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Reactions of Enamines with Selectfluor: A Straightforward Route to Difluorinated Carbonyl Compounds

Weimin Peng and Jean'ne M. Shreeve*

Department of Chemistry, University of Idaho, Moscow, Idaho 83844-2343

jshreeve@uidaho.edu

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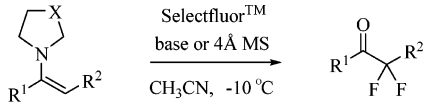

X = CH_2 or OCH_2

Reactions of enamines, preformed from β-dicarbonyl and monocarbonyl compounds, with Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) under mild conditions (triethylamine (TEA) or molecular sieves) easily led to the corresponding difluorinated carbonyl compounds in high yields.

The presence of two fluorine atoms adjacent to a carbonyl functionality increases the electrophilicity of the carbonyl carbon atom dramatically and consequently facilitates the addition of nucleophiles. Nucleophilic addition of an enzyme active site to the carbonyl group of fluorinated ketones has been suggested as being responsible for the inhibition of a variety of enzymes.[1] Numerous efforts have been made to prepare α,α-difluoro carbonyl compounds by direct fluorination of the corresponding nonfluorinated substrates through the use of a variety of electrophilic fluorinating agents,[2] such as F_2,[3] XeF_2,[4] ClO_4F,[5] $(CF_3SO_2)_2NF$,[6] NF_3O,[7] etc. However, low availability, disadvantage of hazardous and toxic characteristics, and high reactivity of these reagents, along with little or no selectivity,[8] have curtailed their usefulness. While a variety of N−F electrophilic fluorinating reagents are available, currently 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor; F-TEDA-BF_4), a commercially available, stable, nonvolatile, nonhygroscopic, and easy to handle solid, is more widely used for site-selective fluorination of a variety of carbonyl compounds.[9]

Monocarbonyl compounds are difficult to difluorinate.[10] Even when promoted by microwave irradiation in the presence of a strong base, only minor amounts of monofluorinated products were obtained. Derivatization of monocarbonyl compounds to form metal enolates, enol acetates, and trimethylsilyl enol ethers followed by fluorination only produced the corresponding monofluorinated products.[11] A two-step procedure to obtain the difluorinated derivative of 1-keto-5-tosylbenzazepine included a double preparation of the corresponding enol ether or enol acetate and twice fluorination of that product with Selectfluor.[12] Although β-dicarbonyl compounds can be difluorinated with Selectfluor directly under neutral conditions, because the difluorinating step was a much slower process than the first,[3] these reactions required a very long time to reach completion.[13] Not surprisingly, fluorination occurred more rapidly with compounds that exist (at least in part) in enolic form. Since the monofluoro derivatives exist essentially as their keto forms because of the electron withdrawing effect of the fluorine atom, they are not readily fluorinated further by Selectfluor. This indicates that the reaction occurred *via* the enol or enolate form and is ionic in nature. Although difluorinated products can be obtained in a very straightforward manner by using microwave,[14] it was of interest to find an alternate method of fluorination that did not require special apparatus.

As nitrogen analogues of enols, enamines have proved to be useful alternate reactive intermediates for the introduction of fluorine on the carbon α to a carbonyl group. With the greater ability of the nitrogen atom to donate electrons to the double bond, the reactivity of the enamines with some electrophilic fluorinating reagents was enhanced relative to an enol ester.[15] However, in most cases, the reactions of enamines with electrophilic fluorinating agents only gave the corresponding monofluorinated carbonyl products.[16] In only two instances was a difluorinated product obtained in very low yield in the reaction of a steroidal enamine with perchloryl fluoride.[17] The reactions of imines with *N*-fluorobis[(trifluoromethyl)sulfonyl]amine gave the corresponding difluorinated

