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Synthesis and Reactivity of Fluorinated Cyclic Ketones: Initial Findings

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Abstract Using cyclic ketone scaffolds, several novel trifluoroacetylated 1,3-diketones and selectively α-fluorinated ketones have been prepared in yields ranging from 20-77% using the Claisen condensation and electrophilic fluorination by the Selectfluor® reagent, respectively. We report tendencies in the difluorinated and trifluoroacetylated products to form hydrates as well as an unusual range of substrate reactivity toward the Selectfluor® reagent. In general, initial spectroscopic studies suggest that cyclic 2-trifluoroacetylated-1,3-diketones undergo rapid hydration resulting in an equilibrium mixture favoring the diketo hydrate over the keto-enol hydrate. Fluorination of ketone species by Selectfluor® was found to be governed by a combination of steric and electronic effects. Plausible mechanisms for both mono- and difluorination, involving a keto-enol or enolic tautomer, are proposed.

Keywords 2-trifluoroacetyl-1,3-diketone, Selectfluor®, tautomerism, ^{19}F NMR

1. Introduction

The preparation of molecules with broad appeal in the pharmaceutical, chemical and forensics communities having a ketone moiety is a field of widening interest. For example, certain indanone derivatives are precursors to pharmaceuticals which have anticoagulant properties and industrial products such as near infrared dyes. In addition, the 1,2-indanedione family of compounds are used in the forensic sciences to aid in latent fingerprint elaboration.[1-8]

Since fluorine is known to alter bioactivity and other physico-chemical properties in many classes of compounds [6-8], the preparation of new fluorinated examples of these molecules is desirable. Additionally, new insights may be obtained from structure-activity relationship studies and upon determining their bioactivity or efficacy relative to known cases.

The preparation and unique keto-enol properties of fluorinated and trifluoromethylated β-diketones have been thoroughly investigated.[9-12] However, the synthesis and study of cyclic 1,3-diketones possessing the trifluoroacetyl group is relatively limited, especially as it relates to the formation of hydrated species.[11-18] Furthermore, while Selectfluor® has found wide application in the preparation of selectively fluorinated molecules[19-21], this work reveals several instances where the usual fluorination conditions fail to produce mono-fluorinated ketone products, lead to more than one fluorinated species or result in difluorination.

The desired molecules of interest in this study, which include alicyclic and fused-ring aromatic ketones, are shown in Figure 1. This paper addresses the design and synthetic approach to prepare these fluorinated ketones, interesting hydration properties of these groups as well as the limitations of reactivity and selectivity observed for the Selectfluor® reagent in this series of ketones.

2. Results and Discussion

2.1. General Synthesis Results

Scheme 1 shows the results of our synthesis efforts. Compounds **1a**-**7a** are commercially available and were used without further purification. Compounds **1b** and **2b** were synthesized in low to moderate yields using a modified Claisen condensation[11,12].

Compounds **1c**, **1d**, **2c**, **2d**, **5b**, **6c**, and **7b** were prepared by direct fluorination with Selectfluor® in yields ranging from 10-77%. Attempts to obtain the fluorinated compounds **3b**, **4b** and **6b** were unsuccessful.

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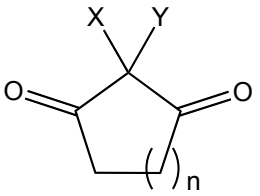
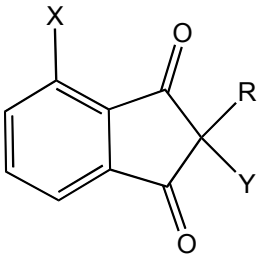
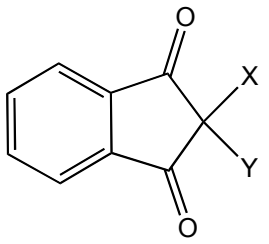


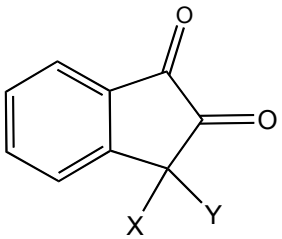
1b: n=1, X=H, Y= $COCF_3$
1c: n=1, X=H, Y= F
2b: n=2, X=H, Y= $COCF_3$
2c: n=2, X=H, Y= F



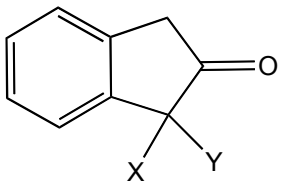
3b: X= H, Y= F, R= $COCH_3$
4b: X= NO_2, Y=F, R= $COCH_3$



