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Facile One-Pot Synthesis of *N*-Difluoromethyl-2-pyridone Derivatives

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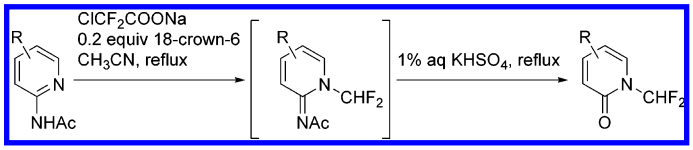
ABSTRACT



A novel one-pot synthesis of *N*-difluoromethyl-2-pyridones is described. *N*-(Pyridin-2-yl)acetamide derivatives were excellent precursors for the preparation of *N*-difluoromethyl-2-pyridone derivatives. Difluoromethylation of 2-acetaminopyridine derivatives was achieved with sodium chlorodifluoroacetate as a difluorocarbene source in the presence of a catalytic amount of 18-crown-6. Subsequent in situ hydrolysis of resultant 1,2-dihydro-2-acetimino-1-difluoromethylpyridines proceeded under mild acidic conditions to afford the corresponding *N*-difluoromethyl-2-pyridones in moderate to good yields.

The replacement of hydrogen atoms with fluorine is a well-established strategy for the design and optimization of biologically active molecules and can improve the biological and physicochemical profiles of lead structures.[1] Therefore, the synthesis of organic compounds containing fluorine functional groups is an area of active interest.[2] Our medicinal chemistry program has revealed that substituted *N*-difluoromethyl-2-pyridones appear to be important substructures that improve binding affinity for a target receptor; e.g., *N*-difluoromethyl-2-pyridone derivatives were ca. 5-fold more potent than the corresponding *N*-methyl-2-pyridone derivatives.[3] *N*-Methyl-2-pyridone structures are frequently found in biologically active molecules such as anticancer agents[4] and multiple sclerosis immunomodulators;[5] hence, *N*-difluoromethyl-2-pyridone may be an ideal surrogate that imparts biological benefits to molecules bearing *N*-methyl-2-pyridone. No high-yield, scalable synthetic methods for *N*-difluoromethyl-2-pyridones have been reported;[6] therefore, we needed to develop a generalizable synthetic method. Here, we describe a facile and scalable one-pot synthesis of *N*-difluoromethyl-2-pyridone derivatives.

Difluoromethylation of phenolic hydroxyl groups is effected by sodium chlorodifluoroacetate ($ClCF_2COONa$),[7] ethyl bromodifluoroacetate ($BrCF_2COOEt$),[7c] 2,2-difluoro-

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(2) For recent reviews, see: (a) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214. (b) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (c) Dolbier, W. R., Jr.; Battiste, M. A. *Chem. Rev.* **2003**, *103*, 1071. (d) Langlois, B. R.; Billard, T. *Synthesis* **2003**, 185.

(3) For examples of biological benefits of the difluoromethyl group, see: (a) Grunewald, G. L.; Seim, M. R.; Lu, J.; Makboul, M.; Criscione, K. R. *J. Med. Chem.* **2006**, *49*, 2939. (b) Guay, D.; Hamel, P.; Blouin, M.; Brideau, C.; Chan, C. C.; Chauret, N.; Ducharme, Y.; Huang, Z.; Girard, M.; Jones, T. R.; Laliberte, F.; Masson, P.; McAuliffe, M.; Piechuta, H.; Silva, J.; Young, R. N.; Girard, Y. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1457. (c) Narjes, F.; Koehler, K. F.; Koch, U.; Gerlach, B.; Colarusso, S.; Steinkuhler, C.; Brunetti, M.; Altamura, S.; Francesco, R. D.; Matassa, V. G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 701.