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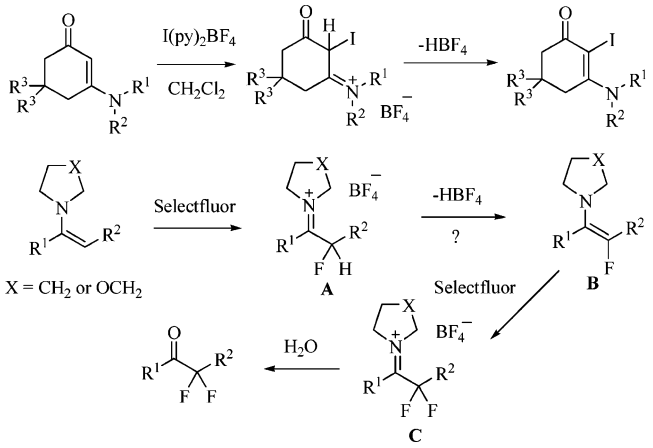
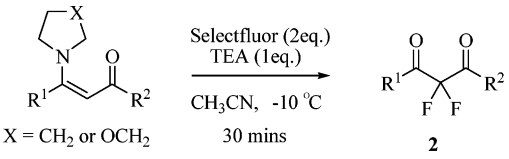
SCHEME 1



products suggesting that the enamine intermediate plays a key role in the reactions.[18] Enamines, which have long been recognized as valuable synthetic intermediates, are easily prepared from amines and ketones or aldehydes, and a variety of new methods have been added.[19] Our interest in development of a safer, more facile, milder and cost-effective method for difluorinating carbonyl compounds, especially monocarbonyl compounds, prompted us to study the reactions of enamines with Selectfluor.

It was reported previously that the reaction of enaminones with bis(pyridine) iodonium(I) tetrafluoroborate (a electrophilic iodating regeant) resulted in the preparation of α-iodo enaminones in almost quantitative yields through a monoiodation pyrrolidinium intermediate (Scheme 1).[20] An enamine can easily be reacted with Selectfluor to give the monofluorinated pyrrolidinium salt **A**. But in our case, the difluorination of the enamine was our intended transformation. If the monofluorinated enamine **B**, which is equivalent to α-iodo enaminone, can be regenerated from **A**, it could be readily fluorinated by another equivalent of Selectfluor to give the difluorinated pyrrolidinium salt **C**. Then aqueous hydrolysis could readily lead to a difluorinated carbonyl compound in a one-pot reaction of enamine with Selectfluor (Scheme 1). This result suggested that the monofluorinated enamine **B** was generated in a similar manner from monofluorinated pyrrolidinium salt **A** in a way which is a key to this difluorination transformation of enamine.

TABLE 1. Fluorination of Enamine 1 with Selectfluor



entry	enamine **1**	R^1	R^2	X	product[a]	yield,[b] %	^{19}F NMR δ (ppm)
1	**1a**	Me	Me	CH_2	**2a**	50	−115.89
2	**1b**	Me	OEt	CH_2	**2b**	47	−114.81
3	**1c**	Ph	OEt	CH_2	**2c**	88	−107.58
4	**1d**	Ph	Ph	CH_2	**2d**	81	−102.61
5	**1e**	Me	Ph	CH_2	**2e**	71	−108.94
6	**1f**	Ph	*i*-propyl	CH_2	**2f**	97	−108.21
7	**1g**	Ph	*3*-chloroPh	CH_2	**2g**	95	−102.61
8	**1h**	Ph	Me	OCH_2	**2e**	89	−108.94

[a] Known compounds except compound **2g**; ref 21. [b] Isolated yields, except entries 1 and 2 which were determined by ^{19}F NMR spectroscopy by addition of α,α,α-trifluorotoluene as an internal standard.

It was very encouraging to find when even a single equivalent of Selectfluor was reacted with enamine **1a** (as a example of enamines prepared from 1, 3 dicarbonyl compounds), a mixture of difluorinated and monofluorinated products was obtained in a 3:2 ratio. Unfortunately, increasing the amounts of Selectfluor beyond 2 equiv did not cause the reaction to give only the difluorinated product. Although Selectfluor can be decomposed by base, it was found that when a weak base, such as triethylamine (TEA) or Na_2CO_3, was added to the reaction system, no monofluorinated product was detected by ^{19}F NMR spectroscopy. In this case, Selectfluor was not decomposed by base. This was attributed to the rapid reaction rate between the enamine and Selectfluor.

