BrF_3, an Underutilized Reagent in Organic Chemistry: A Novel C−C−N to C−N−C Rearrangement

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Little is known about bromine trifluoride in organic chemistry. Under the right conditions, it can be a useful tool and generate a new and unprecedented chemistry. Thus, when reacted with oxime methyl ethers of α-ketoesters, BrF_3 was able to convert the oxime group into a CF_2 group and through a new type of rearrangement cause a shift of the carboxylate group to the nitrogen atom. The novel structure of the α,α-difluorocarbamate was also proven by ^{15}N NMR as demonstrated for compounds **3**, **8**, **9**, **12**, **15**, and **18**. Another novel "double rearrangement" was observed during the formation of **19**. Dynamic ^{19}F NMR experiments indicate a high nitrogen inversion-rotation (NIR) barrier for these novel carbamates of about 12.5 kcal/mol.

Bromine trifluoride has been extensively used for the synthesis of several modern anesthetics such as desflurane,[1] sevoflurane,[2] and the promising 1,2-bis(fluoromethoxy)-1,1,3,3,3-pentafluoropropane (BFPP).[3] Still, it is seldom found in the organic chemistry literature, and the existing research concentrates on some oxidative[4] and tertiary[5] fluorinations as well as on efficient electrophilic bromination of very deactivated aromatic rings.[6] It also resembles IF[7] in its ability to transform carbonyls, via the corresponding hydrazones, to the CF_2 group, but it is much more potent than iodine monofluoride, and we were able for the first time to convert carbonyls to the CF_2 group also through the corresponding azines, DNPs,[8] thioesters,[9] dithioesters,[10] and more. Recently, we have used bromine trifluoride also for constructing various aliphatic and aromatic trifluoromethyl ethers from alcohols and their respective xanthates.[11]

Unlike IF, bromine trifluoride can also react with oxime methyl ethers made with methoxylamine which in general are more soluble than most other types of hydrazones.[8] Methoxylamine is also somewhat more selective than hydrazines in differentiating between two carbonyls in molecules such as α-ketoesters and react preferentially with the ketonic one. We thought that there is a chance of developing a new reaction pathway toward the preparation of α,α-difluorocarboxylic acid derivatives which are important as enzyme inhibitors.[12] Additional support for the notion of using oxime methyl ethers α to a carboxylic ester was derived from the fact that BrF_3 reacts best when there are at least two electron-donor groups close to each other in the target molecule.[13] Such donors serve as complexing anchors to the electron-depleted bromine atom bringing the reagent close to the reacting site and preventing it from rapid, undiscriminating radical attacks on most CH bonds, attacks for which BrF_3 is feared and known for.[14]

There are several literature preparations for pyruvic acid derivatives starting with acetylene compounds,[15] *β*-keto sulfur derivatives,[16] dimethyloxalate,[17] and more. In the present study, we have prepared such substrates also by direct α-hydroxylation using the $HOF{\cdot}CH_3CN$ complex, a novel method we recently published in memory of the late Prof. Barton,[18] followed by oxidation with CrO_3.

To avoid volatility problems, we have prepared the 1,1,1-trichloroethyl pyruvate (**1**) and reacted it with methoxylamine forming the corresponding oxime methyl ether **2** (Scheme 1). This material was subject to a reaction with 1.5 mol/equiv of BrF_3 forming a product in 60% yield. To our surprise, however, this product was not the anticipated α,α-difluoroester, but proved eventually to be *N*-(1,1-difluoroethyl)-*N*-methoxy-2,2,2-trichloroethyl carbamate (**3**). The product's most conspicuous spectral feature was the ^{19}F NMR, which showed a broad signal at −77.1 ppm, $W_{h/2} = 85$ Hz. This chemical shift is in sharp contrast to the α,α-difluoroester moiety found

