layer was first washed with water and then with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to give a white solid (95 mg, 99%), mp 91-93 °C. GC analysis revealed only one product. The $^1H$ NMR spectrum showed signals at $\delta$ 7.33 (2 H, d, $J$ = 7.69 Hz), 7.25 (2 H, t, $J$ = 7.40 Hz), 7.10 (1 H, t, $J$ = 7.28 Hz), 5.00 (1 H, s, vinyl H trans to $CH_3$), 4.80 (1 H, s, vinyl H cis to $CH_3$), 2.77 (2 H, br s), 2.15-1.20 (15 H, multiplets with sharp $CH_3$ singlet rising at 1.55) ppm. The $^{13}C$ NMR spectrum showed signals at $\delta$ 150.5, 146.3, 127.8, 126.8, 125.0, 111.0, 52.1, 38.0, 33.6, 33.3, 31.3, 27.6, 27.3, and 18.8 ppm. The IR spectrum ($CCl_4$) showed strong absorptions at 3085, 2912, 2857, 1632, 1450, 1101, and 700 $cm^{-1}$; MS $m/z$ 253 ($M^+$ + 1, 8), 252 ($M^+$, 34), 237 ($M^+ - CH_3$, 100), 211 (6), 195 (4), 167 (5), 155 (12), 141 (17), 129 (19), 117 (20), 91 (48), 79 (25), 77 (14), and 41 (4). Anal. Calcd for $C_{19}H_{24}$: C, 90.42; H, 9.58. Found: C, 90.38; H, 9.58. These properties are consistent with the structure of 2-isopropenyl-2-phenyladamantane (2).

**Acknowledgment.** Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and The University of Toledo Faculty Research Awards and Fellowships Program for support of this work, the State of Ohio Academic Challenge Program for the funds for the high-field NMR spectrometer, the U.S. Department of Education for a cost-sharing grant for the purchase of the GC/MS/DS instrument, and the College of Arts and Sciences of The University of Toledo for providing resources for the X-ray Diffraction Center. We are grateful to the Ohio Supercomputer Center for a grant of time on the CRAY Y-MP8/864 computer and thank Professors J. E. Gano and D. A. Forsyth for incisive comments regarding analysis of the stable ion NMR spectra.

**Supplementary Material Available:** Text of X-ray data collection and reduction, structure solution and refinement, and references, tables of crystal structure data, positional parameters, bond distances, bond angles, torsional angles, hydrogen positional parameters, and anisotropic temperature factors for compound 1a (11 pages). Ordering information is given on any current masthead page.

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# Conversion of the Carbonyl Group to $CF_2$ Using IF

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A novel method for the transformation of CO → $CF_2$ is described. The easily made hydrazone derivatives of the carbonyl moiety are reacted under mild conditions with IF prepared directly from the corresponding elements. Various hydrazones have been examined and compared with each other. Unsubstituted ones are usually the most suitable although they are not always easy to purify and store. *N*-Methyl- and *N,N*-dimethylhydrazones also give quite satisfactory results. The more easily made dinitrophenyl hydrazones (DNPs), semicarbazones, and tosylhydrazones also react, but the yields of the desired $CF_2$ compounds are usually lower. Oximes could also be successfully reacted. The two main byproducts of the reaction are the parent carbonyl compounds, which can be recycled, and the $\alpha$-iododifluoro derivatives. The latter upon treatment with $LiAlH_4$ or $Bu_3SnH$ were reduced to the desired product, thus increasing the overall yields.