Finally, we observed that only 1 equiv of TEA was needed for the high-yield formation of the difluorinated product without concomitant formation of the monofluorinated species (Table 1) (see the Experimental Section).[21] When the R^1 group bonded directly to the enamine moiety is alkyl (**1a**,**b**,**e**), the yield is lower than when R^1 is aryl (**1c**,**d**,**1f**−**h**). The higher yield with R^1 bonded directly to the enamine is also demonstrated by comparing the yield of enamine **1e** to that of **1h** since both enamines gave the same product **2e** (Table 1, entries 5 and 8). When the reaction of Selectfluor with the monofluorinated product of benzoyl ethyl acetate was attempted in the presence of TEA, no difluorinated product was formed and the Selectfluor was decomposed. Therefore, the fluorinated enamine intermediate **B** (Scheme 1), that was regenerated from the pyrrolidinium salt **A** under the effect of base, plays a crucial role in the process.

Given the success of the difluorination of the enamines obtained from 1,3-dicarbonyl compounds, this methodology was applied to the difluorination of the enamine

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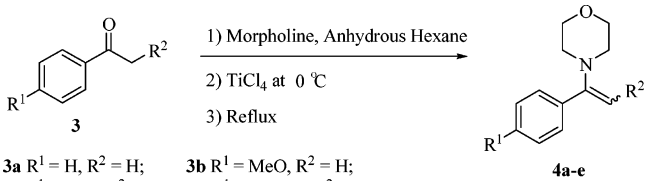
SCHEME 2

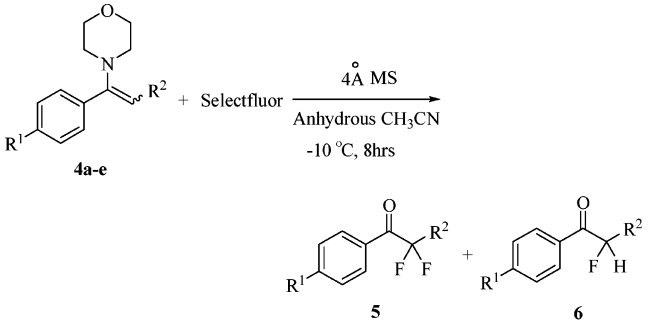


3a R^1 = H, R^2 = H; **3b** R^1 = MeO, R^2 = H;
3c R^1 = NO_2, R^2 = H; **3d** R^1 = EtOOC, R^2 = H
3e R^1 = H, R^2 = Me

prepared from a monocarbonyl compound since this had not been possible earlier through direct fluorination. Preparation of the corresponding enamine by condensation of acetophenone and morpholine in the presence of a Brønsted acid using the conventional Dean−Stark trap technique was not successful. The acetophenone remained in large amounts and required separation using high vacuum and high-temperature distillation which resulted in loss of product. The literature method which employed titanium tetrachloride as reaction promoter and as a water scavenger to prepare these enamines[22] did not work well because the preformed sticky $TiCl_4$−amine complex made stirring difficult precluding complete reaction of the acetophenone. This method was modified by adding a solution of $TiCl_4$ in hexane dropwise into the solution of acetophenone and morpholine in hexane (because acetophenone **3b**−**d** did not dissolve well in hexane, some benzene could be added). The $TiCl_4$−amine complex produced in situ reacted with the acetophenone immediately, and fine particles of TiO_2 precipitated quickly. After completing the addition, the reaction mixture was refluxed gently to complete the conversion of acetophenone. Filtration gave the corresponding essentially pure enamine in nearly quantitative yield. No further purification was required (Scheme 2).

When the method used to fluorinate enamine **1** was employed in the reaction of enamine **4a** with Selectfluor, a mixture of difluorinated and monofluorinated products was obtained in low yield in a ratio of 1:2. Since a large amount of nonfluorinated acetophenone was recovered, most of the Selectfluor was apparently consumed in reaction with TEA. However, the reaction of enamine **4a**[23] with 2 equiv of Selectfluor in anhydrous acetonitrile gave the difluorinated acetophenone **5a** in moderate yield (50%). The monofluorinated acetophenone **6a** was also formed in 13% yield. Addition of molecular sieves (MS) to the reaction system increased the yield of the difluorinated product to ∼60% but the product ratio (di:mono) was changed dramatically (9:1). It may be that MS can facilitate the regeneration of the fluoro enamine intermediate **B** (Scheme 1). After optimizing the reaction conditions by balancing the yield of the difluorinated product and the chemoselectivity, enamines **4a**−**d**[23−25] were reacted with two equivalents of Selectfluor in the presence of 4 Å MS in anhydrous acetonitrile for 7−8 h to give the corresponding difluorinated products **5a**−**d** in good yields (Table 2, entries 1−4).