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(1) Rozov, L. A.; Huang, C.; Halpern, D. F.; Vernice, G. G. U.S. Patent 5,283,372, 1994.
(2) Halpern, D. F.; Robin, M. L. U.S. Patent 4,996,371, 1991.
(3) Ruzicka, J. A.; Hrdy, J. B.; Baker, M. T. *J. Fluorine Chem.* **1995**, *75*, 191.
(4) Soelch, R. R.; Mauer, G. W.; Lemal, D. M. *J. Org. Chem.* **1985**, *50*, 5845.
(5) Boguslavskaya, L. S.; Kartashov, A. V.; Chuvatkin, N. N. *Russ. Chem. Rev.* **1990**, *59*, 501 (translated from *Uspekhi Khimii* **1990**, *59*, 865.)
(6) Rozen, S.; Lerman, O. *J. Org. Chem.* **1993**, *58*, 239.
(7) Rozen, S.; Zamir, D. *J. Org. Chem.* **1991**, *56*, 4695.
(8) Rozen, S.; Mishani, E.; Bar-Haim, A. *J. Org. Chem.* **1994**, *59*, 2918.
(9) Rozen, S.; Mishani, E. *J. Chem. Soc., Chem. Commun.* **1993**, 1761.
(10) Rozen, S.; Mishani, E. *J. Chem. Soc., Chem. Commun.* **1994**, 2081.
(11) Ben-David, I.; Rechavi, D.; Mishani, E.; Rozen, S. *J. Fluorine Chem.* **1999**, *97*, 75.
(12) See, for example: Tsukamoto, T.; Haile, W. H.; McGuire, J. J.; Coward, J. K. *J. Med. Chem.* **1996**, *39*, 2536.
(13) Unpublished results.
(14) Bromine trifluoride can react violently with hexane or other similar molecules via radical reactions.
(15) Muller, P.; Godoy, J. *Tetrahedron Lett.* **1982**, *23*, 3661.
(16) Fortes, C. C.; Souto, C. R. O.; Okino, E. A. *Synth. Commun.* **1991**. *21*, 2045.
(17) Itoh, K.; Kori, M.; Inada, Y.; Nishikawa, K.; Kawamatsu, Y.; Sugihara, H. *Chem. Pharm. Bull.* **1986**, *34*, 1128.
(18) Dayan, S.; Bareket, Y.; Rozen, S. *Tetrahedron* **1999**, *55*, 3657.

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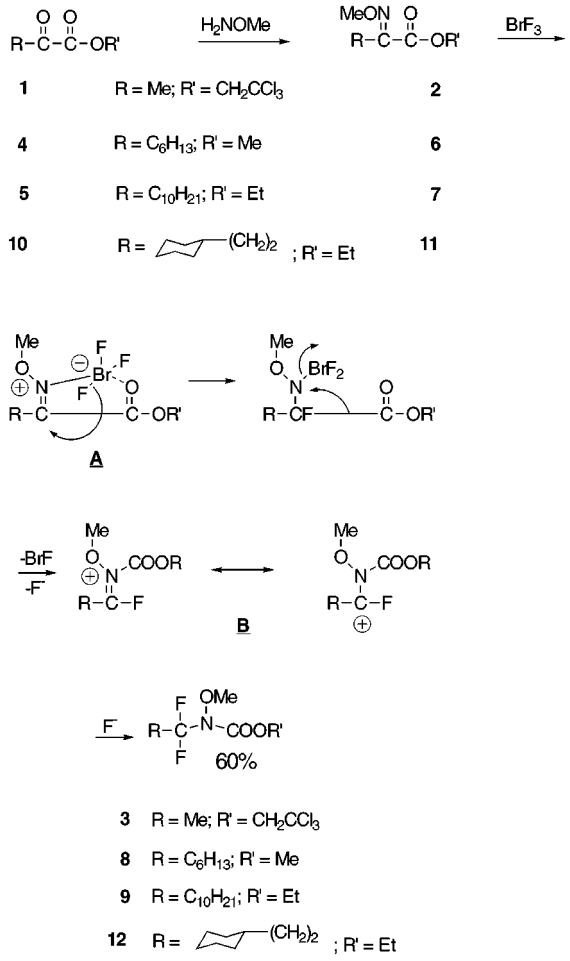
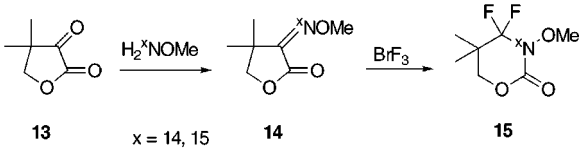
Scheme 1



invariably between −103 and −107 ppm.[19] Although it will be discussed later, we would like to mention now that at higher temperature (+68 °C) this signal turned into a quartet at −74.5 ppm (J = 16 Hz) indicating a presence of a CH_3CF_2 moiety. The ^{1}H NMR spectrum clearly shows a triplet at 2.07 ppm (J = 16 Hz) for the above group and two singlets for the methoxy group and the 1,1,1-trichloroethoxy group at 3.90 and 4.85 ppm, respectively. The ^{13}C NMR shows a triplet at 121.9 ppm (CF_2, $^1J_{CF}$ = 250 Hz), while the carbonyl signal at 152.8 ppm has only a small coupling constant (t, $^3J_{CF}$ = 2.5 Hz) indicating that it is separated by one atom from the CF_2 group.

Since the product and the reaction leading to it are not trivial and involve an unprecedented ester group migration, we looked for additional proofs beyond the highlighted above spectral properties, high-resolution MS, and microanalysis which are in excellent agreement with the proposed structure of **3**. One such support could have been provided by ^{15}N NMR, but even with a highly concentrated sample, we were unable to detect any useful signal. We therefore repeated the synthesis with 25% ^{15}N-enriched H_2NOMe prepared from $Na^{15}NO_2$, according to a known procedure.[20] The ^{15}N NMR of the enriched product, $CH_3CF_2{}^{15}N(OMe)COOCH_2CCl_3$ (**3**), indeed showed a triplet at −197 ppm (CH_3NO_2 serving as reference) with $^2J_{NF}$ of 19 Hz, placing the nitrogen atom in the vicinity of the CF_2 group. The ^{15}N atom in its turn was responsible for the additional splitting of the vicinal carbons in the ^{13}C NMR 121.9 (CF_2, dt, $^1J_{CF}$ = 250 Hz, $^1J_{CN}$ = 13.5 Hz) and 152.8 ppm (*C*O, dt, $^3J_{CF}$ = 2.5 Hz, $^1J_{CN}$ = 22.5 Hz) in accordance with the proposed structure.

