Nucleophilic Di- and Tetrafluorination of Dicarbonyl Compounds

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Received May 17, 2001

Reactions of various diketo compounds with Deoxofluor [$(CH_3OCH_2CH_2)_2NSF_3$] have been investigated. When reacted with Deoxofluor, α-diketones, R_1COCOR_2 ($R_1 = R_2 =$ Ph; $R_1 = R_2 =$ 4-Me-C_6H_4; $R_1 =$ Ph, $R_2 =$ Me; $R_1 =$ Me, $R_2 =$ Et) (**1a**−**d**) formed difluoro derivatives (**2a**−**d**) in the presence of a catalytic amount of HF and/or tetrafluoro (**3a**−**d**) products depending on the reaction conditions and stoichiometry used. Reactions of β-diketones, $R_3COCH_2COR_4$ ($R_3 = R_4 =$ Ph; $R_3 = R_4 =$ Me; $R_3 =$ Me, $R_4 =$ Ph) (**4e**−**g**), with Deoxofluor in the presence of a catalytic amount of HF led to the formation of difluoroalkenones as a mixture of *E* (**5e**−**g**) and *Z* (**6e**−**g**) isomers in good yield. Reaction of other diones, R_5CO-X-COR_6 ($R_5 = R_6 =$ Ph, X = −CH=CH−; $R_5 = R_6 =$ Me, X = $-C_6H_4C_6H_4-$; $R_5 = R_6 =$ Ph, X = $-CH_2CH_2CH_2-$; $R_5 = R_6 =$ Me, X = $-CH_2CH_2-$) (**7h**−**k**) with Deoxofluor produced mainly difluoro products (**8h**−**k**) with low yields of tertrafluoro derivatives (**9h**−**k**). Acyclic α-keto amides react poorly to give the corresponding difluoro derivatives, whereas cyclic α-keto amides (**10l**−**p**) react smoothly under very mild conditions to produce the corresponding difluoro products (**11l**−**p**) in >88% isolated yield.

Introduction

Fluorine or a fluorinated group is a highly important substituent in the field of organic chemistry, most often bringing about some remarkable changes in the physical, chemical and biological properties of new compounds/materials that makes them suitable for diverse applications in the areas of materials science, agrochemistry, and industry.[1−5] The powerful electron-withdrawing ability of these species and relatively small size of the trifluoromethyl group (only two and one-half times the volume of a methyl group) lead to significant changes in the chemistry of substituted compounds when compared with their nonfluorinated analogues. The influence of a fluorine atom or a fluorinated group in biologically active molecules is often associated with increased lipophilicity[4,6] that these substituents impart giving rise to active pharmaceutical and agrochemical compounds with improved transport characteristics *in vivo* and facilitating lower dose rates. While a wide variety of methods have been developed for introducing difluoro groups into organic compounds,[7] the use of Deoxofluor as a nucleophilic difluoromethylating reagent is being explored.[8,9] Utilization of Deoxofluor in the conversion of a simple system such as aldehydes and ketones, into the corresponding difluoro derivatives was reported recently,[8,9] but this methodology was not extended to polycarbonyl compounds. Recently, we have reported the double nu-

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(1) For the general applications of organofluorine compounds, see: *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum: New York, 1994.

(2) For the use of organofluorine compounds in medicinal and biomedical chemistry, see: (a) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996. (b*) Organic Chemistry in Medicinal Chemistry and Biomedical Applications*; Filler, R., Ed.; Elsevier: Amsterdam, 1993. (c) Welch, J. T.; Eswaraksrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley and Sons: New York, 1991. (d) Filler, R.; Kirk, K. Biological Properties of Fluorinated Compounds. In *Chemistry of Organic Fluorine Compounds II: A Critical Review*; Hudlicky, M., Pavlath, A. E., Eds.; ACS Monograph 187; Americal Chemical Society: Washington, DC, 1995. (e) Elliot, A. J. Fluorinated Pharmaceuticals. *Chemistry of Organic Fluorine Compounds II*; ACS Monograph 187; Americal Chemical Society: Washington, DC, 1995. (f) Sholoshonok, V. A., Ed. *Enantiocontrolled Synthesis of Organo-Fluorine Compounds: Stereochemical Challenge and Biomedical Targets*; John Wiley and Sons: 1999.

(3) For the use of of organofluorine compounds in agrosciences, see: (a) Cartwright, D. *Recent Developments in Fluorine-Containing Agrochemicals*. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum: New York, 1994. (b) Lang, R. W. Fluorinated Agrochemicals. *Chemistry of Organic Fluorine Compounds II*; ACS Monograph 187; American Chemical Society: Washington, DC, 1995.

(4) The ability of fluorine to change the properties of organic molecules has been discussed extensively elsewhere. For example, see: Smart, B. E. *Characteristics of C−F systems*. In *Organofluorine Chemistry*: *Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum: New York, 1994.

(5) For recent discussions on the controversial topic of fluorine hydrogen bonds, see: (a) O'Hagan, D. O.; Rzepa, H. S. *J. Chem. Soc., Chem. Commun.* **1997**, 645. (b) Dunitz, J. D.; Taylor, R. *Eur. Chem. J.* **1997**, *3*, 89−92. (c) Howard, J. A. K.; Hoy, V. J.; O'Hagan, D. O.; Smith, G. T. *Tetrahedron* **1996**, *52*, 12613−12622.

(6) *Organofluorine Chemicals and Their Industrial Applications*; Banks, R. E., Ed. Ellis Harwood Ltd.: Chichester, 1979. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123−3197.