TABLE 2. Fluorination of Enamine 4 with Selectfluor



entry	enamine 4	R^1	R^2	product	yield,[a] %	^{19}F NMR δ (ppm)	5/6[b]
1	**4a**	H	H	**5a**[c]	74	−121.9	11:1
2	**4b**	MeO	H	**5b**[c]	64	−121.3	2.8:1
3	**4c**	NO_2	H	**5c**[d]	95	−121.5	100:0
4	**4d**	EtOOC	H	**5d**[d]	72	−122.0	100:0
5	**4e**	H	Me	**6e**[c]	89[e]	−181.2	1:19

[a] Isolated yield except entry 1, in which the yield was determined by ^{19}F NMR by addition of α,α,α-trifluorotoluene as internal standard. [b] Determined by ^{19}F NMR of the reaction mixture. [c] Known compounds confirmed by spectral data; ref 18. [d] New compound. [e] One equivalent of Selectfluor was used.

The ratios of the difluorinated to the monofluorinated products formed, which can be readily separated by flash chromatography, were a function of the 4-substituent on the phenyl ring. When the latter was an electron-withdrawing group, no monofluorinated product was formed (Table 2, entries 3−4), while the electron-donating methoxy substituted enamine **4b** gave the two products in a ratio of 2.8:1 (Table 2, entry 2). After the reaction was completed, the reaction mixture had become acidic and all of the starting enamine substrate had been hydrolyzed to regenerate the starting acetophenone. The enamines themselves are liable to hydrolysis, e.g., if the sample in the NMR tube was held at ambient temperature for 1 day, about one-third of the enamine had hydrolyzed. It was very curious that the reaction of enamine **4e**,[26] synthesized from propiophenone **3e**, with Selectfluor under analogous conditions gave the monofluorinated product **6e** as the major product in high yield (Table 2, entry 5). Even when two equivalents of Selectfluor were used, only a trace of the difluorinated product **5e** could be detected by ^{19}F NMR spectroscopy. Thus, a methyl group attached to the position at which fluorination was to occur has a significant effect on the reaction result by reducing the acidity of the proton of pyrrolidinium salt **A** (Scheme 1), precluding enolization and resulting in hydrolysis of **A**.

We have developed a practical and straightforward method to obtain difluorinated carbonyl compounds in high yields from readily available enamines via fluorination with Selectfluor without requiring a strong base to generate the corresponding anion. However, a base, such as TEA, or molecular sieves was crucial to regenerate

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the monofluorinated enamine, the key intermediate in obtaining the difluorinated carbonyl compound. Since this method uses a commercially available and easily handled reagent and has wide functional group tolerance, it offers a promising alternative in the synthesis of some highly functionalized bioactive difluorinated compounds.

Experimental Section

See the Supporting Information for general methods and analytical and spectral data.

General Procedure for Synthesis of a 1,3-Dicarbonyl Compound from Enamine 1 via Fluorination. To a solution of Selectfluor (2 mmol, 746 mg) in 20 mL of acetonitrile cooled to −10 °C was added triethylamine (1 mmol, 101 mg, 0.14 mL). A solution of the preformed enamine **1** (1 mmol) in 5 mL of acetonitrile was added dropwise over 10 min. It was stirred for 30 min with continued cooling. Silica gel (2.5 g) was added to the reaction mixture, and the solvent was evaporated to dryness. The mixture was chromatographed on silica gel (60−200 micron, 60 Å) with *n*-hexanes−ethyl acetate as eluent to give the difluorinated product **2**. (For determination of reaction yield, in some cases, 1 mmol α,α,α-trifluorotoluene was added to the reaction mixture, and the ^{19}F NMR spectrum was obtained.)