Scheme 2



The formation of this novel type of molecule[21] can be explained by the tendency of BrF_3 to complex with two electron rich sites, prior to the nucleophilic attack of the fluoride on the oxime carbon atom, intermediate **A**. This is followed by the formation of intermediate **B**, which derives its relative stability from being a fluorocarbocationic one (Scheme 1). It should be noted that adding radical chain inhibitors such as dinitrobenzene, the presence of oxygen, or conducting the reaction under complete darkness does not change the outcome, reducing the possibility of any radical involving mechanism.

This reaction is not limited to alkyl pyruvates, and other α-keto esters behave similarly. Methyl 2-ketooctanoate (**4**) and ethyl 2-ketododecanoate (**5**) were converted to their methyl oxime ethers **6** and **7**, respectively, and then reacted with BrF_3. In both cases, the reactions proceeded smoothly, and the products were identified as *N*-(1,1-difluoroheptyl)-*N*-methoxy methyl carbamate (**8**) and *N*-(1,1-difluoroundecyl)-*N*-methoxy ethyl carbamate (**9**). Alicyclic compounds containing tertiary hydrogens also gave the rearranged products, despite the fact that they are more sensitive to electrophilic attacks.[22] Thus, ethyl 4-cyclohexyl-2-ketobutanoate (**10**) was transformed via its methyl oxime ether **11** to *N*-(3-cyclohexyl-1,1-difluoropropyl)-*N*-methoxy ethyl carbamate (**12**) in 45% yield.

An interesting case involving a ring enlargement is the reaction of dihydro-4,4-dimethyl-2,3-furandione (**13**) (Scheme 2). We made the mono-oxime methyl ether (**14**) with both ^{14}N and ^{15}N isotopes and reacted it with BrF_3. The product was identified as a six member lactone, 4,4-difluoro-4,5-dihydro-5,5-dimethyl-*N*-methoxyoxazine-2-one (**15**) whose ^{15}N NMR shows a peak at −203 ppm (t, $^2J_{NF}$ = 18 Hz).

Dimethyl 2-oxoglutarate (**16**) provided us an interesting insight of the rearrangement process. When its methyl oxime ether **17** (prepared with both isotopes ^{14}N and ^{15}N) was reacted with bromine trifluoride, two main products were isolated and purified. The minor one was the expected by now rearranged product *N*-(3-carbomethoxy-1,1-difluoropropyl)-*N*-methoxy methyl carbamate (**18**), an oil at room temperature. In contrast to all other products described so far, however, the major product did crystallized at room temperature, and so apart from the usual battery of analytical tests it was also subjected to an X-ray analysis.[23] All results point toward yet another rearranged product, *N*-(4,4-difluoro-4-methoxybutanoyl)-*N*-methoxy methyl carbamate (**19**) (Scheme 3).

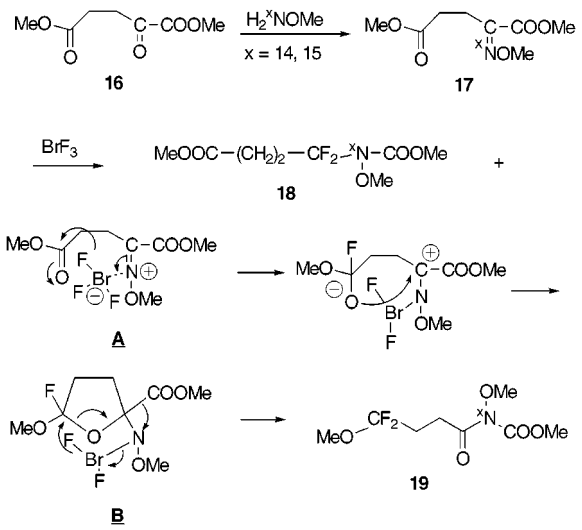
(19) See for example Yang, Z. Y.; Burton, D. J. *J. Org. Chem.* **1991**, *56*, 5125.

(20) Hjeds, H. *Acta Chem. Scand.* **1965**, *19*, 1764.

(21) A somewhat similar family of compounds, $CF_3N(X)COF$ (X = OCF_3, OMe and alike), had been synthesized by treating perfluoro oxaziridines with nucleophiles: Sekiya, S.; DesMarteau, D. D. *J. Fluorine Chem.* **1980**, *15*, 183.