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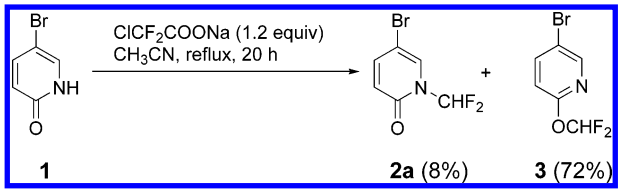
2-(fluorosulfonyl)acetic acid (FSO_2CF_2COOH),[8] or dibromodifluoromethane (CBr_2F_2)[9] as the difluorocarbene source.[10] These difluoromethylation protocols for phenolic hydroxyl groups have potential application to 2-pyridones, anticipating sufficient chemoselectivity based on the precedented chemoselective alkylation of 2-pyridones.[11] Unfortunately, difluoromethylation of 5-bromo-2-pyridone (**1**) gave the undesired O-difluoromethylated product **3** in 72% yield, whereas the desired product **2a** was isolated in only 8% yield (Scheme 1). Because chemoselective difluoromethylation appeared to be unfeasible,[12] we investigated the alkylation of 2-acetaminopyridines to 1,2-dihydro-2-acetimino-1-alkylpyridines followed by hydrolysis of the resulting imino intermediates to the corresponding N-alkylated pyridones.[13] The difluoromethylation of 2-acetamino-5-bromopyridine (**4a**) with 1.2 equiv of $ClCF_2COONa$ proceeded smoothly in refluxing acetonitrile to give the expected acetimide **5** in 95% yield (Scheme 2).

Scheme 1. Difluoromethylation of 5-Bromopyridin-2(1*H*)-one (**1**)



Subsequent acidolysis with 6 N hydrochloric acid did not give **2a**; instead, deacetylation of **5** proceeded rapidly to afford **6** in good yield. Monitoring the difluoromethylation of **4a** by HPLC[14] revealed the formation of a trace amount of **2a**. On the basis of this observation, we speculated that milder acidic conditions may be suitable for the hydrolysis of acetimide **5**. In fact, the hydrolysis of **5** with 1% aqueous potassium hydrogensulfate afforded **2a** in 82% yield after purification by chromatography (Scheme 2).[15]

This promising N-difluoromethylation procedure prompted exploratory modification of the reaction conditions and realization that the two sequential reactions could be accomplished in one pot (Table 1). After difluoromethylation of **4a** was completed, the mixture was treated directly with

Scheme 2. Difluoromethylation of *N*-(5-Bromopyridin-2-yl)acetamide (**4a**) and Conversion to *N*-Difluoromethyl-2-pyridone

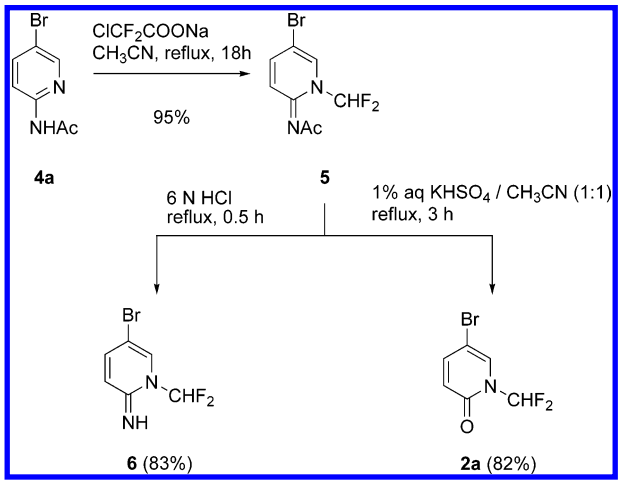
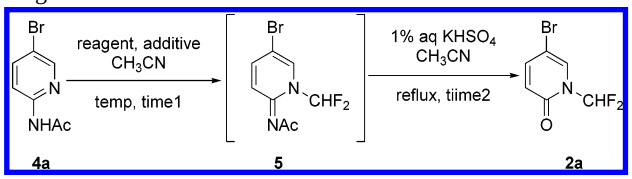