2,2-Difluoro-1-phenyl-3-(3-chlorophenyl)-1,3-propanedione (2g): pale yellow heavy oil (*n*-hexane/AcOEt (10/1), R_f 0.5); ^1H NMR δ 8.20−7.90 (m, 4H), 7.80−7.40 (m, 5H); ^{19}F NMR δ 102.6; ^{13}C NMR δ 188.0 (t, J = 27.1 Hz), 187.3 (t, J = 25.4 Hz), 136.2, 136.0, 135.8, 134.0 (t, J = 1.4 Hz), 132.3 (t, J = 1.6 Hz), 131.1 (t, J = 2.7 Hz), 131.1, 130.8 (t, J = 2.6 Hz), 129.8, 129.2 (t, J = 3.2 Hz), 113.4 (t, J = 266.6 Hz); GC−MS (EI) 294/296 (M^+), 139/141, 111/113, 105, 77, 51; IR (KBr) 3395, 3072, 1702, 1595, 1570, 1475, 1448, 1425, 1294, 1242, 1163, 1111, 965, 898, 788, 748, 713, 684, 577 cm^{-1}. Anal. Calcd for $C_{15}H_9F_2O_2$: C, 61.14; H, 3.08. Found: C, 61.40; H, 3.26.

General Procedure for Preparing Enamine 4 from Acetophenone 3. Into a nitrogen-filled three necked flask equipped with a dropping funnel, a reflux condenser, and a magnetic stirrer, and cooled to 0 °C, was added 20 mL of anhydrous *n*-hexane (10 mL anhydrous benzene was also needed in the case of acetophenone **3b**−**d**), acetophenone **3** (2 mol), and morpholine (9.2 mmol, 0.8 g, 0.8 mL). Then $TiCl_4$ (1.4 mmol, 0.26 g, 0.15 mL) in 5 mL of anhydrous *n*-hexane was added dropwise over 20 min. Fine particles of TiO_2 precipitated. The reaction mixture was heated at reflux for 10 min to 1 h after $TiCl_4$ addition to the solution depending on the acetophenone used. After cooling and filtration of TiO_2, the filtrate was evaporated in vacuo to give the enamine nearly quantitatively and essentially pure (traces of acetophenone may remain).

General Procedure Fluorination of Enamine 4 To Form Monocarbonyl Compounds. To the mixture of Selectfluor (2 mmol, 746 mg) and 4 Å MS (2 g) in 20 mL of anhydrous acetonitrile cooled at −10 °C under nitrogen was added a single portion of enamine **4** (1 mmol) in 5 mL of anhydrous acetonitrile. After the reaction mixture was stirred for 7−8 h at −10 °C, it was filtered and 2.5 g of silica gel was added to the filtrate. The solvent was removed under vacuum, and the remaining solid was chromatographed using *n*-hexanes−ethyl acetate as eluent to give the difluorinated product **5**.

2,2-Difluoro-1-(4-ethoxycarbonylphenyl)ethanone (5d): white solid (mp 57−58 °C; *n*-hexane/CH_2Cl_2/AcOEt (2/1/0.1), R_f 0.2); ^1H NMR δ 8.22−8.12 (AB system, J = 8.7 Hz, 4H), 6.30 (t, J = 53.4 Hz, 1H), 4.44 (q, J = 7.1 Hz, 2H), 1.44 (t, J = 7.1 Hz, 3H); ^{19}F NMR δ −122.0 (d, J = 53.7 Hz); ^{13}C NMR δ 188.1 (t, J = 25.9 Hz), 166.2, 136.6, 135.3 (t, J = 2.0 Hz), 130.8, 130.4 (t, J = 2.4 Hz), 112.0 (t, J = 254.0 Hz), 62.5, 15.1; GC−MS (EI) 228 (M^+), 213, 207, 183, 177, 155, 149, 127, 121, 104, 93; IR (KBr) 2989, 1711, 1610, 1471, 1398, 1371, 1291, 1239, 1181, 1137, 1112, 1059, 1021, 971, 883, 843, 769, 726, 694, 661, cm^{-1}. Anal. Calcd for $C_{11}H_{10}F_2O_3$: C, 57.90; H, 4.42. Found: C, 57.66; H, 4.43.

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Supporting Information Available: Analytical and spectral data for **4c**, **4d**, and **5c**. ^1H NMR spectra for compounds **2c**−**f**, **4a**,**b**,**e**, **5b**, and **6e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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