(22) Rozen, S.; Gal, C. *J. Org. Chem.* **1987**, *52*, 2769 and 4928.

Scheme 3



As has already been stated, the key step for ionic reactions with BrF_3 is its complexation with electron donors. There are two favorable ways for such groups in **17** to attract the electrophilic bromine atom through the participation of the oxime moiety with either the vicinal or the more remote carbomethoxy group. While the first pathway gives rise to the expected **18**, the very accommodating space created by the second possibility encourages the formation of the intermediate **A** (Scheme 3). The creation of the five-membered ring (**B**) and its consecutive opening are responsible for the overall double rearrangement of both the keto oxygen and the carboxylic group to give the unexpected **19**.[24]

In most products described so far, the nitrogen atom is surrounded by three highly electronegative groups namely CF_2, OMe, and COOR. Such a situation is usually responsible for high nitrogen inversion-rotation (NIR) barriers. These barriers turn the two geminal fluorine atoms into diastereotopic ones and indeed, they are not equivalent at room temperature. The ^{19}F NMR spectrum of **8** may serve as an illustrative example. At +20 °C we find two signals, one for each fluorine atom, at −81.5 (bs, $W_{h/2}$ = 960 Hz) and at −85.9 ppm (bs, $W_{h/2}$ = 950 Hz). Cooling the sample to −4 °C shifts these signals slightly to −80.7 and −86.8 ppm, but with narrower $W_{h/2}$: 445 and 427 Hz correspondingly. Further cooling to −53 °C decreases the inversion-rotation around the nitrogen atom to such an extent that one fluorine atom resonates at −79.3 ppm (ddd, J_{FF} = 201 Hz, $J_{H(1)F}$ = 12 Hz, $J_{H(2)F}$ = 5 Hz) while the other at −87.7 ppm (dt, J_{FF} = 201 Hz, J_{HF} = 20 Hz). Heating the sample, on the other hand, reveals a coalescence at +31 °C (−82.8 ppm, bs, $W_{h/2}$ = 2000 Hz). Higher temperatures reduces the effect of the NIR barrier and at +68 °C the two fluorine atoms resonate at −82.5 ppm (bs, $W_{h/2}$ = 230 Hz). It requires heating to 154 °C to achieve a complete free inversion-rotation around the nitrogen atom and the ^{19}F NMR spectrum shows one signal at −82.6 ppm (t, J = 14.5 Hz). These data and further measurements at the temperature range between −53 and +154 °C enabled us to calculate[25] the $\Delta G^{\ddagger}$ of the NIR barrier for **8** to be 12.4 ± 0.1 kcal/mol, which indeed is considered to be relatively high.[26] Further variable-temperature ^{19}F NMR studies for compounds **12** and **18** reveal similar $\Delta G^{\ddagger}$ for the NIR barrier of 12.6 and 12.4 kcal/mol, respectively.

In conclusion, it has been demonstrated that BrF_3 can be used in organic chemistry without destroying sensitive molecules and perform "counter intuitive" novel reactions and even "double rearrangements" as in the case of the formation of **19**.

Experimental Section

^1H, ^{13}C, and ^{15}N NMR spectra were recorded with $CDCl_3$ as a solvent and Me_4Si as an internal standard. ^1H and ^{13}C NMR were measured at 500 and 125.76 MHz, respectively. The ^{15}N NMR spectra were measured at 50.68 MHz and are reported in ppm upfield from CH_3NO_2 which also served as an external standard. The ^{19}F NMR spectra were measured at 338.8 MHz and are reported in parts per million upfield from $CFCl_3$ serving as an internal standard. Variable temperature experiments were recorded with acetone as a solvent for low temperatures and DMSO for high ones. High-resolution mass spectra were measured with a VG micromass 7070H instrument. IR spectra were recorded in $CHCl_3$ solution or in KBr pellets on a FTIR spectrophotometer. A Nonius Kappa CCD diffractometer with Mo Kα radiation (λ = 0.7107 Å) was used for the crystal structure elucidation.

Preparation and Handling of BrF_3. Although commercially available, we prepare our own BrF_3 by simply passing 0.58 mol of pure fluorine through 0.2 mol of bromine placed in a copper reactor at 0 to +10 °C. When no excess of bromine is present, the BrF_3 obtained is a pale yellow liquid that freezes at 7−9 °C and has a density of 2.5.[27] At that reaction temperature, the higher oxidation state derivative − BrF_5 will not form in any appreciable amount,[28] although we always use a small excess of bromine, thereby keeping the reagent from disproportionation to BrF_5. This is also responsible for the reddish coloration of the reagent. We store the reagent in Teflon containers for long periods, but all reactions were carried in glassware with no appreciable damage even after many reactions. *BrF_3 is a strong oxidizer and tends to react very exothermically with water and oxygenated organic solvents. The work with BrF_3 should be conducted in a well ventilated area and caution and common sense be exercised*. A detailed description of our setup for working with fluorine has been reported.[18]

Preparation of Noncommercial α-Ketoesters. These starting materials have been prepared by several routes. Although isolated and purified, no attempts have been made to obtain analytical samples before the reaction with methoxylamine.