(7) For general discussion on the synthesis of organofluorine compounds, see: (a) Olah, G. A.; Prakash, G. K. S.; Chambers, R. D. *Synthetic Fluorine Chemistry*; Wiley and Sons: New York, 1992. (b) Furin, G. G. *Synthetic Aspects of the Fluorination of Organic Compounds*; Harward Academic Publisher: London, 1991. (c) Furin, G. G. Introduction of Fluorine by N−F Compounds. *Methods of Organic Chemistry (Houben-Weyl) Organo-Fluorine Compounds*; Georg Thieme Verlag: Stuttgart, New York, 1999; pp 432−499. (d)Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431−12477. (e) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555−6666. (f) Rozen, S. *Chem. Rev.* **1996**, *96*, 1717−1736. (g) Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505−519. (h) Rozen, S.; Mishani, E. *J. Chem. Soc., Chem. Commun.* **1994**, 2081. (i) Rozen, S.; Mishani, E.; Bar-haim, A. *J. Org. Chem.* **1994**, *59*, 2918. (j) Middleton, W. J.; Bingham, E. M. *J. Org. Chem.* **1980**, *45*, 2883−2887. (k) Rozen, S.; Lerman, O.; Kol, M.; Hebel, D. *J. Org. Chem.* **1985**, *50*, 4753−4758.

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10.1021/jo0157674 CCC: $20.00
Published on Web 08/18/2001

Scheme 1

1a-d **2a-d** **3a-d**

a: $R_1 = R_2$ = Ph; **b**: $R_1 = R_2$ = 4-Me-C_6H_4; **c**: R_1 = Me, R_2 = Ph;
d: R_1 = Me, R_2 = Et (* addition occurred at either carbonyl)

cleophilic trifluoromethylation reactions of various diketo compounds with Me_3SiCF_3 to achieve the corresponding bis(trifluoromethylated) compounds.[10] In our continuing efforts to perfluoroalkylate organic compounds nucleophilically,[11] we have extended the scope of Deoxofluor by utilizing it to introduce two or four fluorine atoms into the organic backbone of molecules.

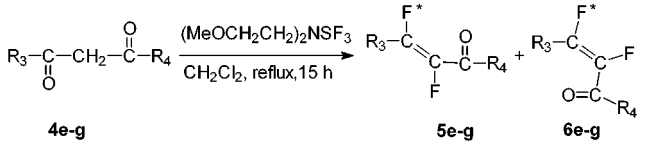
Results and Discussions

Deoxofluor was found to be a very useful reagent[8,9] for introducing a difluoro or terafluoro moiety in organic molecules using a single-step reaction. During the course of our research in the area of nucleophilic perfluoroalkylation, it was realized that the use of Deoxofluor with di and polycarbonyl systems could provide a straightforward route to the syntheses of the corresponding tetrafluoro and polyfluorinated compounds in a single step. To study the chemistry of Deoxofluor with dicarbonyl compounds, various substrates were selected in which the two carbonyl units often are located in different chemical environments. This chemistry is described as follows.

Reaction of Deoxofluor with α-Diketones. The reactions of α-diketones with Deoxofluor are very much dependent on the nature of the substituents vicinal to the keto functionalities. For example, the reaction of benzil (**1a**) with 3 equivalents of Deoxofluor at 60 °C for 24 h, in the presence of a catalytic amount of HF (generated by adding a drop of ethanol time to time), gave the corresponding tetrafluoro derivative (**3a**) in 75% yield with concomitant formation of the corresponding difluoro product (**2a**) in trace amounts as determined by GCMS (Scheme 1). The earlier syntheses of **3a** reported in the literature result in either low yields[12] or require the use of elemental fluorine,[13] xenon difluoride,[14] or bromine monofluoride.[15] When Deoxofluor, which is a thermally stable, easy-to-handle liquid, is used as a fluorinating reagent, reactions are easily controlled. Under similar reaction conditions, the reaction of 4,4′-dimethylbenzil (**1b**) with Deoxofluor produced the tetrafluoro product (**3b**) in 72% yield. This material is an useful additive to decrease the viscosity of liquid crystal compounds.[16] Formation of **2b** was observed in trace amounts.

With some of the substrates, selectivity is often observed. For example, the reaction of 1-phenyl-1,2-propanedione (**1c**) with excess Deoxofluor under similar

Scheme 2



4e-g **5e-g** **6e-g**

e: R_3 = Ph, R_4 = Ph; **f**: R_3 = Me, R_4 = Me;
g: R_3 = Me, R_4 = Ph (* addition occurred at either carbonyl)

reaction conditions gave only the difluoro compound (**2c**) in 88% yield whereas the formation of a tetrafluoro derivative (**3c**) was observed in trace amounts by GCMS. Not unexpectedly, with 1-phenyl-1,2-propanedione (**1c**) the carbonyl group vicinal to phenyl was the only reactive one under the conditions used. Reactivity of 2,3-pentanedione(**1d**) was also tested under similar reaction conditions and the formation of a mixture of difluoro (**2d**) and tetrafluoro (**3d**) products was observed but in low yields (Scheme 1). They were characterized as a mixture by NMR using ^{19}F NMR, $CH_3CF_2COCH_2CH_3$ gave rise to a quartet at δ −100.81 with J = 19.5 Hz whereas $CH_3COCF_2CH_2CH_3$ showed a triplet at δ −109.59 with J = 17 Hz. The tetrafluoro product, $CH_3CF_2CF_2CH_2CH_3$, gave two multiplets centered at δ −96.66 and δ −133.41.