5b: X=F, Y=H
5c: X=Y=F

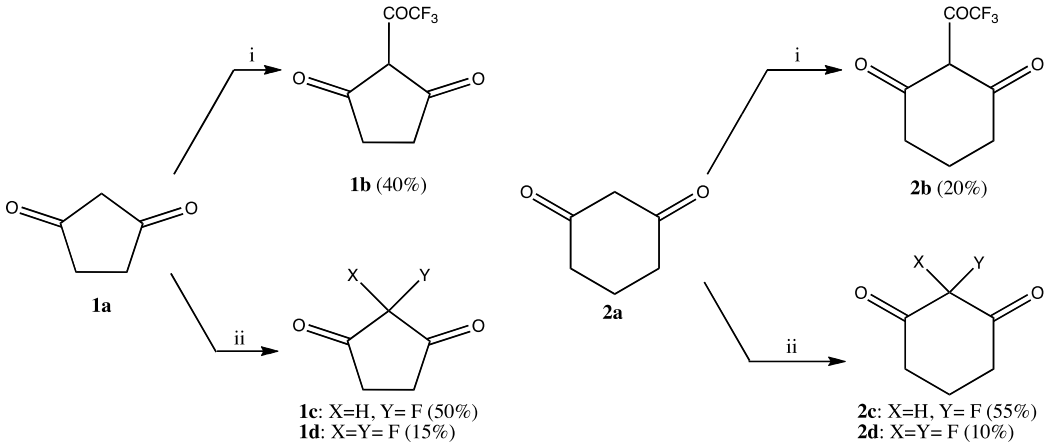


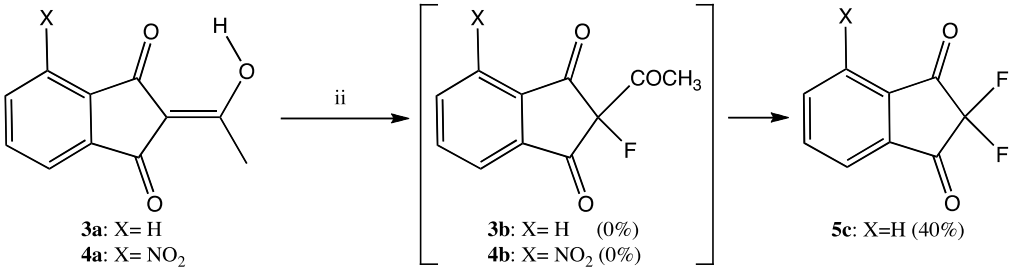
6b: X=H, Y=F
6c: X=Y=F

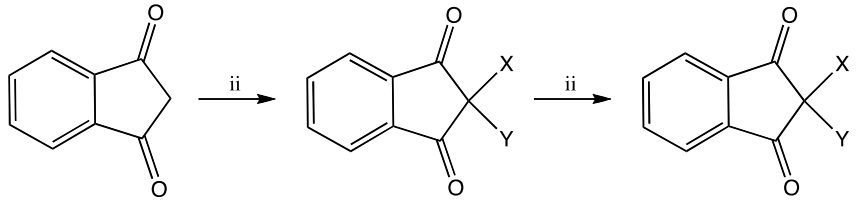


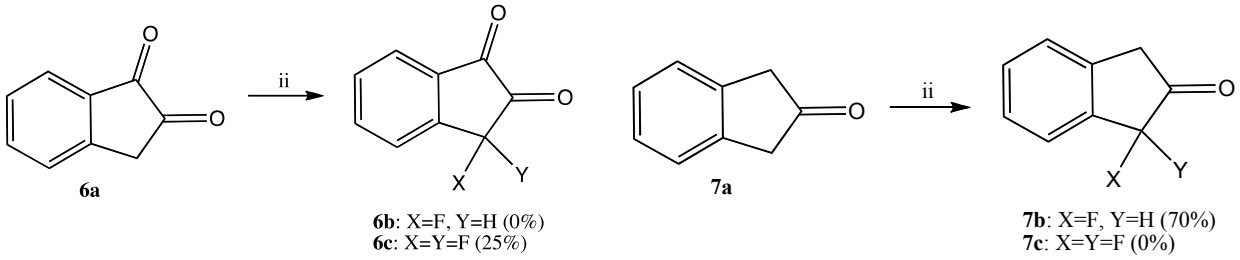
7b: X=H, Y=F
7c: X=Y=F

Figure 1. Target molecules of interest









Conditions: i) CF_3CO_2Et, NaOMe, Et_2O, rt, 18h. ii) Selectfluor®, CH_3CN, RT→reflux, 10-96h.

Scheme 1. Fluorinated ketone synthesis

2.2. Trifluoracetylation Results

While the trifluoroacetylation of **1a** and **2a** provided **1b** and **2b** in relatively low yields, some interesting results were nonetheless obtained. During the reactions, samples of the reaction mixture were removed at various intervals, neutralized and the reaction progress monitored by ^{19}F NMR. The appearance of fluorine resonances noted ca. δ = -75.7 ppm and -76.3 ppm was consistent with the formation of the keto-enol forms of **1b** and **2b**, respectively.[22] See Figure 2.

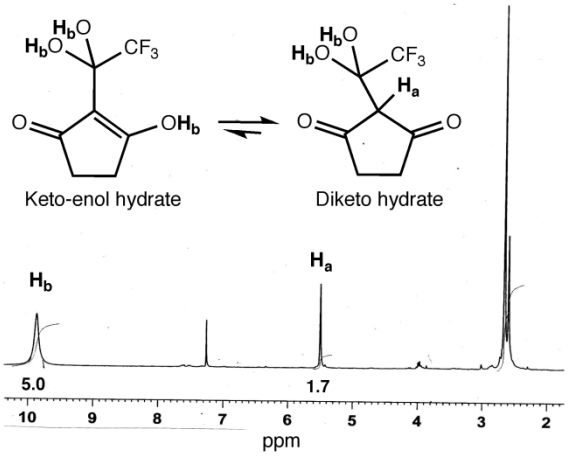
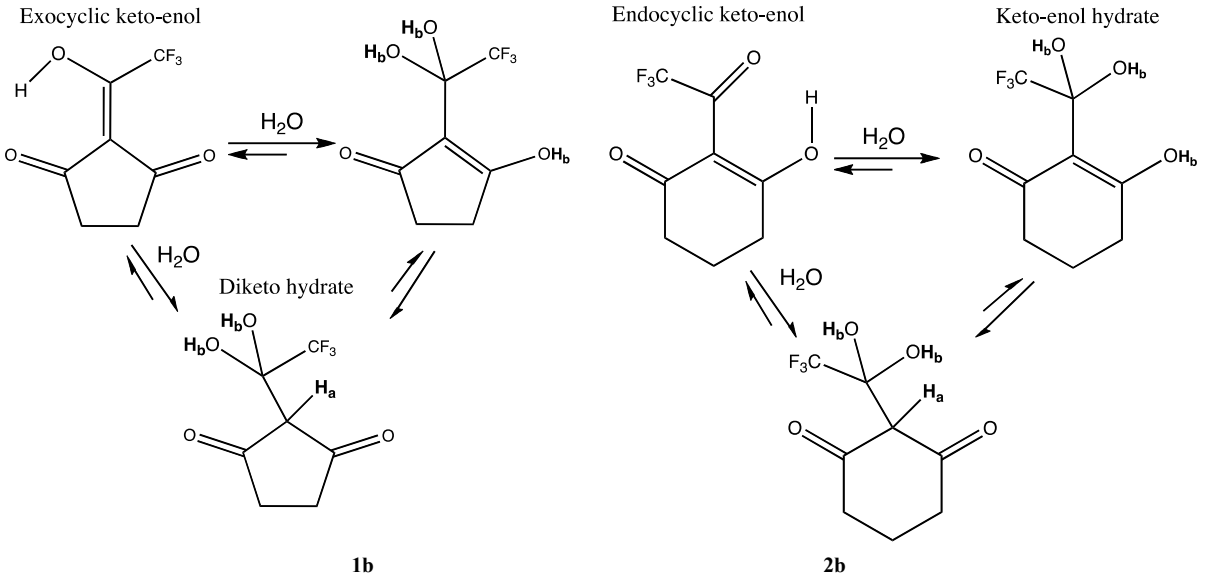