2,2,2-Trichloroethyl pyruvate (1) was prepared by direct esterification of pyruvic acid and trichloroethanol using DCC. The compound was mentioned previously in a patent,[29] but was never properly described: $bp_{(2\ mm)}$ of 87−92 °C; IR 1737, 1758 cm^{-1}; ^1H NMR 4.9 (2 H, s), 2.56 ppm (3 H, s); ^{13}C NMR 189.9, 158.5, 93.8, 74.8, 26.8 ppm.

(23) Crystal data for $C_8H_{13}F_2NO_5$ (**19**): M = 241.19, triclinic, space group $P\bar{1}$, a = 8.9090(4) Å, b = 11.2080(5) Å, c = 11.5810(7) Å, α = 103.24(3)°, β = 103.446(3)°, γ = 90.875(3)°, U = 1091.9(1) Å^3, z = 4, 2261 unique reflections were measured (R_{int} = 0.0000). The structure was solved by direct methods and refined by full-matrix least squares on F^2. The final refinement converged at R_1 = 0.0456, and wR_2 = 0.1282 [$I > 2\sigma(I)$] and at R_1 = 0.0490, and wR_2 = 0.1323 for all data (see also the Supporting Information section).

(24) A somewhat similar "double" attack of a nucleophilic nitrogen on a remote carbocationic center resulting on a bicyclic product was observed in the past with the reaction of 2,5-dibromoadipanilides with KF. Shahak, I.; Rozen, S.; Bergmann, E. D. *J. Org. Chem.* **1971**, *36*, 501.

(25) Gunther, H. *NMR Spectroscopy*; John Wiley & Sons: New York, 1995; p 343

(26) Belostotskii, A. M.; Hassner, A. *J. Phys. Org. Chem.* **1999**, *12*, 659.

(27) Simons, J. H. *Inorg. Synth.*; McGraw-Hill: New York, 1950; Vol. III, p 184.

(28) Stein, L. *J. Am. Chem. Soc.* **1959**, *81*, 1269.

(29) Gleason, J. G.; Holden, K. G.; Huffman, W. F. U.S. Patent 4,-103,086, 1978; *Chem. Abstr.* **1979**, *90*, 54957u.

Ethyl 2-ketododecanoate (5)[30] was prepared from decylmagnesium bromide and diethyloxalate. A 1 M THF solution of the Grignard reagent (75 mmol) was added dropwise under N_2 atmosphere to a cold (−75 °C) solution of 10 mL (68 mmol) of diethyloxalate in 100 mL of dry ether. After the addition was complete, the reaction mixture was stirred at −75 °C for an additional 0.5 h. The reaction was quenched with diluted HCl, the aqueous layer was extracted with ether (3 × 100 mL), and the combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, and evaporated: oil; >90% yield; IR 1730 cm^{-1}; ^1H NMR 4.32 (2 H, q, J = 7 Hz), 2.83 (2 H, t, 7 Hz), 1.63 (2 H, m), 1.37 (3 H, t, J = 7 Hz), 1.40−1.25 (14 H, m), 0.88 ppm (3 H, t, J = 6.5 Hz); ^{13}C NMR 195, 161, 62.2, 39.2, 31.8, 29.4, 29.2, 28.9, 22.9, 22.6, 13.9 ppm; HRMS (CI) calcd for $C_{14}H_{27}O_3$ 243.1960 $(M + H)^+$, found 243.1952.

Ethyl 4-cyclohexyl-2-ketobutanoate (10)[17] was prepared according to a published procedure[18] from ethyl 4-cyclohexylbutanoate. This ester was α-hydroxylated with $HOF{\cdot}CH_3CN$ and then further oxidized with CrO_3 in an overall yield of 40%: oil; IR 1750, 1729 cm^{-1}; ^1H NMR 4.31 (2 H, q, J = 7 Hz), 2.84 (2 H, t, 7.5 Hz), 1.74−1.67 (5 H, m), 1.52 (2 H, q, J = 7 Hz), 1.37 (3 H, t, J = 7 Hz), 1.31−1.15 (4 H, m), 1.0−0.87 ppm (2 H, m); ^{13}C NMR 195, 161, 62, 36.8, 36.6, 32.8, 30, 26.2, 25.9, 13.7 ppm; HRMS calcd for $C_{12}H_{20}O_3$ 212.1412 $(M)^+$, found 212.1413.

Methyl 2-ketooctanoate (4) was also prepared by α-hydroxylation of methyl octanoate with $HOF{\cdot}CH_3CN$. Its physical properties fully matched those published in the literature.[31]

Dihydro-4,4-dimethyl-2,3-furandione (13) and **dimethyl-2-oxoglutarate (16)** were purchased from Aldrich and used without further purification.