Reaction of Deoxofluor with β-Diketones. Both symmetrical and unsymmetrical β-diketones were found to be more reactive with Deoxofluor than α-diketones. Interestingly, the products obtained were the vicinal difluoroenones that were isolated in good yields as mixtures of *E* and *Z* isomers. It has been observed that after the formation of the vicinal difluoroenone, the reaction proceeds further to produce the tetrafluoro derivatives of the corresponding difluoroenone in low yield. Reaction of dibenzoylmethane (**4e**) with 3 equiv of Deoxofluor at 25 °C for 5 h gave the vicinal difluoroenone (**5e, 6e**) as a mixture of *E* and *Z* isomers in a ratio of ∼1:1 in 80% yield (Scheme 2). The tetrafluoro derivative, of the *E* isomer of the type $PhCF{=}CFCF_2Ph$, was isolated in 10% yield. The earlier synthesis to prepare vicinal difluoroenone compounds (**5e**, **6e**) using DAST [(bis-(diethylamino)sulfur trifluoride] as a fluorinating reagent with dibenzoylmethane as substrate was not very useful where only minor amounts of the desired products were reported; however, somewhat better results were obtained with 4f.[17] Under similar reaction conditions, acetylacetone (**4f**) with Deoxofluor gave a mixture of *E* and *Z* isomers of vicinal difluoroenone (**5f**, **6f**) in the ratio of ∼1:1 in 72% yield (Scheme 2). A much shorter period is required for the completion of the reaction, but using DAST as a fluorinating reagent, 48−64 h reaction time has been reported with the formation of the products in 40−60% yield.[17] When an unsymmetrical β-diketone such as 1-benzoylacetone (**4g**) was used as the substrate, the formation of two different vicinal difluoroenones and their corresponding *E* and *Z* isomers were observed. These observations showed that the reactivity of aryl and alkyl β-diketones with Deoxofluor are very similar. All of the β-diketone reactions occurred without the addition of HF or a substance which would permit generation of HF in situ.

In general, the reactions of β-diketones with DAST as a fluorinating reagent were similar However, with DAST

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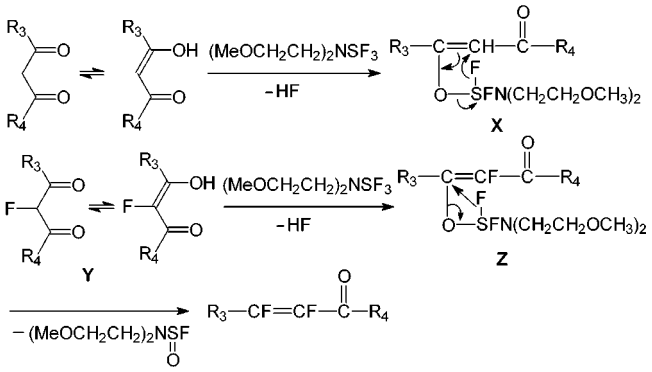
Scheme 3

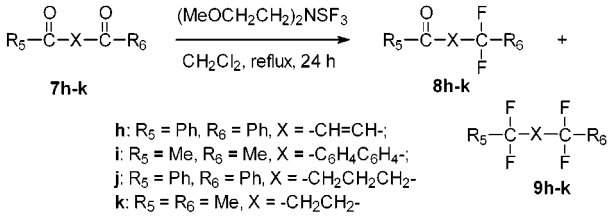


the yield of the vicinal difluoroenone from β-diketones was found to be low (40−60%) and reaction required 48−64 h to reach completion.[17] Since the structures of DAST and Deoxofluor are very similar, the reaction mechanism of vicinal difluoroenone formation from β-diketones with Deoxofluor would be expected to be essentially identical to that of DAST[18,19] (Scheme 3). It is well-known that β-diketones exist as an equilibrium mixture of keto and enol forms. The enol form of the β-diketone reacts with Deoxofluor to replace the hydroxyl proton eliminating HF and forming the intermediate **X**. Intramolecular fluorine transfer generates the α-fluorinated species **Y** that reacts in its enol form with Deoxofluor to produce an expected intermediate **Z**. Migration of fluorine to the β-carbon and elimination of $(MeOCH_2CH_2)_2NS(O)F$ gave the α,β-difluoroenone as a mixture of *E* and *Z* isomers as the final product.

Reaction of Deoxofluor with Other Diones. The diones where the two keto groups are separated by two methylene spacers or an aromatic moiety were also examined and their reactivity was found to be sluggish at 25 °C. However, when the reaction was carried at 60 °C for 24 h in the presence of a catalytic amount of HF (generated by adding a drop of ethanol from time to time), the difluoro products were obtained in moderate yields. These were slowly converted into the corresponding tetrafluoro products but in low yield. For example, in the presence of a catalytic amount of HF in dichloromethane at 60 °C, the reaction of *trans*-1,2-dibenzoylethylene (**7h)** with 3 equiv of Deoxofluor gave the difluoro compound (**8h**) in 66% and the tetrafluoro product (**9h**) in 10% yields. Reaction with 4,4′-diacetylbiphenyl (**7i)** was essentially analogous at 60 °C with three equivalents of Deoxofluor to produce mainly the difluoro derivative (**8i**) in 72% yield. Formation of the tetrafluoro compound (**9i**) was observed in ∼10% yield. Reaction of 1,3-dibenzoylpropane (**7j)** with Deoxofluor produced the corresponding difluoro product (**8j**) in 65% yield and the tetrafluoro product (**9j**) in traces as detected by GCMS. Acetonylacetone (**7k**) under similar reaction conditions produced mainly the difluoro product (**8k**) in 62% yield (Scheme 4).

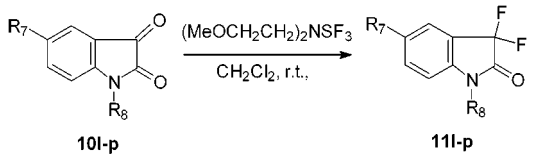
Reaction of Deoxofluor with Acyclic and Cyclic α-Ketoamides. Initially the reactions of acyclic α-keto amides, such as $PhCOCONEt_2$, were carried out with 3 equiv of Deoxofluor. After 24 h at reflux, in the presence

Scheme 4



h: R_5 = Ph, R_6 = Ph, X = -CH=CH-;
i: R_5 = Me, R_6 = Me, X = -$C_6H_4C_6H_4$-;
j: R_5 = Ph, R_6 = Ph, X = -$CH_2CH_2CH_2$-
k: R_5 = R_6 = Me, X = -CH_2CH_2-