The importance of the $CF_2$ group, especially in biologically related chemistry, is well established, and numerous derivatives have been prepared during the last three decades. Most of those compounds have been made by reacting carbonyls with either $SF_4$ under high pressures and elevated temperatures[1] or with its easier to handle but the expensive (diethylamino)sulfur trifluoride (DAST).[2] Some attempts have also been made to utilize $MoF_6$[3] or incorporate the whole $CF_2$ group in the substrate by using $CF_2XY$, X and Y being variations of hydrogen, halogens, and the carboxylic moiety.[4] A different and interesting approach was initiated by Patrick, who converted benzylic hydrazones and diazo compounds to the corresponding $ArCF_2$ using elemental fluorine.[5,6]

Recently, interhalogen fluorides have emerged as an important tool for the construction of the $CF_2$ moiety. We have shown that IF, made directly from the elements, can react very efficiently with acetylenes resulting in the $CF_2CX_2$ group.[7] Katzenellenbogen has shown that dithiolans, when treated with *N*-bromoimides/HF mixtures, could also be smoothly transformed into the $CF_2$ moiety.[8] We present here yet another broad general method using IF for the CO → $CF_2$ transformation via various hydrazones and oxime derivatives.[9] The main idea guiding this work was to utilize the fact that the electrophilic iodine in IF should polarize the imine bond, enabling the unsolvated and hence relatively strong nucleophilic fluoride to form the desired carbon fluorine bond.

Hydrazone preparation is usually a well-established high-yield procedure.[10] In many cases, however, purification is tedious and can result in formation of a large

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[1] See for example: Boswell, G. A.; Ripka, W. C.; Schribner, R. M.; Tullock, C. W. *Org. React.* **1974**, *21*, 1.

[2] Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

[3] See, for example: Barnette, W. E. *CRC Crit. Rev. Biochem.* **1984**, *15*, 201.

[4] See, for example: McDonald, I. A.; Lacoste, J. M.; Bey, P.; Palfreyman, M. G.; Zreika, M. *J. Med. Chem.* **1985**, *28*, 186. Morikawa, T.; Uejima, M.; Kobayashi, Y. *Chem. Lett.* **1988**, 1407. Hertel, L. W.; Kroin, J. S.; Misner, J. W.; Trustin, J. M. *J. Org. Chem.* **1988**, *53*, 2406.

[5] Patrick, T. B.; Scheibel, J. J.; Cantrell, G. L. *J. Org. Chem.* **1981**, *46*, 3917.

[6] Patrick, T. B.; Flory, P. A. *J. Fluorine Chem.* **1984**, *25*, 157.

[7] Rozen, S.; Brand, M. *J. Org. Chem.* **1986**, *51*, 222.

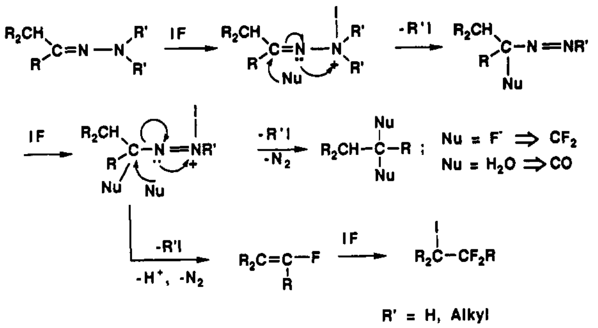
[8] Sondej, S. C.; Katzenellenbogen, J. A. *J. Org. Chem.* **1986**, *51*, 3508.

[9] For a preliminary communication, see: Rozen, S.; Brand, M.; Zamir, D.; Hebel, D. *J. Am. Chem. Soc.* **1987**, *109*, 896.

[10] Pross, A.; Sternhell, S. *Aust. J. Chem.* **1970**, *23*, 989. Campbell, J. R.; Pross, A.; Sternhell, S. *Aust. J. Chem.* **1971**, *24*, 1427.

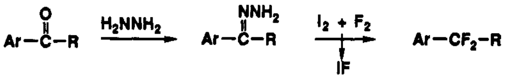
0022-3263/91/1956-4695$02.50/0

Scheme I



proportion of an azine, a common byproduct. Fortunately it was found that reacting crude hydrazones with the in situ prepared IF[11] was quite satisfactory and full purification is not necessary in most cases.