Figure 2. Proton NMR for **1b** hydrate tautomers

Following the acidic workup and isolation of these products, we found that rapid and quantitative hydration of both the exocyclic keto-enol **1b** and endocyclic keto-enol **2b** occurred unless the products were kept in moisture-free environments. Possible equilibria for these tautomeric hydrates are shown in Scheme 2.



Scheme 2. Keto-enol ⇌hydration product equilibria of **1b** and **2b**

The equilibria exhibited by these compounds were examined by ^{19}F and ^{1}H NMR spectroscopy. Previous work by Salman *et al* and Ebraheem *et al*, showed that 2-trifluoroacetylcyclopentanone derviatives preferred an exocyclic keto-enol structures; this was our observation likewise for compound **1b**.[14,16,22] Furthermore, chemical shifts to higher frequencies were noted in the ^{19}F NMR spectra for the CF_3 groups of **1b** and **2b** following workup of ~ 6 ppm (**1b**: -82.2 ppm and **2b**: -82.9 ppm) indicating hydration similar to that found previously by Ebraheem.[15] In the proton NMR spectra, observation of the H_a singlet ca. 5.1-5.6 ppm indicates the presence of the diketo hydrate and a broad, singlet absorbance for H_b ca. 9.0-9.9 ppm corresponds to overlapping protons of the diketo and keto-enol hydrate tautomers. See Figure 2.

When the H_b signal is normalized to five protons (corresponding to all overlapping hydrate and enol proton signals), the integrated value of the H_a signals permits us to calculate K_{eq} for the diketo hydrate⇌keto-enol hydrate equilibrium. For both **1b** and **2b**, the diketo hydrate is the dominant form. See Table 1.

Table 1. Hydrate Species Equilibrium Constant, K_{eq}

Compd	H_a Integrated value	H_b Integrated value	K_{eq} [diketo hydrate]/ [keto-enol hydrate]
1b	1.70	5.00	1.70
2b	1.20	5.00	1.20

2.3. Fluorination Results and Efficacy Testing

Standard fluorination conditions employing the Selectfluor® reagent ranged from those conducted at room temperature to reflux with reaction times varying from 10 to 96 h, with acetonitrile serving as the solvent. Reaction progress was monitored by ^{1}H and ^{19}F NMR. To test the efficacy of Selectfluor® as a monofluorination reagent, compounds **1a**-**7a** were subjected to fluorination under a variety of conditions. The results are compiled in Table 2.

The cyclic 1,3-diketones **1a** and **2a** were reactive toward Selectfluor®, giving the monofluorinated products **1c** and **2c** in 50% and 55% yields, respectively. The detection of resonances in the ^{19}F NMR at δ_F(**1c**)= -161.4 ppm and -195.5 ppm as well as at δ_F(**2c**)= -167.7 ppm confirmed successful α-fluorination. See Figure 3.

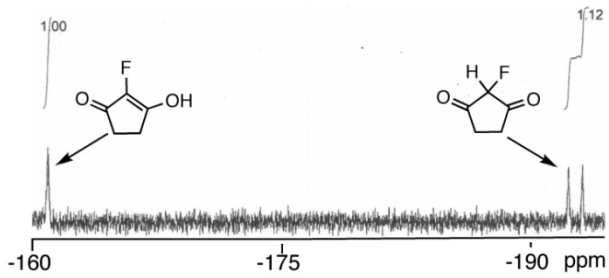


Figure 3. ^{19}F NMR for **1c** tautomers

An interesting finding concerns the observation that while both the keto-enolic and diketonic tautomers were observed for **1c**, compound **2c** exhibited only the keto-enol form. The structures are depicted in Figure 4. In the case of **2c**, we surmise that the predominance of the keto-enolic monofluorinated product observed here is likely due to the stability of the enol form of 2-fluoro-1,3-cyclohexanedione, previously proposed by Whangbo and Bumgardner.[23] A detailed ab initio study of the keto-enol diketo equilibrium for a series of cyclic 2-fluoro-1,3-diketones is underway and will be published separately.