Scheme 5



I: R_7 = H, R_8 = Ph; **m**: R_7 = H, R_8 = Me; **n**: R_7 = H, R_8 = CH_2Ph;
o: R_7 = F, R_8 = CH_2Ph; **p**: R_7 = OCF_3, R_8 = CH_2Ph

of a catalytic amount of HF, $PhCF_2CONEt_2$ was found in 20% yield based on GCMS. The yield of the product did not change even after 3 days at reflux. A similar lack of reactivity was observed when 1-(*N*-morpholino)-2-phenylethane-1,2-dione was used as a substrate. On the other hand, cyclic α-keto amides such as **10l** react with 3 equiv of Deoxofluor in the presence of a catalytic amount of HF at room temperature for 8 h to give **11l** in 90% isolated yield. Under identical reaction conditions, **10m**−**p** led to the formation of the corresponding difluoro amides (**11m**−**p**) in >90% isolated yields (Scheme 5). With DAST, **11m** was obtained in 95% yield.[7j] In both α-keto amides only the α-keto group was found to be reactive. This likely arises from deactivation of the carbonyl vicinal to the nitrogen atom by the donation of the lone pair of electrons from the nitrogen to the carbonyl carbon, thus reducing its electrophilic character.

In summary, in an effort to synthesize both difluoro and tetrafluoro derivatives, we have studied the reactions of α, β, and γ dicarbonyl compounds with Deoxofluor. With α-ketodiones, the products formed varied as a function of the substitutent groups. For example, in the case of benzil, the tetrafluoro product was achieved whereas when one phenyl group was replaced with methyl (1-phenyl-1,2-propanedione), the difluoro product was the major one even in the presence of excess Deoxofluor. This difference in products may arise from a decrease in the electrophilicity of the carbonyl group alpha to the methyl group. The reaction of β-diketones such as dibenzoylmethane or 2,4-pentanedione with Deoxofluor under mild conditions led to the formation of the vicinal difluoroenone as a mixture of *E* and *Z* isomers. In diones where the two carbonyl groups are separated by at least two or more bonds, the reaction was found to be slow and only a single carbonyl group was found to be fluorinated. Acyclic α-ketoamides with Deoxofluor reacted poorly whereas cyclic ones gave the corresponding difluoro products in very good yield. This is in agreement with the results obtained when AcOF was used as an electrophilic fluorinating agent with nonbenzylic acyclic enones.[7k] In both the cases, only the α-keto group of the amide was found to result in the corresponding difluoro amide. In general, with Deoxofluor reactions with various substrates appear to occur more rapidly and often give superior yields compare to DAST.

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Experimental Section

General Methods. All reactions were performed under dry nitrogen atmosphere. Diketo compounds were obtained from Aldrich and were used as received. Deoxofluor was a gift from Air Products. Products were purified by flash chromatography using a mixture of diethyl ether and pentane as an eluent. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded in $CDCl_3$ on a spectrometer operating at 200, 188, and 50 MHz, respectively. Chemical shifts are reported in ppm relative to the appropriate standard, $CFCl_3$ for ^{19}F and TMS for ^{1}H and ^{13}C NMR spectra. IR spectra were recorded using NaCl plates for neat liquids and KBr pellets for solids. Mass spectra were measured on an electron impact 70 ev spectrometer and high-resolution mass spectra (HRMS) were obtained using a suitable mass spectrometer.

Reaction of α-Diketones with Deoxofluor. In a typical experiment, α-diketones (2 mmol) (**1a**−**c**) were dissolved in dichloromethane (5 mL), Deoxofluor (6 mmol) was added at room temperature and followed by the addition of 2 drops of ethanol (to generate a catalytic amount of HF). The reaction mixture was heated at 60 °C for 24 h. Reaction was quenched by the slow addition of aqueous $NaHCO_3$ solution until effervescence was complete. The dichloromethane layer was separated and dried over anhydrous $MgSO_4$. It was filtered and removal of solvent afforded the product.

1,1,2.2-Tetrafluoro-1,2-diphenylethane (3a).[12a] Yield: 75%. Colorless solid. Mp 115 °C. IR (film): 1449, 1255, 1145, 1078, 933, 878, 751, 696, 657 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.3−7.5 (m, 10H). ^{19}F NMR ($CDCl_3$) δ: −112.26 (s, 4F). ^{13}C NMR ($CDCl_3$) δ: 116 (t, J_{C-F} = 251.5 Hz), 126.8, 126,9, 127.0, 127.2, 127.5, 128.0, 130.8. MS (EI) *m*/*z* (species, rel int): 254 (M^+, 12), 235 ($M^+ - F$, 1), 215 ($M^+ - HF_2$, 1), 127 ($PhCF_2^+$, 100), 77 (Ph^+, 17). HRMS: calcd for $C_{14}H_{10}F_4$ 254.0719, found 254.0704.

2,2-Difluoro-2-phenyl-acetophenone (2a).[15] Yield is trace as detected by MS. MS (EI) *m*/*z* (species, rel int) 232 (M^+, 1), 213 ($M^+ - F$, 1), 194 [($M^+ - 2F$, 1), 127 ($PhCF_2^+$, 10), 105 ($PhCO^+$, 100), 77 (Ph^+, 53).

1,1,2.2-Tetrafluoro-1,2-bis(4-methylphenyl)ethane (3b). Yield: 72%. Colorless solid. Mp: 130−131 °C. IR (film): 3050, 1450, 1261, 1140, 1078, 929, 875, 750, 696 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.34 (s, 6H), 7.0−7.5 (m, 8H). ^{19}F NMR ($CDCl_3$) δ: −111.56 (s, 4F). ^{13}C NMR ($CDCl_3$) δ: 116 (t, J_{CF} = 251.5 Hz), 126.8, 126,9, 127.0, 127.2, 127.5, 128.0, 130.8. MS (EI) *m*/*z* (species, rel int): 282 (M^+, 10), 263 ($M^+ - F$, 1), 243 ($M^+ - HF_2+$, 1], 228 [$M^+ - (HF_2^+ + Me)$, 1], 141 ($MeC_6H_4CF_2^+$, 100). Anal. Calcd for $C_{16}H_{14}F_4$: C, 68.06; H, 5.00. Found: C, 67.92; H, 4.89.