Reacting the crude hydrazone of acetophenone (1) with IF at −78 °C for 1 h resulted in an 80% yield of 1,1-difluoro-1-phenylethane (2)[6] accompanied by 5% of the monoiodo derivative 1,1-difluoro-2-iodo-1-phenylethane (3). Other benzylic hydrazones also gave satisfactory results. Thus the hydrazones of propiophenone (4) and phenyl benzyl ketone (5) formed 1,1-difluoro-1-phenylpropane (6)[12] and 1,1-difluoro-1,2-diphenylethane (7)[6] in good yields.

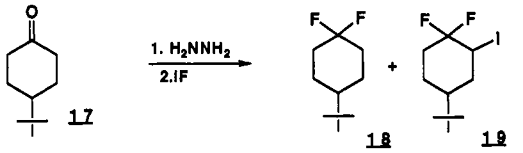


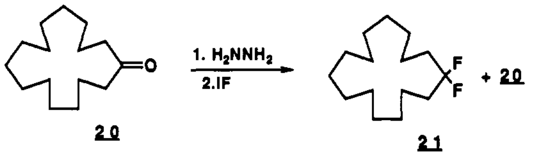
| | | |
|---|---|---|
| 1 | Ar = Ph, R = $CH_3$ | 2 + $PhCF_2CH_2I$ (3) |
| 4 | Ar = Ph, R = $CH_2CH_3$ | 6 |
| 5 | Ar = Ph, R = $CH_2Ph$ | 7 |
| 8 | Ar = R = Ph | 9 + PhCOPh<br>(if $H_2O$ is present) |
| 10 | Ar = $p$-$O_2NC_6H_4$, R = $CH_3$ | 11 + $ArCF_2CH_2I$ (12) |
| 13 | Ar = $p$-$O_2NC_6H_4$, R = H | 15 |
| 14 | Ar = $p$-$NCC_6H_4$, R = H | 16 |

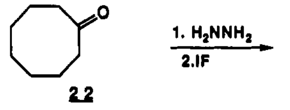
We believe that the reaction starts with the electrophilic iodine attacking the basic amine-like nitrogen followed by HI elimination (in the case of unsubstituted hydrazones) and nucleophilic attack of the almost naked fluoride[13] (Scheme I). This process is repeated and eventually $N_2$ is evolved.[14] When the intermediate contains a stable carbocation there is a chance for the fluoride ion to diffuse out of the ion pair, thus letting the nucleophilic water, if present, attack the positive carbon leading to the parent carbonyl. Thus when the hydrazone of benzophenone (8) was treated with IF without excluding the moisture, the yield of the difluorodiphenylmethane (9)[15] was 65% along with another 35% of benzophenone itself. Under drier conditions the yield of 9 was raised to 83%. When on the other hand the respective carbocation is less stable, one of the possible stabilizing routes is an α-proton elimination. The resulting olefin reacts immediately with IF in a well-defined regiochemistry[7] producing eventually the byproduct containing the $CF_2CI$ moiety. This was demonstrated by 4-nitroacetophenone hydrazone (10), which produced the expected difluoro derivative (11)[16] in only 30% yield accompanied by another 30% of the α-iodo byproduct 12.

Aromatic aldehydes are also good candidates for this reaction as evident from 4-nitro- and 4-cyanobenzaldehyde (13 and 14), which were converted to the corresponding α,α-difluorotoluenes 15[17] and 16.[16] It should be noted that substrates containing activated aromatic rings are not suitable for this reaction since the reagent's electrophilic iodine can iodinate such rings.[18]