Small quantities of α,α-difluorinated products were also obtained from the fluorinations of **1a** and **2a**. Detection of a single resonance in the ^{19}F NMR at δ_F= -123.4 ppm and a lone signal in the ^{1}H NMR at δ_H=2.01 ppm corresponding to the four equivalent α-hydrogens is indicative of 2,2-difluoro-1,3-cyclopentanedione (**1d**). In accord with previously reported spectral data, 2,2-difluoro-1,3-cyclohex anedione (**2d**) was confirmed by a resonance in the ^{19}F NMR at δ_F(**2d**) = -119.1 ppm.[24-26] See Figure 4.

Consistent with previous work, the α,α-difluoro compounds **1d** and **2d** underwent hydration when exposed to moisture to give the monohydrates depicted in Figure 4. The hydrate of **1d** shows a resonance in the ^{19}F NMR at δ_F= -132.7 ppm and a pair of triplet signals in the ^{1}H NMR at δ_H=2.05 and 2.45 ppm corresponding to the four non-equivalent α-hydrogens on the cyclopentanone ring. The spectroscopic and physical constant data are consistent with literature values for the hydrate of **1d**.[24] In a fashion similar to that of **1d**, the hydration of **2d** was also observed as evidenced by a resonance in the ^{19}F NMR at δ_F(**2d-hydrate**) = -128.1 ppm. This phenomenon was reported by Chambers and coworkers, who found that hydration occurred during the preparation of 2,2-difluoro-1,3-cyclohexanedione with dilute fluorine gas in formic acid.[25,26] We found that hydration was reversed when the samples were subjected to high temperatures under vacuum.

Indanone derivatives **3a** and **4a** were found to be unreactive toward Selectfluor® under the reaction conditions examined. This is likely due a combination of steric crowding at the site of fluorination via the bulky Selectfluor® reagent, and the stability of the keto-enol structure shown in Figure 5, which is the major tautomer present for these species in acetonitrile solution. The proton NMR spectra of **3a** and **4a** acquired in d_3-acetonitrile show singlet signals corresponding to H_b at δ_H ~ 3.9 ppm present in only 5% proportion, supporting assignment of the keto-enol tautomer in solution.

Even though the fluorinations of **3a** and **4a** were unsuccessful, an interesting side reaction was noted for **3a**. During fluorination under refluxing conditions, **3a** was deacetylated, and fluorines were substituted resulting in compound **5c** in about 40% yield. At present, it is unclear how this transformation occurs, but in earlier work, we noted an analogous deacetylation in the Claisen condensation of 2-acetyl-1-tetralone.[19]

Table 2. Fluorination Product Yields Under Differing Reaction Conditions

Starting Material / Product	Reaction Conditions[a] (% yield)[b] A	B	C	D	E	F	G	H
1a / **1c** / **1d**[c]	(5) [0]	(12) [0]	(15) [4]	(21) [7]	(12) [3]	(30) [6]	(41) [11]	(50) [15]
2a / **2c** / **2d**[c]	(3) [0]	(7) [0]	(11) [2]	(16) [3]	(10) [2]	(27) [5]	(42) [7]	(55) [10]
3a / **3b**	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
4a / **4b**	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
5a / **5b**	(7)	(13)	(17)	(25)	(22)	(53)	(67)	NA
6a / **6b** / **6c**[c]	(0) [0]	(0) [0]	(0) [0]	(0) [0]	(0) [4]	(0) [8]	(0) [15]	(0) [25]
7a / **7b**	(0)	(0)	(0)	(0)	(14)	(29)	(50)	(70)

[a]Reaction Conditions: A. Room temperature, 10h. B. Room temperature, 24h. C. Room temperature, 48h. D. Room temperature, 96h. E. Reflux, 10h. F. Reflux, 24h. G. Reflux, 48h. H. Reflux, 96h.
[b]Determined by ^{1}H and ^{19}F NMR. [c][ ] refers to % yield of α,α-difluoro products.

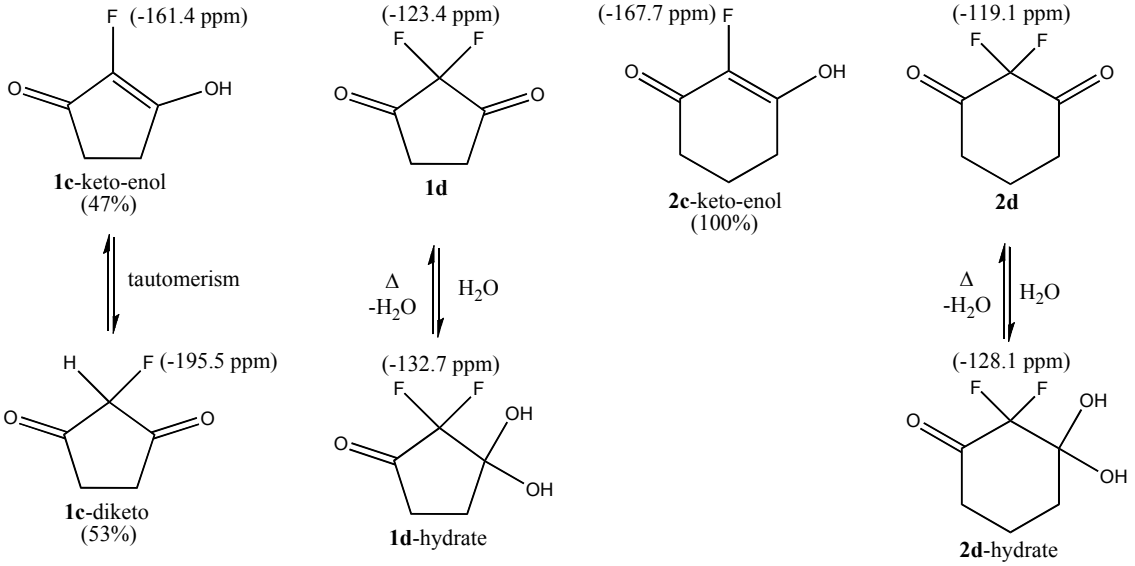
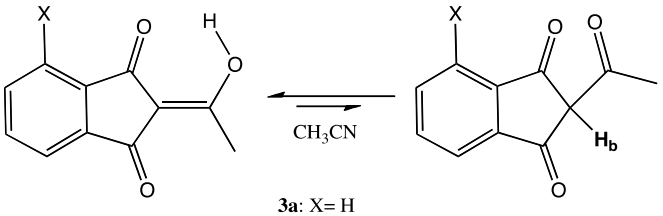