1,1-Difluoro-1-phenylpropanone (2c). Yield: 88%. Viscous liquid. IR (film): 1747, 1450, 1361, 1262, 1128, 1090, 1067, 969, 939, 762, 695 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −107.00 (s, 2F); ^{1}H NMR ($CDCl_3$) δ 2.29 (t, 3H, J = 1.7 Hz), 7.3−7.6 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 24, 115.8 (t, J_{CF} = 252 Hz), 125.5 (t, J = 6 Hz), 128.8, 131.0, 131.8 (t, J_{CCF} = 25.2 Hz), 197 (t, J_{CCF} = 32.6 Hz). MS (EI) *m*/*z* (species, rel int): 170 (M^+, 14), 155 ($M^+ - Me$, 1), 127 ($PhCF_2^+$, 100), 77 (Ph^+, 12), 43 (CH_3CO^+, 85).

1,1,2,2-Tetrafluoro-1-phenylpropane (3c).[13a] Yield is trace as detected by MS. MS (EI) *m*/*z* (species, rel int): 192 (M^+, 14), 177 ($M^+ - CH_3$, 1), 173 ($M^+ - F$, 1), 127 ($PhCF_2^+$, 100), 77 (Ph^+, 18).

Reaction of *β*-Diketones with Deoxofluor. In a typical experiment, *β*-diketones (2 mmol) (**4d**−**f**) were dissolved dichloromethane (5 mL) Deoxofluor (6 mmol) was added at room temperature. The reaction mixture was stirred at 25 °C for 5 h. The workup procedure was identical to that used for **1a**−**c**.

(*E*)-2,3-Difluoro-1,3-diphenyl-2-propen-1-one (5e). Yield: 42%. Viscous liquid. IR (film): 3060, 1685, 1597, 1495, 1448, 1348, 1273, 1175, 1136, 1099, 1029, 918, 845, 793, 767, 717, 688 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.4−8.0 (m, 10H). ^{19}F NMR ($CDCl_3$) δ −136.01 (d, 1F, J = 129 Hz), −154.93 (d, 1F, J = 129 Hz). ^{13}C NMR ($CDCl_3$) δ 127.1 (d, J = 8 Hz), 127.2 (d, J = 8 Hz), 128.4, 128.8 (d, 2 Hz), 129.0, 129.9, 131.3 (d, J = 2 Hz), 133.3, 134.9,138.8, 145.5 (dd, J = 250 Hz, J = 45 Hz), 154.4 (J = 250 Hz, J = 45 Hz), 194.5. MS (EI) *m*/*z* (species, rel int) 244 (M^+, 64), 243 ($M^+ - H$, 82), 167 ($M^+ - Ph$, 2), 105 ($PhCO^+$, 100), 77 (Ph^+, 59).

(*Z*)-2,3-Difluoro-1,3-diphenyl-2-propen-1-one (6e). Yield: 38%. Viscous liquid. IR (film): 3062, 1651, 1493, 1448, 1325, 1277, 1184, 1100, 977, 881, 847, 766, 717, 692, 658 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.2−7.9.0 (m, 10H). ^{19}F NMR ($CDCl_3$) δ: −108.56 (d, 1F, J = 8 Hz), −139.92 (d, 1F, J = 8 Hz). ^{13}C NMR ($CDCl_3$) δ: 128.2, 128.4, 128.8 (d, J = 3 Hz), 128.9 (d, J = 3 Hz), 129.4 (d, J = 4 Hz), 131.2, 133.5, 135.7, 143.1 (dd, J = 258 Hz, J = 18 Hz), 155.1 (J = 258 Hz, J = 18 Hz), 188.4. MS (EI) *m*/*z* (species, rel int): 244 (M^+, 62), 243 ($M^+ - H$, 91), 167 ($M^+ - Ph$, 3), 105 ($PhCO^+$, 100), 77 (Ph^+, 70). HRMS: calcd for $C_{15}H_{10}F_{20}$ 244.0700, found 244.0712.

(*E*)-1,2,3,3-Tetrafluoro-1,3-diphenylpropene. Yield: 10%. ^{1}H NMR ($CDCl_3$) δ: 7.1−7.7 (m, 10H). ^{19}F NMR ($CDCl_3$) δ: −97.25 (d, 1F, J = 23.5 Hz), −97.34 (d, 1F, J = 23.5 Hz), −148.35 (doublet of triplet, 1F, J = 129 Hz, J = 24 Hz), −161.33 (doublet of triplet, 1F, J = 129, 17 Hz). MS (EI) *m*/*z* (species, rel int): 266 (M^+, 100), 246 ($M^+ - HF$, 15), 188 [$M^+ - (Ph + H)$, 47], 169 [$M^+ - (Ph + HF)$, 29], 127 ($PhCF_2^+$, 65), 77 (Ph^+, 20). HRMS: calcd for $C_{15}H_{10}F_4$ 266.0719, found 266.0733.

(*E*)-3,4-Difluoro-3-penten-2-one (5f).[17] Yield: 39%. Viscous liquid. ^{1}H NMR ($CDCl_3$) δ: 2.0−2.3 (m, 6H). ^{19}F NMR ($CDCl_3$) δ: −116.55 (broad multiplet, 1F, J = 129 Hz), −163.33 (broad doublet, 1F, J = 127 Hz) [lit.[17] −117.70 (broad, 1F, J = 130 Hz), −162.90 (broad, 1F, J = 128 Hz)]. MS (EI) *m*/*z* (species, rel int) 120 (M^+, 35), 105 ($M^+ - Me$, 30), 77 ($M^+ - COMe$, 24), 43 ($MeCO^+$, 100).