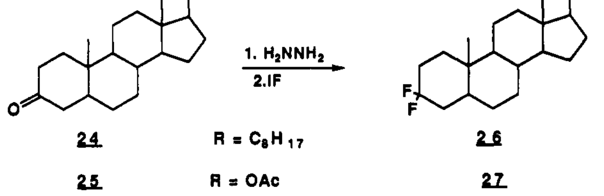
The reaction with IF is not confined only to benzylic carbonyls. The cyclic derivative 4-*tert*-butylcyclohexanone hydrazone (17) for example, is converted in 65% yield to the 4,4-difluoro-1-*tert*-butylcyclohexane (18).[19] Since, however, the positive charge evolved on $C_4$ on the intermediate is not as stable as in the benzylic derivatives, higher activation energies are required. This is reflected in much slower reaction rates, which could be accelerated by raising the temperature to −10 °C. This relatively unstable carbocation is also responsible for the additional formation of 25% of 3-iodo-4,4-difluoro-1-*tert*-butylcyclohexane (19). Similar behavior was observed with cyclopentadecanone hydrazone (20), which at −78 °C was transformed to 1,1-difluorocyclododecapentane (21) in 20% yield while at +25 °C the yield was more than doubled. The only byproduct detected in this case was the parent ketone itself which could, of course, be recycled. Similarly, cyclooctanone hydrazone (22) was transformed into 1,1-difluorocyclooctane (23).







Good yields have been found with 3-keto steroids which were smoothly transformed to the expected difluoro derivatives. Both cholestanone (24) and 17β-acetoxy-5α-androstan-3-one (25) have been converted to their corresponding hydrazones, and when reacted with IF formed the desired 3,3-difluorocholestane (26)[20] and 17β-acetoxy-3,3-difluoro-5α-androstane (27).[21]



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[11] Rozen, S.; Brand, M. *J. Org. Chem.* **1985**, *50*, 3342.

[12] Weigert, F. J. *J. Org. Chem.* **1980**, *45*, 3476.

[13] Since the reaction is performed in aprotic solvents the fluoride is not solvated. It is aggregated, however, with other molecules of the reagent through I···F···I bridges; see: Lehmann, E.; Naumann, D.; Schmeisser, M. *J. Fluorine Chem.* **1976**, *7*, 135.

[14] Although we have not proved absolutely nitrogen release, characteristic gas evolvement is easily observed.

[15] Hasak, W. R.; Smith, W. C.; Engelhardt, V. A. *J. Am. Chem. Soc.* **1960**, *82*, 543.

[16] Mathey, F.; Bensoam, J. *Tetrahedron* **1975**, *31*, 391.

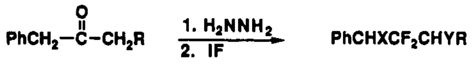
[17] Feiring, A. E. *J. Fluorine Chem.* **1977**, *10*, 375.

[18] Rozen, S.; Zamir, D. *J. Org. Chem.* **1990**, *55*, 3552.

[19] Cantauzene, J.; Jantzen, R. *Tetrahedron Lett.* **1970**, 3281.

[20] Boulton, K.; Cross, B. E. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1354.

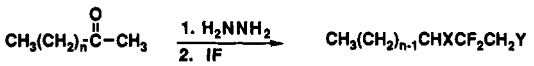
To demonstrate the general use of this reaction we have examined some aliphatic derivatives as well. Hydrazones of diphenylacetone (**28**), benzyl methyl ketone (**29**), 2-decanone (**30**), and 2-dodecanone (**31**) have been prepared in good yields and reacted with IF. Compounds **28** and **29** formed 2,2-difluoro-1,3-diphenyl- (**32**)[22] and 2,2-difluoro-1-phenylpropane (**33**)[12] contaminated with some 10% of the corresponding $\alpha$-iodo derivaties **34–36**. The other two ketones reacted much more slowly, and their reaction temperature had to be raised to +20 °C. At that temperature mainly the desired 2,2-difluorodecane (**37**) and 2,2-difluorododecane (**38**) were formed, but both were contaminated with altogether about 30% of the two possible $\alpha$-iodo derivatives **39–42**. Aliphatic aldehydes, too, were successfully reacted and dodecanal (**43**), for example, was transformed into 1,1-difluorododecane (**44**),[8] widening the scope of this reaction.