Figure 4. Fluorination products of **1a** and **2a** and equilibria exhibited by **1c**, **1d**, **2c** and **2d**



3a: X= H
4a: X= NO_2

keto-enol tautomer (95%) triketo tautomer (5%)

Figure 5. Keto-enol - triketone tautomeric equilibria of 3a and 4a

In contrast, 1,3-indanedione, **5a**, was fluorinated with Selectfluor® to give **5b** in good yield over the range of reaction conditions investigated. Studies of the keto-enol tautomeric equilibrium exhibited by 1,3-indandione reveal that it exists in the diketo form in both nonpolar and polar, aprotic solvents. The reaction stops cleanly with monofluorination, but earlier work by our group demonstrated that **5b** can be fluorinated to give 2,2-difluoro-1,3-indanedione.[19]

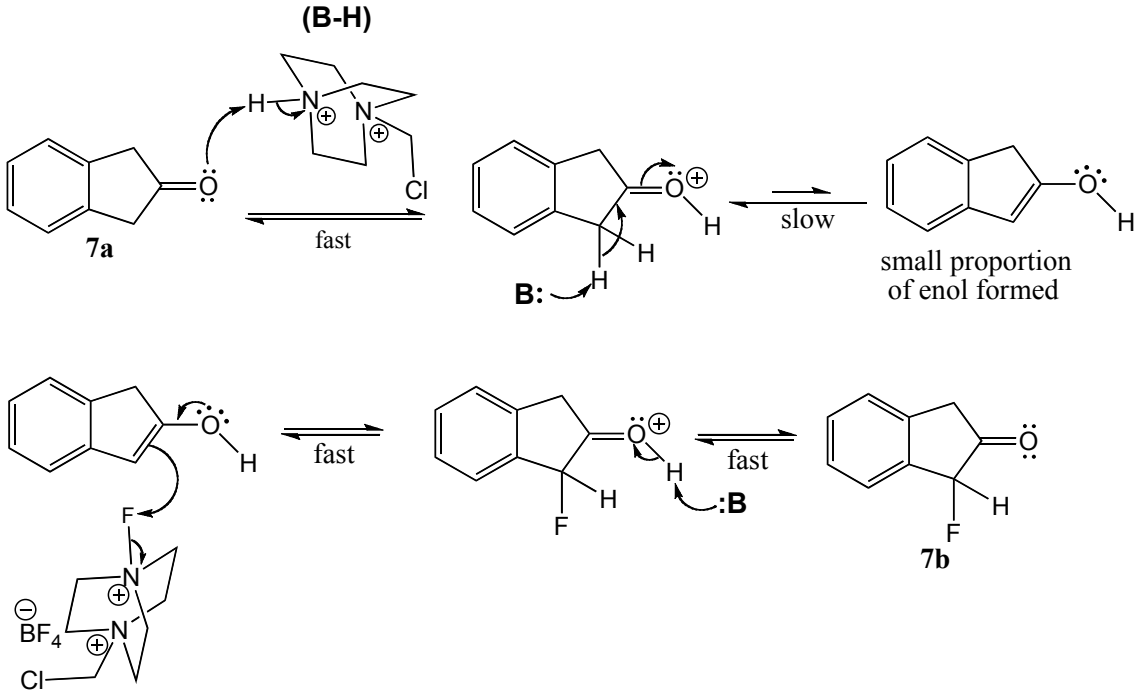
The fluorination of **6a** with Selectfluor® yielded unexpected results. Although we anticipated typical monofluorination adjacent to the C-2 carbonyl group, only the α,α-difluorinated product, **6c**, was obtained in appreciable yield. The proton NMR for **6c** features a multiplet centered at δ_H = 8.14 ppm corresponding to the aromatic protons. A ^{19}F NMR singlet observed at δ_F = -86.1 ppm is consistent with typical R(C=O)CF_2Ar chemical shift values.[27] We are uncertain at this point why no monofluorination occurred under the reaction conditions and yet difluorination occurred at reflux temperature. Unfortunately, attempts to purify **6c** via chromatography for analytical verification led to decomposition of the product. We are currently investigating modifications to the reaction conditions and purification methods to address these issues.

Treatment of **7a** with Selectfluor® provided the α-monofluorinated compound **7b** in 70% overall yield, but only under refluxing conditions. As expected, fluorination occurred adjacent to the carbonyl group and physical and spectroscopic data obtained for **7b** are consistent with literature data.[30] A ^{19}F NMR doublet centered at δ_F = -180.7 ppm ($^2J_{F-H}$ = 52.5 Hz) and a ^{1}H NMR doublet centered at δ_H = 5.55 ppm ($^2J_{H-F}$ = 52.5 Hz) confirm monofluorination on the α-carbon.[27] Attempts to fluorinate **7b** were unsuccessful.