(*Z*)-3,4-Difluoro-3-penten-2-one (6f).[17] Yield: 33%. Viscous liquid. ^{1}H NMR ($CDCl_3$) δ: 2.0−2.3 (m, 6H). ^{19}F NMR ($CDCl_3$) δ: −99.83 (q, 1F, J = 18 Hz), −151.24 (m, 1F) (lit.[17] −99.95 (q 1F, J = 19 Hz), −151.20 (m, 1F). MS (EI) *m*/*z* (species, rel int): 120 (M^+, 32), 105 ($M^+ - Me$, 38), 77 ($M^+ - COMe$, 20), 43 ($MeCO^+$, 100).

(*E*)-2,3-Difluoro-1-phenyl-2-buten-1-one (5g).[17] Yield: 25% (based on GCMS). ^{19}F NMR ($CDCl_3$) δ: −118.48 (doublet of quartet, 1F, J = 128 Hz, 17 Hz), −159.58 (quartet of doublet, 1F, J = 128 Hz, 6.5 Hz). MS (EI) *m*/*z* (species, rel int): 182 (M^+, 41), 181 ($M^+ - H$, 24), 162 ($M^+ - Me$, 5), 105 ($PhCO^+$, 100), 77 (Ph^+, 93).

(*Z*)-2,3-Difluoro-1-phenyl-2-buten-1-one (6g).[17] Yield: 30%. Viscous liquid. ^{1}H NMR ($CDCl_3$) δ: 2.36 (dd, 3H, J = 20 Hz, J = 4.5 Hz), 7.3−8.0 (m, 5H). ^{19}F NMR ($CDCl_3$) δ: −99.16 (q, 1F, J = 20 Hz), −146.36 (broad singlet, 1F, J = 7 Hz). MS (EI) *m*/*z* (species, rel int): 182 (M^+, 57), 181 ($M^+ - H$, 33), 167 ($M^+ - Me$, 6), 163 ($M^+ - F$, 3), 162 ($M^+ - HF$, 8), 105 ($PhCO^+$, 100), 77 (Ph^+, 95).

Reaction of Other Diketones with Deoxofluor. Reactions of **7h**−**k** with Deoxofluor were carried out under conditions identical to those used for **1a**−**c**.

***trans*-4,4-Difluoro-1,4-diphenyl-2-butene-1-one (8h).** Yield: 66%. Viscous liquid. IR (film): 2970, 1680, 1638, 1597, 1450, 1329, 1285, 1257, 1188, 1043, 1015, 963, 773, 694 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −95.14 (d, 2F, J = 10.5 Hz). ^{1}H NMR ($CDCl_3$) δ: 7.00 (t, 1H, J = 10.5 Hz), 6.99 (triplet of doublets, 1H), 7.25−8.0 (m, 9H). ^{13}C NMR ($CDCl_3$) δ: 118.8 (t, J = 239 Hz), 125.3 (t, J = 6 Hz), 127.2 (t, J = 7 Hz), 128.7, 128.8, 128.9, 130.5 (t, J = 2 Hz), 189.2. MS (EI) *m*/*z* (species, rel int): 258 (M^+, 6), 238 ($M^+ - HF$, 2), 131 ($M^+ - PhCF_2$, 36), 127 ($PhCF_2$, 13), 105 ($PhCO^+$, 100), 77 (Ph^+, 40). HRMS: calcd for $C_{16}H_{12}F_2O$ 258.0856, found 258.0849.

***trans*-1,4-Diphenyl-1,1,4,4-tetrafluoro-2-butene (9h).** Yield: 10%. Viscous liquid. ^{19}F NMR ($CDCl_3$) δ: −93.86 (d, J = 4 Hz). ^{1}H NMR ($CDCl_3$) δ: 7.2−7.5 (m, 2H). MS (EI) *m*/*z* (species, rel int): 280 (M^+, 10), 260 ($M^+ - HF$, 1), 241 [$M^+ - (HF + F)$, 2], 153 ($M^+ - PhCF_2$, 40), 133 [$M^+ - (PhCF_2 + HF)$, 32], 127($PhCF_2$, 100), 77 (Ph^+, 16).

4-Acetyl-4′-(1,1-difluoroethyl)biphenyl (8i). Yield: 72%. Colorless solid. Mp: 149 °C. IR (film): 2965, 1677, 1395, 1174, 1122, 910, 820, 730 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −87.75 (q, 2F, j = 18 Hz). ^{1}H NMR ($CDCl_3$) δ: 1.90 (t, 3H, J = 18 Hz), 2.63 (s, 3H), 7.5−7.7 (m, 8H). ^{13}C NMR ($CDCl_3$) δ: 25.9 (t, J = 29.5

Hz), 26.6, 121.1 (t, J = 237 Hx), 125.2 (6 hz), 127.2, 127.3, 128.9, 136.2, 137.9 (t, J = 26.5), 141.2, 144.7, 197.62. MS (EI) m/z (species, rel int): 260 (M^+, 38), 245 (M^+ − Me, 100), 225 (M^+ − (Me + HF), 3], 152 ($C_6H_4C_6H_4^+$, 37), 2], 65 ($MeCF_2^+$, 10), 43 ($MeCO^+$, 18). Anal. Calcd for $C_{16}H_{14}F_2O$: C, 73.82; H, 5.42. Found: C, 73.69; H, 5.47.

4,4′-Bis(1,1-Difluoroethyl)biphenyl (9i). Yield: 10%. Colorless solid. Mp: 140 °C. IR (film) 2964, 1390, 1296, 1261, 1166, 1016, 912, 819, 731 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −112.55 (s, 2F). ^{1}H NMR ($CDCl_3$) δ: 3.20 (s, 3H), 6.87 (d, 1H, J = 8 Hz), 7.16 (t, 1H, J = 8 Hz), 7.4 − 7.6 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 121.7 (t, J = 237 Hz), 125.2 (t, J = 6 Hz), 127.2, 137.5 (t, J = 27 Hz), 141.7. MS (EI) m/z (species, rel int): 282 (M^+, 52), 267 (M^+ − Me, 100), 263 (M^+ − F), 4), 247 (M^+ − Me + HF, 16), 152 [M^+ − (2MeCF$_2$), 4], 126 ($C_6H_4CF_2^+$, 33), 65 ($MeCF_2^+$, 6). HRMS: calcd for $C_{16}H_{14}F_4$ 282.1032, found 282.1017.