$$PhCH_2-\overset{O}{\overset{\|}{C}}-CH_2R \xrightarrow[2.\ IF]{1.\ H_2NNH_2} PhCHXCF_2CHYR$$

**28** R = Ph; **29** R = H

**32** X=Y=H; **33** X=Y=H; **34** X=H, Y=I; **35** X=H, Y=I; **36** X=I, Y=H



$$CH_3(CH_2)_n\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow[2.\ IF]{1.\ H_2NNH_2} CH_3(CH_2)_{n-1}CHXCF_2CH_2Y$$

**30** n = 7; **31** n = 9

**37** X=Y=H; **39** X=H, Y=I; **38** X=Y=H; **41** X=H, Y=I; **40** n=7, X=I, Y=H; **42** n=9, X=I, Y=H

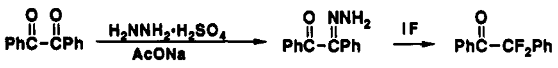
$$CH_3(CH_2)_9CHO \xrightarrow[2.\ IF]{1.\ H_2NNH_2} CH_3(CH_2)_9CHF_2$$

**43** **44**

Although we have not been able to depress the formation of the $\alpha$-iododifluoro contaminants, they could be easily converted to the main products, boosting the overall yield. This can be done by treating the crude reaction mixture with either LiAlH4 or $Bu_3SnH$. The efficiency of both treatments is higher than 90%, which brings the yields of the general reaction $C{=}N \rightarrow CF_2$ into the range of 80–90% (see Table I in the Experimental Section).

$$RCF_2CHIR' \xrightarrow[\text{or } Bu_3SnH;\ h\nu,\ 60h]{LiAlH_4;\ RT;\ 1h} RCF_2CH_2R'$$

If one could make the monohydrazone of a 1,2-diketone,[23] an easy way would be open for the synthesis of the difficult to obtain $\alpha$-difluoro ketones.[24] This potential is demonstrated for benzil (**45**), whose monohydrazone is known[25] and which was converted to 1,1-difluoro-1,2-diphenylethan-2-one (**46**)[5] in 60% yield.

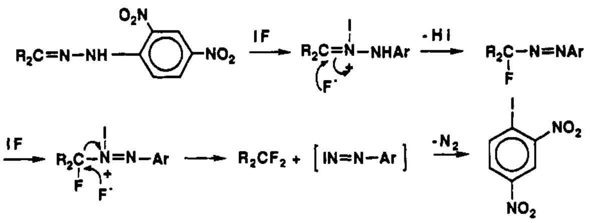


$$Ph\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}Ph \xrightarrow[AcONa]{H_2NNH_2\cdot H_2SO_4} Ph\overset{O}{\overset{\|}{C}}-\overset{NNH_2}{\overset{\|}{C}}Ph \xrightarrow{IF} Ph\overset{O}{\overset{\|}{C}}-CF_2Ph$$

**45** **46**

We have already stated that it is not easy to purify hydrazones, and in quite a few cases they also cannot be stored for long periods. We decided therefore to explore also the reactions of *N*-methyl- and *N*,*N*-dimethylhydrazones[26] with IF. It was found that their reactions were slower than with unsubstituted hydrazones, especially at −78 °C. This is quite understandable since MeI elimination from the intermediates is a less favorable process than HI elimination (see Scheme I). Temperatures of 0–25 °C, however, proved to be ideal for full conversion to be achieved in about 1 h. It should be noted that, as with the unsubstituted hydrazones, $N_2$ elimination was observed in all successful reactions. A very significant benefit was the fact that, unlike with many hydrazones, the use of pure and dry *N*-methyl derivatives could considerably raise the yield of the difluoro products in cases sensitive to hydrolysis. Thus, the pure *N*-methylhydrazone of cyclododecanone (**20**) formed **21** in 80% yield along with only 5% of the ketone **20** compared to the unsubstituted hydrazone which yielded no more than 40% of **21** accompanied by another 50% of the parent ketone **20**.