Table 1. One-Pot Synthesis of *N*-Difluoromethyl-5-bromo-2-pyridone (**2a**) with Various Difluoromethylating Reagents



entry	reagent (equiv)	additive (equiv)	temp (°C)	time1 (h)	time2 (h)	yield[a] (%)
1	$ClCF_2COONa$ (1.2)	none	83	19	1.5	88
2	$ClCF_2COONa$ (1.2)	18-crown-6 (0.2)	83	5	1.5	89 (85)[b]
3[c]	FSO_2CF_2COOH (1.2)	none	rt	0.5	2	84
4[d]	CBr_2F_2 (3.0)	Zn (3.0)	rt	66	1.5	33
5[e]	$BrCF_2COOEt$ (1.5)	K_2CO_3 (1.5)	83	32	1.5	51

[a] Determined by HPLC (220 nm) after extraction with ethyl acetate. [b] Isolated yield. [c] **5** was isolated by aqueous workup before the hydrolysis. [d] THF used as a solvent.

(8) Chen, Q.; Wu, S. *J. Fluorine Chem.* **1989**, *44*, 433.

(9) (a) Morimoto, K.; Makino, K.; Sakata, G. *J. Fluorine Chem.* **1992**, *59*, 417. (b) Xingya, L.; Heqi, P.; Xikui, J. *Tetrahedron Lett.* **1984**, *25*, 4937. (c) Rico, I.; Wakselman, C. *J. Fluorine Chem.* **1982**, *20*, 765. (d) Rico, I.; Wakselman, C. *Tetrahedron Lett.* **1981**, *22*, 323.

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(12) The difluoromethylation of **1** was also attempted by using $BrCF_2COOEt$ and FSO_2CF_2COOH. However, the use of these reagents did not reverse the regioselectivity; O-alkylated compounds were afforded as major products (see Supporting Information for details).

(13) (a) Klutchko, S. R.; Hamby, J. M.; Boschelli, D. H.; Wu, Z.; Kraker, A. J.; Amar, A. M.; Hartl, B. G.; Shen, C.; Klohs, W. D.; Steinkampf, R. W.; Driscoll, D. L.; Nelson, J. M.; Elliott, W. L.; Roberts, B. J.; Stoner, C. L.; Vincent, P. W.; Dykes, D. J.; Panek, R. L.; Lu, G. H.; Major, T. C.; Dahring, T. K.; Hallak, H.; Bradford, L. A.; Showalter, H. D. H.; Doherty, A. M. *J. Med. Chem.* **1998**, *41*, 3276. (b) Deady, L. W.; Loria, P. M.; Quazi, N. H. *Aust. J. Chem.* **1996**, *49*, 485.

(14) YMC−Pack Pro C18 (Size: 150 × 4.6 mm i.d., Particle: S-5 μm, 12 nm) with a liner gradient system of 10−90% CH_3CN in 0.1% aqueous H_3PO_4 over 15 min at a flow rate of 1.0 mL/min.

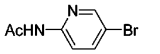
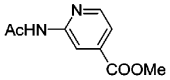
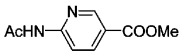
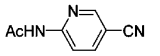
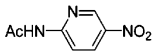
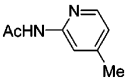
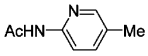
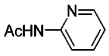
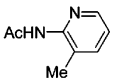
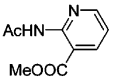
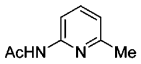
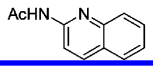
(15) Preparation of **2a** from 2-amino-5-bromopyridine was attempted. Difluoromethylation with $ClCF_2COONa$ gave the difluoromethylated imino compound **6** in moderate yield. Compound **6** was converted to **2a** in 32% yield by diazotization of imine **6** with sodium nitrite followed by in situ hydrolysis of the resulting diazonium salt with 40% sulfuric acid. The hydrolysis of **6** under strong acidic conditions did not proceed (recovery of **6**). Hydrolysis under basic conditions resulted in cleavage of the difluoromethyl group to afford 2-amino-5-bromopyridine (see Supporting Information for details).