5,5-Difluoro-1,5-diphenylpentan-1-one (8j). Yield: 65%. Viscous liquid. IR (film): 3000, 1685, 1597, 1450, 1325, 1269, 1179, 970, 761, 696 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −95.55 (t, 2F, J = 14 Hz). ^{1}H NMR ($CDCl_3$) δ: 1.85 (m, 2H), 2.19 (m, 2H), 2.96 (t, 2H, J = 7 Hz), 7.2 − 8.0 (m, 10H) ^{13}C NMR ($CDCl_3$) δ: 17.2 (t, J = 4 Hz), 37.62, 28.2 (t, J = 27.5 Hz), 123.0 (t, J = 238 Hz), 124 9 (t, J = 6 Hz), 127.9, 128.4, 129.7, 133.1, 136.8, 199.2, 189.2. MS (EI) m/z (species, rel int): 274 (M^+, 1), 254 (M^+ − HF, 20), 234 (M^+ − 2HF, 2), 127 ($PhCF_2^+$, 8), 105 ($PhCO^+$, 100), 77 (Ph^+, 35). Anal. Calcd for $C_{17}H_{16}F_2O$: C, 74.44; H, 5.88. Found: C, 74.81; H, 5.95.

1,1,5,5-Tetrafluoro-1,5-diphenylpentane (9j). Yield is a trace as detected by GCMS. MS (EI) m/z (species, rel int): 296 (M^+, 17), 276 (M^+ − HF, 20), 256 (M^+ − 2HF, 1), 169 (M^+ − $PhCF_2$, 2), 127 ($PhCF_2$, 100), 77 (Ph^+, 8).

5,5-Difluorohexan-2-one (8k). Yield: 62%. Colorless liquid. ^{19}F NMR ($CDCl_3$) δ: −92.83 (m, 2F). ^{1}H NMR ($CDCl_3$) δ: 2.01 (m, 4H), 2.62 (t, 3H, J = 6.7 Hz), 2.65 (s, 3H). MS (EI) m/z (species, rel int): 136 (M^+, 2), 121 (M^+ − Me, 6), 65 ($MeCF_2^+$, 13), 43 ($MeCO^+$, 100).

Preparation of Acyclic Amides (10n−p). In a typical procedure, unprotected isatin (5 mmol) was dissolved in THF (20 mL), and sodium hydride (5 mmol) was added at −20 °C. The reaction mixture was warmed slowly to room temperature and stirred for 3 h. To the mixture was added benzyl bromide (5 mmol) dropwise at room temperature and the resulting mixture stirred for 24 h. Methylene chloride (20 mL) was added, and the solution was washed with water three times. The dichloromethane layer was dried over magnesium sulfate and filtered. The solvent was removed at reduced pressure.

***N*-Benzylisatin (10n):** Yield: 85%. Orange solid. Mp: 126−127 °C. IR (film): 1735, 1612, 1467, 1350, 1177, 1093, 813, 753, 695 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 4.91 (s, 2H), 6.5−7.7 (m, 9H). ^{13}C NMR ($CDCl_3$) δ: 44.0, 110.9, 117.7, 123.8, 125.4, 127.4, 128.1, 129.0, 134.5, 138.2, 150.7, 158.2, 183.2. MS (EI) m/z (species, rel int): 337 (M^+, 68), 180 [M^+ − (COCO + H), 57], 146 (M^+ − $PhCH_2$,100), 91 ($PhCH_2^+$, 67) 77 (Ph^+, 22). Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67. Found: C, 75.52; H, 4.47.

***N*-Benzyl-5-fluoroisatin (10o).** Yield: 80%. Yellow solid. Mp: 130−133 °C. IR (film): 1737, 1620, 1483, 1330, 1264, 1171, 1019, 887, 825, 781, 696 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −118.0 (s, 1F). ^{1}H NMR ($CDCl_3$) δ: 4.87 (s, 2H), 6.4−7.5 (m, 9H). MS (EI) m/z (species, rel int): 255 (M^+, 75), 198 [M^+ − (2CO + H), 48], 164 (M^+ − $PhCH_2$, 100), 108 [M^+ − (2CO + $PhCH_2$), 20], 91 ($PhCH_2$, 80). Anal. Calcd for $C_{15}H_{10}FNO_2$: C, 70.58; H, 3.95. Found: C, 69.68; H, 3.93.

***N*-Benzyl-5-trifluoromethoxyisatin (10p).** Yield: 82%. Yellow solid. Mp: 100−102 °C. IR (film): 1740, 1622, 1483, 1334, 1259, 1174, 1024, 901, 832, 792, 728 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −58.74 (s, 3F). ^{1}H NMR ($CDCl_3$) δ: 4.88 (s, 2H), 6.5−7.5 (m, 9H). ^{13}C NMR ($CDCl_3$) δ: 44.5, 112.3, 118.6, 120.2 (q, J_{CF} = 298 Hz), 127.6, 128.5, 129.3, 131.2, 134.1, 145.5, 149.17, 158.1, 182.4. MS (EI) m/z (species, rel int): 321 (M^+, 74), 264 (M^+ − 3F, 29), 230 (M^+ − $PhCH_2$, 85), 91 ($PhCH_2$, 100), 69 (CF_3^+, 27). Anal. Calcd for $C_{16}H_{10}F_3NO_3$: C, 59.82; H, 3.14. Found: C, 59.50; H, 3.13.

Reaction of α-Keto Amides with Deoxofluor. In a typical experiment, α-ketoamides (2 mmol) (**10l−p**) were dissolved in dichloromethane (5 mL), and Deoxofluor (6 mmol) was added at room temperature followed by the addition of 2 drops of ethanol (to generate a catalytic amount of HF). The reaction mixture was stirred at room temperature for 8 h. Reaction was quenched by the slow addition of aqueous $NaHCO_3$ solution until the effervescence was completed. The dichloromethane layer was separated, dried over anhydrous $MgSO_4$, and removed under reduced pressure.