**Scheme II**



Substituted hydrazones were not immune from the production of the $\alpha$-iododifluoro byproducts, although they usually were formed in lower yield compared to the unsubstituted derivatives. After the hydride treatment, however, the overall yields of the difluoro compounds obtained from both types of hydrazones were found to be comparable (see Table I in the Experimental Section). It should be noted that some years ago, Corey[27] developed an alkylation reaction $\alpha$ to the imine nitrogen in *N*,*N*-dimethylhydrazones, a fact which may indicate new synthetic possibilities for constructing many interesting $CF_2$-containing molecules.

We have also examined the reaction of IF with some more readily prepared imine-type carbonyl derivatives. The well-known and easily prepared crystalline dinitrophenylhydrazones (DNPs) were our first target. They do not react with IF at low temperatures, apparently because the nitrogen atoms are considerably less basic than those of the hydrazones making initial attack by electrophilic iodine more difficult. Raising the reaction temperatures above 0 °C is usually sufficient to start the reaction, and benzylic DNPs, as well as cyclic and aliphatic ones, form the desired $CF_2$ compounds. The yields, however, are generally lower compared to the corresponding hydrazones and found to be in the range of 40–50%, see Table I. As with hydrazones themselves, the formation of the $\alpha$-iodofluoro byproducts could not be suppressed, and they frequently accompanied the main difluoro product. It should be noted that DNPs of aldehydes did not react at all, presumably because of poor solubility in the reaction solvent—a mixture of $CHCl_3$ and $CFCl_3$. We believe that the reaction mechanism with DNP follows the general pattern presented in Scheme I, although the initial attack of the electrophilic iodine should be on the more basic imine nitrogen. As with the previous reactions, we were

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[21] Bird, G. C.; Felsky, G.; Fredericks, M. P.; Jones, R. H. E.; Meakins, D. G. *J. Chem. Res.* **1979**, 4728.

[22] Evans, D. P.; Morgan, V. G.; Watson, H. B. *J. Chem. Soc.* **1935**, 1172.

[23] No general synthetic method for making $\alpha$-keto hydrazones is available, but for their preparation from $\alpha$-bromo ketones, see: Hauptmann, S.; Wilde, H. *J. Prakt. Chem.* **1969**, *311*, 604.

[24] We have developed a method for the construction of $CF_2CX_2$ (X = I, Br), see ref 7. We hope that in the future we will be able to convert the chemically resistant $CX_2$ moiety to a carbonyl thus obtaining the $CF_2CO$ derivatives.

[25] Regitz, M.; Maas, G. *Diazo Compounds Properties and Synthesis*; Academic Press: Orlando, 1986; p 234.

[26] There is quite extensive documentation for the preparation of substituted hydrazones; see for example: Smith, P. A. S.; Most, E. E. *J. Org. Chem.* **1957**, *22*, 358. Newkome, G. R.; Fishel, D. L. *J. Org. Chem.* **1965**, *31*, 677.

[27] Corey, E. J.; Knapp, S. *Tetrahedron Lett.* **1976**, 4687.