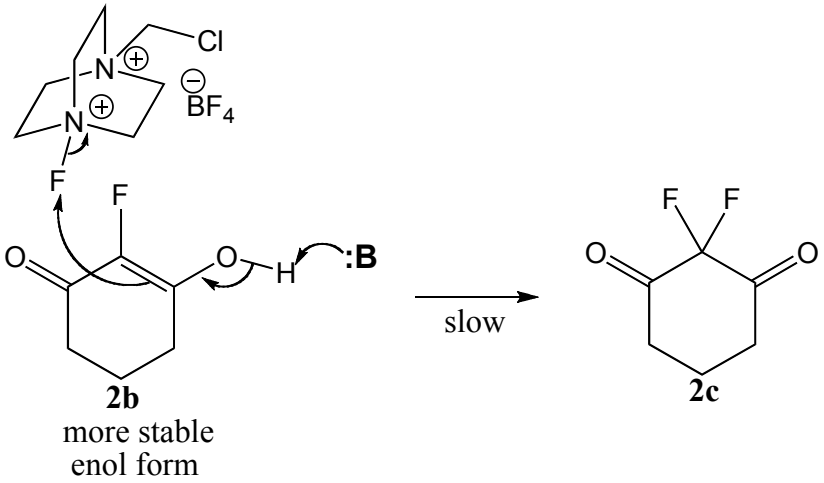
2.4. Plausible Mechanisms for the Electrophilic Fluorination of Cyclic Diketones via Selectfluor®

The literature indicates considerable disagreement concerning the mechanism by which fluorination occurs with reagents such as Selectfluor®. Polar processes where the "F^+" ion is the electrophile and single electron transfer (SET) processes which include a "F· " radical species have been proposed, but mechanistic studies have not established that a single fluorination mechanism operates in all cases.[20]

In the case of the ketone substrates examined in this study, we propose that an enol species initiates the fluorination by having the C=C double bond attack the Selectfluor®. In cases where the enol is formed readily under the reaction conditions or is the major tautomer in the reaction medium, such as cyclic *β*-diketones **1a** and **2a**, the fluorination can occur at room temperature, and difluorination can become a complicating issue. In cases where the keto tautomer predominates and/or enolization is slow (e.g. **7a**), the reaction is slow even under refluxing conditions. However, multiple fluorinations are not as likely. Finally, fluorination via Selectfluor® does not occur in the usual fashion when the keto-enol substrate is very hindered or very stable (eg. triketones **3a** and **4a**). Mechanisms for both monofluorination (Scheme 3) and difluorination (Scheme 4) that are consistent with these findings are presented below using compounds **7a** and **2b**, respectively.



Scheme 3. Monofluorination mechanism of **7a**



Scheme 4. Difluorination mechanism of **2b**

In Scheme 3, the tautomerization of **7a** from ketonic to enolic form occurs slowly in the presence of a proton source, most likely the diazoniabicyclo[2.2.2] octane species depicted above. As reactions involving Selectfluor® in acetonitrile and molecules with enolizable protons proceed, the solution becomes slightly acidic (pH ~5-6), which is sufficient to enable the keto→enol tautomerization. The enol form, which is only present in small quantities under these conditions due to its instability, reacts with the fluorinating agent to give the monofluorinated product **7b**.

In Scheme 4, the enolic form of compound **2b** is the most stable tautomer in solution. Several groups have reported this preference of **2b** based on spectroscopic data and crystal structures of the molecule.[26,29] Whangbo and Bumgardner have offered a frontier molecular orbital rationale for the unusual stability of the enolic form of 2-fluoro-1,3-cyclohexanedione in support of experimental findings.[23] Because difluorination would result in loss of the enol form, the stable enol form reacts very slowly with a second equivalent of Selectfluor® to give small quantities of the difluorinated product **2c**.

While our proposed mechanisms are consistent with the experimental findings, we note that single electron transfer processes could also be operating, especially in the instance of the difluorination-deacetylation observed for **3a** or in cases where the keto⇌enol tautomeric equilibrium favors the keto form, eg. **5a** and **7a**. This may also explain the exceptional behavior of **6a**, which underwent difluorination even though there was no evidence of enolization during the reaction.

3. Conclusions

This work, while still in its initial stages, provides new insight into several areas of current interest regarding selective trifluoroacetylations and fluorinations of cyclic ketones. Trifluoroacetylations of cyclic β-diketones occur under the usual Claisen condensation conditions, but yields are lower than for their acyclic counterparts. [9,11] Trifluoroacetyl groups are subject to hydration due to the enhanced electrophilicity of the carbonyl and these compounds must be maintained in a moisture-free environment to avoid this phenomenon. Likewise, carbonyl groups adjacent to α,α-difluorinated carbons display a tendency for rapid hydration.

Our work has also shed light on the effectiveness of the Selectfluor® reagent in the monofluorination of cyclic ketones, diketones and triketones. Cyclic β-diketones which can tautomerize from the diketo form to a keto-enol form undergo fluorination under mild conditions, but often difluorination can take place as well. When difluorination occurs, hydration at the ketone adjacent to the fluorines frequently takes place. Indanone derivatives such as **3a** and **4a** are unreactive toward Selectfluor® due to a combination of steric and electronic factors arising from the large size of the fluorinating agent as well as the exceptional stability of the keto-enol tautomer. Conversely, ketones that do not tautomerize appreciably due to instability of the enol form react with the Selectfluor® reagent slowly, if at all, and usually do not give difluorinated products. Notable exceptions to this general rule were the successful fluorinations of **5a** and **7a**. Likewise, the formation of compound **6b** is an apparent departure from this general observation. Further studies are needed to address **6b**'s anomalous behavior.

Finally, it is possible that either polar or SET fluorination processes may lead to the products in our study. While we were cautious to ensure that reaction vessels were protected from light so as to minimize radical formation, the fact that fluorination was observed in several cases where enolization was not evident could mean that an SET process might be occurring.

4. Experimental

4.1. Chemicals

All chemicals were obtained from the Aldrich Chemical

Company, Eastman Kodak, or Fisher Chemical Company. All solvents and starting materials were checked for purity by mass spectrometry or proton NMR prior to use.