1-Phenyl-3,3-difluorooxindole (11l). Yield: 90%. Light yellow solid. Mp: 89−90 °C. IR (film): 1759, 1619, 1501, 1469, 1376, 1300, 1126, 1085, 1033, 1001, 945, 840, 763, 700 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −110.85 (s, 2F). ^{1}H NMR ($CDCl_3$) δ: 6.8−7.7 (m, 9H). ^{13}C NMR ($CDCl_3$) δ: 110.5 (t, J_{CF} = 248 Hz), 112.7, 124.3, 126.2, 128.9, 129.9, 132.6, 133.4, 144.2. MS (EI) m/z (species, rel int): 245 (M^+, 100), 216 [M^+ − (CO + H), 31], 198 [M^+ − (CO + F), 94], 77 (Ph^+, 13). HRMS: calcd for $C_{14}H_9F_2NO$ 245.0652, found 245.0661.

1-Methyl-3,3-difluorooxindole (11m).[7j] Yield: 90%. Light yellow solid. Mp: 89−90 °C. IR (film): 3060, 1758, 1622, 1473, 1381, 1350, 1251, 1114, 1076, 1022, 940, 856, 761, 698 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −112.55 (s, 2F). ^{1}H NMR ($CDCl_3$) δ: 3.20 (s, 3H), 6.87 (d, 1H, J = 8 Hz), 7.16 (t, 1H, J = 8 Hz), 7.4−7.6 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 26.30, 109.4, 123.9, 124.6, 123.5, 143.9, 165.3. MS (EI) m/z (species, rel int): 183 (M^+, 100), 168 (M^+ − Me, 8), 164 (M^+ − F, 5), 155 (M^+ − CO, 27), 154 [M^+ − (CO + H), 44], 136 [M^+ − (CO + F), 20], 135 [M^+ − (CO + F + H), 30]. HRMS: calcd for $C_9H_7F_2NO$ 183.0496, found 183.0504.

1-Benzyl-3,3-difluorooxindole (11n). Yield: 92%. Yellow solid. Mp: 76−77 °C. IR (film): 1740, 1622, 1483, 1334, 1259, 1174, 1024, 901, 832, 792, 728 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −111.93 (s, 2F). ^{1}H NMR ($CDCl_3$) δ: 4.87 (s, 2H), 6.4−7.6 (m, 9H). ^{13}C NMR ($CDCl_3$) δ: 42.5, 110.2, (t, J_{CF} = 248 Hz), 123.8, 124.7, 127.2, 128.1, 129.0, 134.2, 149.3. MS (EI) m/z (species, rel int) 259 (M^+, 44), 239 (M^+ − HF, 1), 168 (M^+ − $PhCH_2$, 20), 91 ($PhCH_2^+$, 100), 77 (Ph^+, 2). Anal. Calcd for $C_{15}H_{11}F_2NO$: C, 69.48; H, 4.28. Found: C, 69.56; H, 4.12.

***N*-Benzyl-3,3-difluoro-5-fluorooxindole (11o).** Yield: 88%. Yellow solid. Mp: 58−59 °C. IR (film): 3060, 1753, 1625, 1490, 1371, 1350, 1294, 1263, 1199, 1179, 1138, 1091, 1018, 972, 881, 820, 972, 756, 734, 698 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −112.06 (s, 2F), −117.60 (s, 1F). ^{1}H NMR ($CDCl_3$) δ: 4.86 (s, 2H), 6.4−7.7 (m, 8H). ^{13}C NMR ($CDCl_3$) δ: 44.0, 110.4 (t, J = 248 Hz), 111.6, 111.8, 112.5, 113.1, 119.7, 120.2, 121.2 (t, J = 8 Hz), 127.2, 128.2, 129.1, 133.9, 139.0, 156.9 (t, J = 2.5 Hz), 161.8 (t, J = 2.5 Hz), 165.2 (t, J = 30 Hz). MS (EI) m/z (species, rel int): 277 (M^+, 19), 248 [M^+ − (CO + H), 1], 186 (M^+ − $PhCH_2$, 2), 91 ($PhCH_2$, 100). HRMS: calcd for $C_{15}H_{10}F_3NO$ 277.0714, found 277.0699.

***N*-Benzyl-3,3-difluoro-5-trifluoromethoxyoxindole (11p).** Yield: 90%. Yellow solid. Mp: 85−86 °C. IR (film): 3067, 1759, 1628, 1489, 1371, 1292, 1261, 1182, 1059, 1020, 974, 895, 829, 799, 699 cm^{-1}.^{19}F NMR ($CDCl_3$) δ: −58.74 (s, 3F), −112.18 (s, 2F). ^{1}H NMR ($CDCl_3$) δ: 4.88 (s, 2H), 6.5−7.5 (m, 8H). ^{13}C NMR ($CDCl_3$) δ: 44.1, 110.2 (t, J = 248 Hz), 111.6, 116.5 (t, J = 250 Hz), 118.6, 121.2 (t, J = 8 Hz), 126.6, 127.2, 128.3, 129.1, 133.7, 141.9(t, J = 2.5 Hz), 145.5, 165.0 (t, J = 30 Hz). MS (EI) m/z (species, rel int): 343 (M^+, 14), 314 [M^+ − (CO + H), 1], 252 (M^+ − $PhCH_2$, 2), 91 ($PhCH_2$, 100). Anal. Calcd for $C_{16}H_{10}F_5NO_2$: C, 55.97; H, 2.94. Found: C, 55.58; H, 2.81.

Acknowledgment. This work was supported by the National Science Foundation (Grant No. CHE-9720365) and by the Petroleum Research Fund, administered by the ACS. We are grateful to Dr. G. Knerr for obtaining high-resolution mass spectra. The generosity of Air Products for the gift of Deoxofluor is deeply appreciated.

JO0157674