Preparation of *O*-Methyl Oxime Ethers of the α-Ketoesters. The ketoesters (10 mmol) were dissolved in 100 mL of EtOH. An aqueous solution of methoxylamine hydrochloride (10 mmol) was added and the reaction mixture cooled to −10 °C. If needed, more ethanol should be added until a clear solution is obtained. A 3.6 mL portion of 10% aqueous NaOH was dissolved in EtOH and added dropwise during 30 min, keeping the temperature below −5 °C. The reaction mixture was kept overnight at −15 °C, and then all the liquids were evaporated. Water and ether were added, and the aqueous layer was extracted with more ether. The combined organic layers were washed with saturated NaCl, dried, and evaporated. The oxime methyl ethers, mostly unknown, were purified by chromatography on silica gel. After this procedure the products were more than 90% pure and were subjected to the next reaction step without further purification. It should be noted that if the reaction is carried out at room temperature or under heating, it is much faster, but the differentiation between the two present carbonyls is reduced and about 25% of the attack by the amine occurs on the esteric carbonyl.

2′,2′,2′-Trichloroethyl 2-(*O*-methyl oxime)pyruvate (2): oil; 72% yield; IR 1737 cm^{-1}; ^1H NMR 4.91 (2 H, s), 4.11 (3 H, s), 2.11 ppm (3 H, s); ^{13}C NMR 161.8, 147.5, 94.5, 74.3, 63.4, 11.2 ppm.

Methyl 2-(*O*-methyl oxime)octanoate (6): oil; 68% yield; IR 1725 cm^{-1}; ^1H NMR 4.04 (3 H, s), 3.86 (3 H, s), 2.56 (2 H, t, J = 8 Hz), 1.48 (2 H, m), 1.38−1.27 (6 H, m), 0.90 ppm (3 H, t, J = 6 Hz); ^{13}C NMR 164, 152.5, 63, 52, 31.5, 29, 25.7, 25.2, 22.2, 13.7 ppm; HRMS calcd for $C_{10}H_{19}NO_3$, 201.1365 $(M)^+$, found 201.1364.

Ethyl 2-(*O*-methyl oxime) dodecanoate (7): oil; 87% yield; IR 1720 cm^{-1}; ^1H NMR 4.32 (2 H, q, J = 7 Hz), 4.04 (3 H, s), 2.54 (2 H, dd, J_1 = 8 Hz, J_2 = 7 Hz), 1.47 (2 H, m), 1.35 (3 H, t, J = 7 Hz), 1.38−1.25 (14 H, m) 0.88 ppm (3 H, t, J = 6 Hz); ^{13}C NMR 164, 153, 63, 61.7, 31.9, 29.6, 29.3, 26, 25.5, 22.7, 14.1 ppm; HRMS (CI) calcd for $C_{15}H_{30}NO_3$ 272.2226 $(M + H)^+$, found 272.2225.

Ethyl 2-(*O*-methyl oxime)-4-cyclohexylbutanoate (11):[32] oil; 85% yield; IR 1719 cm^{-1}; ^1H NMR 4.31 (2 H, q, J = 7 Hz), 4.03 (3 H, s), 2.55 (2 H, dd, J_1 = 9 Hz, J_2 = 6.5 Hz), 1.77−1.66 (5 H, m), 1.4−1.29 (2 H, m), 1.35 (3 H, t, J = 7 Hz), 1.26 − 1.1 (4 H, m), 1.0−0.85 ppm (2 H, m); ^{13}C NMR 163, 153, 62.8, 61.4, 37.6, 33.2, 32.8, 26.4, 26.1, 23, 14 ppm; HRMS (CI) calcd for $C_{13}H_{24}NO_3$ 242.1756 $(M + 1)^+$, found 242.1754.

3-(*O*-methyl oxime)dihydro-4,4-dimethyl-furan-2-one (14): 90% yield; mp 110 °C (hexane/CH_2Cl_2); IR 1767 cm^{-1}; ^1H NMR 4.1 (3 H, s), 4.09 (2 H, s), 1.44 ppm (6 H, s); HRMS (CI) calcd for $C_7H_{12}NO_3$ 158.0817 $(M + H)^+$, found 158.0814.

Dimethyl 2-(*O*-methyl oxime)glutarate (17):[33] oil; 70% yield; IR 1741 cm^{-1}; ^1H NMR 4.07 (3 H, s), 3.87 (3 H, s), 3.68 (3 H, s), 2.87 (2 H, t, J = 8 Hz), 2.55 ppm (2 H, t, J = 8 Hz); HRMS (CI) calcd for $C_8H_{14}NO_5$, 204.0872 $(M + H)^+$, found 204.0874.