1% aqueous potassium hydrogensulfate to afford the desired pyridone **2a** in 88% yield (entry 1). The reaction time needed for completion of difluoromethylation was reduced significantly by the addition of a catalytic amount of 18-crown-6 (entry 2).[16] The reaction time was reduced further by the use of the more reactive FSO_2CF_2COOH as a difluorocarbene source. This resulted in completion of the difluoromethylation within 0.5 h at room temperature (entry 3). For entry 3, acetimide **5** was isolated by applying aqueous workup procedures prior to the hydrolysis reaction; otherwise, the yield of **2a** was reduced to 54%. Other commercially available reagents, such as $BrCF_2COOEt$ and CBr_2F_2, did not offer notable improvements (entries 4 and 5). On the basis of these results, $ClCF_2COONa$ appeared to be the most attractive reagent for the synthesis of *N*-difluoromethyl-2-pyridone at the preparative scale.

To gain insights into the scope and limitations of this novel *N*-difluoromethyl-2-pyridone synthesis, various substituted 2-acetaminopyridines were examined (Table 2). In general, 4- and 5-substituted 2-acetaminopyridines were converted to the corresponding *N*-difluoromethyl-2-pyridones in moderate to good yields, regardless of the steric and electrical effects of the substituents in this set of substrates (entries 1−7). Electron-withdrawing substituents decreased the reaction rate for the first difluoromethylation reaction (time1). Difluoromethylation of the 5-bromo, methoxycarbonyl, methyl, and unsubstituted substrates (**4a**, **4c**, **4g**, and **4h**) was completed within 5 h, although more detailed kinetic studies were needed to differentiate among the reaction rates for these four compounds. The difluoromethylation of the more electron-deficient 5-cyanopyridine **4d** required 10 h. For 5-nitropyridine **4e**, reaction was extremely slow, requiring 32 h for complete consumption of the starting pyridine. This observation can be explained by the electron density of the pyridine nitrogen because the reaction presumably occurs via electrophilic attack of the difluorocarbene species. In contrast, electron-donating substituents decreased the reaction rate for the second hydrolysis step (time2). Hydrolysis of the acetimide intermediates derived from the 5-cyano and nitro substrates **4d** and **4e** was completed in 1 h; slightly longer reaction times were needed for the acetimide intermediates derived from the 5-bromo and methoxycarbonyl substrates **4a** and **4c**, respectively. Hydrolysis of the 5-methyl and unsubstituted substrates **4g** and **4h** was notably slow, 11 and 5 h, respectively. Thus, for the 4- and 5-substituted substrates, the reaction gave the desired products in moderate to good yields, and reaction rates for the difluoromethylation and subsequent hydrolysis were significantly different, depending on the electronic effects of the substituents.

For the 3-substituted substrates **4i** and **4j**, the corresponding *N*-difluoromethyl-2-pyridones were isolated only in modest yields. The low yields were attributed to the sluggish first difluoromethylation step; extended reaction times and increased amounts of $ClCF_2COONa$ resulted only in increased formation of unknown side products. The use of more reactive FSO_2CF_2COOH did not offer any improvement. For the 3-substituted substances, the acetyl group of the 2-acetamino substituent may be forced in the proximity of the nitrogen atom of the pyridine ring due to steric interaction with the neighboring 3-substituent, which hinders the approach of difluorocarbene to the nitrogen atom (Figure 1).

Table 2. One-Pot Synthesis of *N*-Difluoromethyl-2-pyridone Derivatives from Substituted 2-Acetaminopyridines[a]

entry	substrate		time1[b] (h)	time2[c] (h)	yield[d] (%)
1		**4a**	5	1.5	85 (**2a**)
2		**4b**	5	2	78 (**2b**)
3		**4c**	5	2	79 (**2c**)
4		**4d**	10	1	67 (**2d**)
5		**4e**	32	1	53 (**2e**)
6		**4f**	5	12	62 (**2f**)
7[e]		**4g**	5	11	71 (**2g**)
8		**4h**	5	5	50 (**2h**)[f]
9		**4i**	5	1	39 (**2i**)
10		**4j**	5	1	19 (**2j**)
11		**4k**	18	-	0
12		**4l**	24	7	73 (**2l**)