4.2. Instrumentation

Melting points were obtained on a Mel-Temp melting point apparatus and are uncorrected. NMR data were collected using an Anasazi-90 spectrometer operating at 90.0MHz for ^{1}H, 84.7MHz for ^{19}F and 22.6MHz for ^{13}C or a Brüker Avance 300 spectrometer operating at 300.0MHz for ^{1}H, 288MHz for ^{19}F and 75.4MHz for ^{13}C. Fluorine-19 NMR chemical shifts were referenced to $CFCl_3$ as an external standard. IR data were collected on a Perkin-Elmer FT-IR spectrometer with resolutions of $1cm^{-1}$.

4.3. General Procedure for the Preparation of Trifluoroacetylated Diketones[11,12]

To 50 mL diethyl ether in a round bottom flask equipped with a magnetic stirrer is added 60 mmol of sodium methoxide slowly. Then, 1eq (60 mmol) of methyl trifluoroacetate is added dropwise slowly while stirring. After 5 minutes, 1eq (60 mmol) of the ketone is added dropwise and stirred overnight at room temperature under a calcium chloride drying tube. The resulting solution is evaporated to dryness under reduced pressure and the solid residue dissolved in 30 mL 3*M* sulfuric acid. The acidic solution is extracted with 3-15 mL aliquots of diethyl ether, and the organic layer dried over $NaSO_4$. The solvent is evaporated under reduced pressure, the crude diketone purified by distillation, recrystallization or radial chromatography, and purity confirmed by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy, mass spectrometry and literature melting or boiling points.

2-trifluoroacetyl-1,3-cyclopentanedione (**1b**) This compound was obtained as a 95:5 mixture of exocyclic enol:triketo tautomers as pale yellow crystals (Et_2O) in 40% yield, mp 138-140°C. NMR: ^{1}H: δ 2.63 (CH_2, 4H, s), 5.41 (keto CH, 1H, s). ^{13}C: δ 30.9, 105.1, 107.2, 115.2 (CF_3, q, $^{1}J_{C\text{-}F}$ =274Hz), 159.5 (C-CF_3, q, $^{2}J_{C\text{-}F}$=36Hz), 195.3, 205.0. ^{19}F: δ -75.7. Analysis calcd for $C_7H_5F_3O_2$: C, 43.32, H, 2.60. Found: C, 43.10, H, 2.52. The **1b**-hydrate was obtained as a reddish oil (1.7:1 mixture of diketo hydrate:keto-enol hydrate). NMR: ^{1}H: δ 2.71 (CH_2, 4H, s), 5.58 (CH, 1H, s), 9.88 (OH, 3H, bs). ^{13}C: δ 30.9, 105.1, 107.2, 115.2 (CF_3, q, $^{1}J_{C\text{-}F}$ =274Hz), 195.3, 205.0. ^{19}F: δ -82.2 (3F, bs).

2-trifluoroacetyl-1,3-cyclohexanedione (**2b**) This compound was obtained in 20% yield as a beige solid, m.p. 71-74°C. NMR: ^{1}H: δ 1.98-2.6 (CH_2, 6H, m). ^{13}C: δ 21.0, 28.8, 30.9, 106.2, 108.1, 117.2 (CF_3, q, $^{1}J_{C\text{-}F}$=271Hz), 162.6 (C-CF_3, q, $^{2}J_{C\text{-}F}$=37Hz), 196.2, 201.0. ^{19}F: δ -76.3 (enol). Analysis calcd for $C_8H_7F_3O_2$: C, 46.16, H, 3.39. Found: C, 46.26, H, 3.31. The **2b**-hydrate was obtained as a red-orange oil (1.2:1 mixture of diketo hydrate:keto-enol hydrate.) ^{1}H: δ 1.98 (CH_2, 2H, m, J=5.55Hz), 2.35 (CH_2, 2H, t, J=6.41Hz), 2.71 (CH_2, 2H, t, J=6.59Hz), 5.49 (hydrate, 1H, s), 9.0 (hydrate and enol, 3H, bs). ^{19}F: δ -82.9 (3F, bs).

4.4. General Procedure for the Preparation of Fluorinated Diketones

A 100mL round bottom flask equipped with a stir bar is charged with 50mL CH_3CN and Selectfluor® (0.78 g, 0.0022mol). Once the Selectfluor® has dissolved, the ketone (1eq, 0.0022mol) is added slowly with stirring. The reaction is capped and allowed to run for 10-96 h at room temperature or under reflux at a temperature of 70°C for 10-96 h. The solvent is removed under reduced pressure. The resulting residue is taken up in ~20mL CH_2Cl_2 and washed with 3 aliquots of ~20 mL distilled water. The organic layers are combined and dried over Na_2SO_4 and the product purified by radial chromatography or recrystallization.

2-fluoro-3-hydroxycyclopent-2-enone and 2-fluoro-1,3-cyclopentanedione (**1c**): This compound was obtained as a 52:48 mixture of keto-enol and diketo tautomers in 50% yield as a yellow-brown solid, mp 70-72°C. NMR: ^{1}H: δ 2.36 (t, $^{3}J_{H\text{-}H}$ = 16.2 Hz, 2H), 2.85 (m, 2H), 5.91 (d, $^{2}J_{H\text{-}F}$ = 47.7 Hz, 1H). ^{13}C: δ 31.1, 90.8 (d, $^{1}J_{C\text{-}F}$ = 251.3 Hz), 122.3 (d, $^{1}J_{C\text{-}F}$ = 233.9 Hz), 210.1 (d, $^{2}J_{C\text{-}F}$ = 31.0 Hz). ^{19}F: keto-enol: δ -161.4 (s, 1F); diketo: δ -195.5 (d, $^{2}J_{F\text{-}H}$ = 47.7 Hz, 1F). Analysis calcd for $C_5H_5FO_2$: C, 51.73, H, 4.34. Found: C, 51.48, H, 4.31.