Reactions with BrF_3. The appropriate methyl oxime ether (5 mmol) was dissolved in 30−40 mL of $CFCl_3$ and cooled to 0 °C. Bromine trifluoride (0.4 mL, 7.5 mmol) dissolved in cold (0 °C) $CFCl_3$ (20 mL) was added dropwise during 10 min. After an additional 5 min, the reaction mixture was treated with a saturated Na_2SO_3 solution until colorless. The two layers were separated; the aqueous layer extracted with CH_2Cl_2, the combined organic layers were washed with saturated NaCl, dried, and the solvent was removed. The residues were purified by flash silica gel chromatography with petroleum ether and benzene serving as eluent.

***N*-(1,1-Difluoroethyl)-*N*-methoxy-2,2,2-trichloroethyl carbamate (3)** was obtained as an oil in 60% yield: IR 1755 cm^{-1}; HRMS (CI) calcd for $C_6H_9Cl_3F_2NO_3$ 285.9616 $(M + H)^+$, found 285.9618. Anal. Calcd for $C_6H_8Cl_3F_2NO_3$: C, 25.15; H, 2.81; F, 13.26; N, 4.89. Found: C, 25.46; H, 2.87; F, 13.66; N, 4.78. ^1H, ^{19}F, ^{13}C, and ^{15}N NMR were presented in the Discussion above.

***N*-(1,1-Difluoroheptyl)-*N*-methoxy methyl carbamate (8)** was obtained as an oil in 65% yield: IR 1748 cm^{-1}; ^1H NMR 3.84 (3 H, s), 3.81 (3 H, s), 2.46−2.23 (2 H, m), 1.55−1.45 (2 H, m), 1.39−1.27 (6 H, m), 0.89 ppm (3 H, t, J = 7 Hz); ^{19}F NMR at various temperature was described in the discussion section above; ^{13}C NMR 155, 123 (t, $^1J_{CF}$ = 252 Hz), 65.1, 53.6, 35.2 (t, $^2J_{CF}$ = 26 Hz), 31.4, 28.6, 22.4, 22.3, 13.9 ppm; HRMS (CI) calcd for $C_{10}H_{20}F_2NO_3$ 240.1411 $(M + H)^+$, found 240.1399. Anal. Calcd for $C_{10}H_{19}F_2NO_3$: C, 50.20; H, 8.00; N, 5.85. Found: C, 49.77; H, 7.79; N, 5.47.

***N*-(1,1-Difluoroundecyl)-*N*-methoxy ethyl carbamate (9)** was obtained as an oil in 35% yield: IR 1738 cm^{-1}; ^1H NMR 4.28 (2 H, q, J = 7 Hz), 3.81 (3 H, s), 2.45−2.20 (2 H, m), 1.58−1.45 (2 H, m), 1.35 (3 H, t, J = 7 Hz), 1.38−1.25 (14 H, m), 0.88 ppm (3 H, t, J = 6 Hz); ^{19}F NMR 295 K (22 °C) (coalescence) −84.5 ppm ($W_{h/2}$ = 1800 Hz); HRMS (CI) calcd for $C_{15}H_{30}F_2NO_3$ 310.2194 $(M + H)^+$, found 310.2199. Anal. Calcd for $C_{15}H_{29}F_2NO_3$: C, 58.23; H, 9.45; N, 4.53. Found: C, 58.63; H, 9.52; N, 4.15.

***N*-(3-Cyclohexyl-1,1-difluoropropyl)-*N*-methoxy ethyl carbamate (12)**: oil; 45% yield; IR 1742 cm^{-1}; ^1H NMR 4.28 (2 H, q, J = 7 Hz), 3.80 (3 H, s), 2.47−2.23 (2 H, m), 1.73−1.65 (5 H, m), 1.46−1.10 (6 H, m), 1.35 (3 H, t, J = 7 Hz), 0.98−0.83 ppm (2 H, m),. ^{19}F NMR 250 K (−23 °C) −79.8 (d, J = 197 Hz), −87.2 ppm (d, J = 197 Hz), 306 K (33 °C) (coalescence) −84.5 ppm ($W_{h/2}$ = 1700 Hz), 427 K (154 °C) −82.4 ppm (bs, $W_{h/2}$ = 38 Hz); ^{13}C NMR 154, 124 (t, $^1J_{CF}$ = 252 Hz), 65.1, 63.0, 37.1, 33.0 (t, $^2J_{CF}$ = 26 Hz), 33.0, 29.6, 26.5, 26.2, 14.2 ppm; HRMS (CI) calcd for $C_{13}H_{24}F_2NO_3$ 280.1724 $(M + H)^+$, found 280.1727. Anal. Calcd for $C_{13}H_{23}F_2NO_3$: C, 55.90; H, 8.30; N, 5.01. Found: C, 55.66; H, 8.23; N, 5.04.