[a] Difluoromethylation was conducted using 1.2 equiv of $ClCF_2COONa$ and 0.2 equiv of 18-crown-6 under reflux, and the subsequent hydrolysis was conducted under reflux after adding 1% aqueous $KHSO_4$ to the reaction mixture. [b] Reaction time for the difluoromethylation of **4a**−**l**. [c] Reaction time for hydrolysis after adding 1% aqueous $KHSO_4$ to the reaction mixture. [d] Isolated yield. [e] 1.5 equiv of $ClCF_2COONa$ was used. [f] Yield was due to the volatile nature of the product **2h**.

(16) (a) Kagabu, S.; Ando, C.; Ando, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 739. (b) Bessard, Y.; Muller, U.; Schlosser, M. *Tetrahedron* **1990**, *46*, 5213.

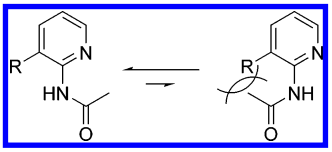


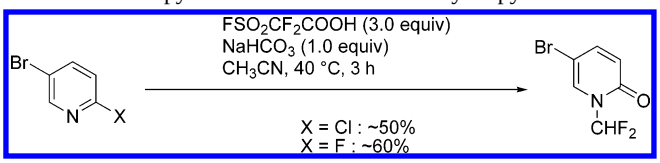
Figure 1. Proposed conformation of 3-substituted 2-acetaminopyridines.

The reaction of a 6-substituted substrate such as *N*-(6-methylpyridin-2-yl)acetamide (**4k**) failed to give the desired product; the starting 2-acetaminopyridine was recovered (entry 11). In this case, the first difluoromethylation did not proceed, most likely because of steric hindrance around the nitrogen atom of the 2-acetaminopyridine caused by a neighboring 6-substituent. Interestingly, the conversion of *N*-quinoline-2-ylacetamide (**4l**) to the corresponding pyridone **2l** was achieved under the standard reaction conditions, resulting in 73% yield of the desired product. A substantially longer reaction time was needed for completion of the first difluoromethylation of **4l** (entry 12).

To investigate the factors involved in reactions with 3- and 6-substituted substrates, research is being continued to identify other 2-substituted pyridine precursors. The 2-substituent of the pyridine precursor is required to be sterically less demanding than the acetamino group and to be hydrolyzed smoothly after the difluoromethylation. We recently found that 2-chloropyridine and 2-fluoropyridine are difluoromethylated and hydrolyzed to the corresponding *N*-difluoromethyl-2-pyridones by the action of FSO_2CF_2COOH (Scheme 3). Optimization of the reaction conditions is underway, and application to the synthesis of 3- and 6-substituted *N*-difluoromethyl-2-pyridones will be forthcoming.

In conclusion, we developed a novel one-pot synthetic method for the preparation of *N*-difluoromethyl-2-pyridone

Scheme 3. Conversion of 2-Fluoropyridine and 2-Chloropyridine into *N*-Difluoromethyl-2-pyridone



derivatives. The procedure involves difluoromethylation of 2-acetaminopyridines by the action of $ClCF_2COONa$, followed by hydrolysis of the resultant 1,2-dihydro-2-acetimino-1-difluoromethylpyridines to the corresponding *N*-difluoromethyl-2-pyridones under mild acidic conditions. This synthetic method gave moderate to good yields of the desired *N*-difluoromethyl-2-pyridones for 4- and 5-substituted substrates; however, only modest yields were observed for 3-substituted substrates. The 6-substituted substrates did not participate in the reaction, with the exception of the benzo-fuzed substrate **4l**. This facile method should allow straightforward scaleup, allowing application of the *N*-difluoromethyl-2-pyridone structure to the design of biologically active molecules.

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Supporting Information Available: Detailed synthetic and spectroscopic characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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