2,2-difluoro-1,3-cyclopentanedione (**1d**): This compound was obtained in 15% yield as tan crystals, mp 41-43°C. NMR: ^{1}H: δ 2.21 (H_2C-C=O, 4H, m). ^{13}C: δ 31.1, 110.8 (t, $^{1}J_{C\text{-}F}$ = 248.3 Hz), 199.3 (t, $^{2}J_{C\text{-}F}$ = 28.0 Hz). ^{19}F: δ -123.4 (s, 2F). Analysis calcd for $C_5H_4F_2O_2$: C, 44.79, H, 3.01. Found: C, 44.68, H, 3.12.

2,2-difluoro-3,3-dihydroxy-1-cyclopentanone (**1d-hydrate**): This compound was obtained from the hydration of **1d** as beige crystals (ethyl acetate), m.p. 71-74°C [lit. 24] m.p. 70-72°C. NMR: ^{1}H: δ 2.04 (m, 2H), 2.45 (m, 2H), 6.91 (s, hydrate, 2H). ^{13}C: δ 31.0, 32.1, 94.6 (t, $^{2}J_{C\text{-}F}$ = 20.9 Hz), 112.5 (t, $^{1}J_{C\text{-}F}$ = 254.8 Hz), 210.8 (t, $^{2}J_{C\text{-}F}$ = 18.5 Hz). ^{19}F: δ -132.7 (s, 2F).

2-fluoro-3-hydroxycyclohex-2-enone (**2c**): This compound was obtained in 55% yield as pale tan crystals (ethyl acetate), m.p. 150-152°C [lit. 25] (m.p. 152-153°C). NMR: ^{1}H: δ 1.90-2.50 (m, 6H), 11.4 (bs, 1H). ^{13}C: δ 20.1, 22.2, 33.0, 106.1, 37.9, 139.8.1 (d, $^{1}J_{C\text{-}F}$ = 235.3 Hz), 200.1 (d, $^{2}J_{C\text{-}F}$ = 14.5 Hz). ^{19}F: δ -167.7 (s, 1F).

2,2-difluoro-1,3-cyclohexanedione (**2d**): This compound was obtained in 10% yield as pale tan crystals (ethyl acetate), m.p. 68-70°C [lit. 25] (m.p. 70°C). NMR: ^{1}H: δ 1.9 (m, 2H), 2.4 (m, 4H). ^{13}C: δ 18.0, 37.9, 114.1 (t, $^{1}J_{C\text{-}F}$ = 257.6 Hz), 195.2 (t, $^{2}J_{C\text{-}F}$ = 23.5 Hz). ^{19}F: δ -119.0 (s, 2F).

2,2-difluoro-3,3-dihydroxy-1-cyclohexanone (**2d-hydrate**): This compound was obtained from the hydration of **2d** as pale tan crystals (ethyl acetate), m.p. 68-76°C [lit. 25] NMR: ^{1}H: δ 1.85 (m, 2H), 2.11 (m, 2H), 2.49 (m, 4H). ^{13}C: δ 20.0, 35.0, 96.0 (t, $^{1}J_{C\text{-}F}$ = 257.6 Hz), 114.2 (t, $^{1}J_{C\text{-}F}$ = 257.0 Hz), 197.3 (t, $^{2}J_{C\text{-}F}$ = 24.5 Hz). ^{19}F: δ -128.1 (s, 2F).

2-fluoro-1,3-indanedione (**5b**). This compound was obtained in 67% yield as pale yellow crystals (EtOH), m.p.

95–97°C [lit 19] (m.p. 96–98°C). NMR: ^{1}H: δ 5.4 (d, $^{2}J_{H-F}$ = 51.0 Hz, 1H), 7.65–8.22 (m, 4H). ^{13}C: δ 90.1 (d, $^{1}J_{C-F}$ = 211.2 Hz), 125.3, 138.9, 141.9, 193.5 (d, $^{2}J_{C-F}$ = 24.0 Hz). ^{19}F: δ −207.3 (d, $^{2}J_{F-H}$ = 51.1 Hz, 1F).

2,2-difluoro-1,3-indanedione (**5c**). This compound was obtained in 77% yield as a yellowish-brown solid (EtOH), m.p. 115–117°C [lit 21] (m.p. 117–118°C). NMR: ^{1}H: δ 8.0–8.18 (m, 4H). ^{13}C: δ 104.1 (t, $^{1}J_{C-F}$ = 264 Hz), 128.6, 138.1, 139.2 (t, $^{3}J_{C-F}$ = 4.3 Hz), 185.8 (t, $^{2}J_{C-F}$ = 24.1Hz). 19F: δ −125.8 (s, 2F).

3,3-difluoro-1,2-indanedione (**6b**): This compound was obtained in 25% yield as yellow-brown crystals, m.p. 99-103°C, dec. NMR: ^{1}H: δ 7.1-8.6 (m, 4H). ^{19}F: δ -86.1 (s, 2F). Purification by column chromatography resulted in decomposition of the product, so further characterization was not possible at the time of this publication.

(±)1-fluoro-2-indanone (**7b**) This compound was obtained in 70% yield as a racemic mixture of enantiomers as a brown oil [lit 29]. NMR: ^{1}H: δ 3.58 (s, 2H), 5.7 (d, $^{2}J_{H-F}$ =52.5Hz, 1H), 7.0-7.6 (m, 4H). ^{19}F: δ -180.8 (d, $^{2}J_{F-H}$ =52.5Hz, 1F).

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