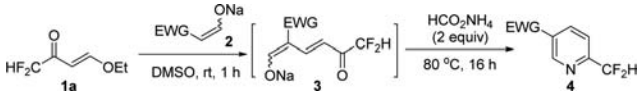
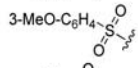
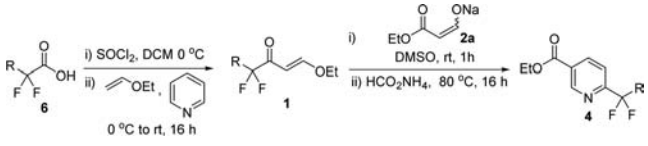
Table 2. Scope of 2-DFMP Synthesis from 1a and Enolates[a]

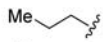
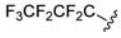


entry	EWG	enolate	pyridine	yield (%)[b]
1		2a	4a	91 (90)[c]
2		2b	4b	87
3		2c	4c	98
4		2d	4d	83
5		2e	4e	74
6		2f	4f	98
7		2g	4g	94
8		2h	4h	79
9		2i	4i	59

[a]*Intermediate formation*: Enolate (1.2 equiv), butenone (1 equiv), DMSO, 1 h, rt. *Pyridine formation*: HCO_2NH_4 (2 equiv), 80 °C, 16 h. [b]Isolated yields. [c]Parentheses indicate yield on 3.31 mol scale.

Table 3. Scope of CF_2R Pyridines Synthesis from 2a and Various 4-Ethoxy-1,1-difluoroalkylbut-3-en-2-ones[a,b]



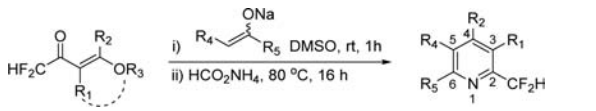
entry	R	butenone	pyridine	yield (%)[c]
1		1b	4j	83
2		1c	4k	81
3		1d	4l	88
4		1e	4m	70
5		1f	4n	82
6		1g	4o	95
7		1h	4p	83
8		1i	4q	85

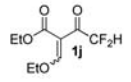
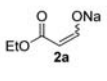
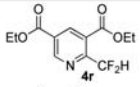
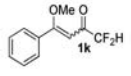
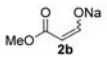
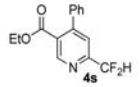
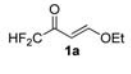
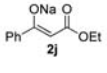
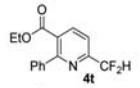
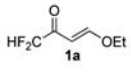
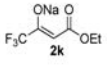
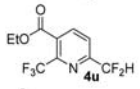
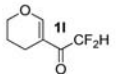
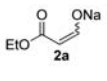
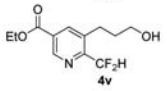
[a]*Butenone* **1** *formation*: (i) Carboxylic acid (1 equiv), $SOCl_2$ (1 equiv), CH_2Cl_2, 0 °C to rt, 1.5 h. (ii) Pyridine (2.1 equiv), ethyl vinyl ether (1.25 equiv), CH_2Cl_2, 0 °C to rt, 12 h. [b]*Pyridine formation*: (i) Enolate (1.2 equiv), butenone (1 equiv), DMSO, 1 h at rt. (ii) HCO_2NH_4 (2 equiv), 80 °C, 16 h. [c]Isolated yields.

pyridines, respectably, in excellent yield (entries 7−8). **4p** could be further functionalized using known radical methods, to access higher order difluoroalkyl pyridines.[27]

Looking to further diversify the methodology, an approach was sought to access different substitution patterns on the pyridine ring (Table 4). To accomplish this, the structure of our butenone **1** was first varied. Initially the reactivity of commercially available butenone **1j** was explored. Using **1j**, a 3,5-diester pyridine was successfully prepared in 53% yield (Table 4, entry 1). To introduce a substituent at the 4-position,

Table 4. Scope of 2-DFMP Synthesis from Enolates and Substituted 4-Ethoxy-1,1-difluorobut-3-en-2-ones[a]



entry	butenone	enolate	product	yield (%)[b]
1				53
2[c]				76
3[c]				61
4[c]				44
5				48

[a]Reaction conditions unless otherwise noted: (i) Enolate (1.2 equiv), butenone (1 equiv), DMSO, 1 h at rt. (ii) HCO_2NH_4 (2 equiv), 80 °C, 16 h. [b]Isolated yields. [c]Intermediate formation required heating to 50 °C for 16 h.

a phenyl group was installed on the butenone (entry 2, **1k**) which led to the corresponding pyridine **4s** in good yield (entry 2). Enolates **2j** and **2k** could be used successfully to synthesize pyridines functionalized at position 6 (entries 3, 4). Next, a displaceable *β*-alkoxy substituent was tethered to butenone **1l** which furnished pyridine **4v** in 48% yield (entry 5).

In summary, we have disclosed a general, scalable methodology for the *de novo* construction of 2-DFMPs in good to excellent yields starting from commodity chemicals. Using this approach, modifications can be made to the pyridine ring or to the difluoromethyl group itself by selection of the appropriate enolate or butenone precursor. This method was extended to the synthesis of difluoroalkyl pyridines, a target whose preparation is nontrivial. Finally, the robustness of this new protocol was established on the multimole scale.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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