4,4-Difluoro-4,5-dihydro-5,5-dimethyl-*N*-methoxyoxazine-2-one (15): oil; 50% yield; IR 1764 cm^{-1}; ^1H NMR 4.0 (2 H, t, J = 1 Hz), 3.95 (3 H, s), 1.24 ppm (6 H, s); ^{19}F NMR 299 (26 °C) −98.5 ppm (bs, $W_{h/2}$ = 160), 402K (129 °C) −96.6 ppm (s, $W_{h/2}$ = 13 Hz); ^{13}C NMR 148.5 (dt, $^3J_{CF}$ = 1.5 Hz, $^1J_{CN}$ = 19.5 Hz), 120.7 (dt, $^1J_{CF}$ = 253 Hz, $^1J_{CN}$ = 13.5 Hz), 71, 65, 38.0 (t, $^2J_{CF}$ = 22 Hz), 18 ppm (t, $^3J_{CF}$ = 2.5 Hz); ^{15}N NMR:

(30) Jahnke, D.; Reinhenkel, H. Ger. Patent DD85071, 1971; *Chem. Abstr.* **1973**, *78*, 110621.

(31) Dubowchik, G. M.; Padilla, L.; Edinger, K.; Firestone, R. A. *J. Org. Chem.* **1996**, *61*, 4676.

(32) Itoh, K.; Kori, M.; Inada, Y.; Nishikawa, K.; Kawamatsu, Y.; Sugihara, H. *Chem. Pharm. Bull.* **1986**, *34*, 1128.

(33) Blomberg, S.; Cronholm, T. *Eur. J. Biochem.* **1979**, *101*, 111.

−203 ppm (t, $^2J_{NF}$ = 18 Hz); HRMS (CI) calcd for $C_7H_{12}F_2NO_3$, 196.0785 $(M + H)^+$, found 196.0786. Anal. Calcd for $C_7H_{11}F_2NO_3$: C, 43.08; H, 5.68; F, 19.47; N, 7.18. Found: C, 43.42; H, 5.65; F, 18.84; N, 6.81.

***N*-(3-Carbomethoxy-1,1-difluoropropyl)-*N*-methoxy methyl carbamate (18):** oil; 22% yield; IR 1743 cm^{-1}; ^1H NMR 3.85 (3 H, s), 3.81 (3 H, s), 3.70 (3 H, s), 2.74 (2 H, tt, J_1 = 14.5 Hz, J_2 = 8 Hz), 2.57 ppm (2 H, t, J = 8 Hz); ^{19}F NMR 218 K (−55 °C) −80.1 ppm (dd, J_1 = 201 Hz, J_2 = 11 Hz), −88.0 (dt, J_1 = 201 Hz, J_2 = 18.5 Hz), 301 K (28 °C) (coalescence), 423 K (150 °C) −84 ppm (bs, $W_{h/2}$ = 48 Hz); ^{13}C NMR 171.8, 154.6 (dt, $^3J_{CF}$ = 2.5 Hz, $^1J_{CN}$ = 20.4 Hz), 122.3 (dt, $^1J_{CF}$ = 253 Hz, $^1J_{CN}$ = 12.7 Hz), 65, 53.5, 51.6, 30.7 (t, $^2J_{CF}$ = 27 Hz), 27.3 ppm (t, $^3J_{CF}$ = 4 Hz); ^{15}N NMR −198 (t, $^2J_{NF}$ = 19 Hz); HRMS (CI) calcd for $C_8H_{13}FNO_5$ 222.0778 $(M - HF + H)^+$, found 222.0779. Anal. Calcd for $C_8H_{13}F_2NO_5$: C, 39.84; H, 5.43; N, 5.81. Found: C, 40.17; H, 5.31; N, 5.53.

***N*-(4,4-Difluoro-4-methoxybutanoyl)-*N*-methoxy methyl carbamate (19):** 35% yield; white solid; mp 39−41 °C (hexane); IR 1742, 1710 cm^{-1}; ^1H NMR 3.92 (3 H, s), 3.82 (3 H, s), 3.53 (3 H, s), 3.0 (2 H, t, J = 8 Hz), 2.36 ppm (2 H, tt, J_1 = 10.5 Hz, J_2 = 8 Hz); ^{19}F NMR −78.4 ppm (t, J = 10.5 Hz); ^{13}C NMR 169.4 (d, $^1J_{CN}$ = 9 Hz), 152.7 (d, $^1J_{CN}$ = 23 Hz),125.2 (t, $^1J_{CF}$ = 261 Hz), 63.8, 54.1, 49.8 (t, $^3J_{CF}$ = 4 Hz), 30.5 (t, $^3J_{CF}$ = 3.4 Hz), 30.36 ppm (t, $^2J_{CF}$ = 31 Hz); ^{15}N NMR −169 (s); HRMS (CI) calcd for $C_8H_{13}FNO_5$ 222.0778 $(M - HF + H)^+$, found 222.0773. Anal. Calcd for $C_8H_{13}F_2NO_5$: C, 39.84; H, 5.43; F, 15.75; N, 5.81. Found: C, 39.54; H, 5.19; F, 15.82; N, 6.10.

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Supporting Information Available: X-ray crystal structure data and an ORTEP diagram for compound **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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