**Table I. Yields, Reaction Time (h), and Reaction Temperature [°C] of the $CF_2$ Derivatives**

| starting ketone → $CF_2$ | hydrazone | *N*-methylhydrazone | *N*,*N*-dimethylhydrazone | DNP | semicarbazone | tosylhydrazone | oxime |
|---|---|---|---|---|---|---|---|
| **1** → **2** | 80 + 5$^{a}$<br>(1) [−78] | | | | 25 + 30$^{a,c}$<br>(3) [rt] | | 80<br>(0.5) [−78] |
| total$^{b}$ | 84 (LAH) | | | | 50 (LAH) | | |
| **4** → **6** | 50<br>(0.5) [−78] | | | 50<br>(1) [0] | 30<br>(1) [rt] | | |
| **5** → **7** | 55<br>(0.5) [−78] | | | | | | |
| **8** → **9** | 83 + 8$^{c,d}$<br>(1) [−78] | | | 40<br>(1) [rt] | 87<br>(1) [rt] | 30<br>(2) [−78] | 40<br>(4) [−78] |
| **10** → **11** | 30 + 30$^{a}$<br>(1.5) [−78] | 60 + 30$^{a}$<br>(1) [rt] | | | 50<br>(0.75) [+10] | | |
| total$^{b}$ | 58 (Sn) | 90 (Sn) | | | | | |
| **13** → **15** | 80<br>(0.5) [−78] | | | NR | 40 + 30$^{c}$<br>(0.75) [+10] | | |
| **14** → **16** | 65<br>(4) [−78] | | | NR | | | |
| **17** → **18** | 65 + 25$^{a}$<br>(1) [rt] | 70 + 10$^{a}$<br>(1) [rt] | 60 + 30$^{a}$<br>(1) [rt] | 40 + 20$^{a}$<br>(2) [rt] | | 50<br>(1) [rt] | |
| total$^{b}$ | 90 (LAH) | 80 (LAH) | 90 (LAH) | 60 (LAH) | | | |
| **20** → **21** | 40 + 50$^{c,e}$ | 80 + 5$^{c}$ | | | | | |
| **22** → **23** | 10$^{f}$<br>(1) [−10] | | | | 12<br>(2.5) [rt] | | |
| **24** → **26** | 70$^{g}$<br>(0.5) [rt] | | | | | | |
| **25** → **27** | 70$^{g}$<br>(0.5) [rt] | | | | | | |
| **28** → **32** | 50 + 10$^{a}$<br>(2) [−78] | | NR | NR | | | |
| total$^{b}$ | 60 (LAH) | | | | | | |
| **29** → **33** | | 50 + 25$^{a,h}$<br>(0.5) [0] | | | | | |
| total$^{b}$ | | 72 (Sn) | | | | | |
| **30** → **37** | 60 + 33$^{a,h}$<br>(1) [rt] | 65 + 20$^{a,h}$<br>(1) [rt] | 55 + 38$^{a,h}$<br>(1) [rt] | 31 + 11$^{a,h}$ + 20$^{c}$ | 42 + 50$^{c}$ | | |
| total$^{b}$ | 90 (LAH) | 85 (LAH) | 90 (LAH) | | | | |
| **31** → **38** | 40 + 25$^{a,h}$<br>(1) [rt] | | | | 40 + 25$^{a}$ + 25$^{c}$ | | 30 |
| total$^{b}$ | 60 (LAH) | | | | | | |
| **43** → **44** | 60<br>(1) [rt] | | | | | | |
| **45** → **46** | 60<br>(2) [−78] | | | | | | |

[a] Yield of the α-iododifluoro byproducts. [b] Total yield of the desired $CF_2$ compound after treatment with either $LiAlH_4$ (LAH) or $Bu_3SnH$ (Sn). The following are typical procedures for these reductions: 220 mg of $LiAlH_4$ in 50 mL of dry THF was stirred at room temperature under $N_2$. A crude solution of the main compound and its α-iodo byproduct (2 g in 20 mL of dry THF) were slowly added and stirred for 1 h. The $LiAlH_4$ excess was destroyed with cold water; the reaction mixture was extracted with $CHCl_3$ and worked up as usual. Alternatively, 1.5 g of the same crude reaction mixture was dissolved in 30 mL of dry THF into which a 3-fold excess of $Bu_3SnH$ was added. The reaction mixture was kept at room temperature under $N_2$ and irradiated with a sun lamp for 60 h followed again by the usual workup procedure. [c] Yield of the parent ketone or aldehyde. [d] In the presence of water the yield of the difluoro derivative drops to 65%, while the yield of acetophenone rises to 35%. [e] At −78 °C the yield of the difluoro derivative was 20%, while the starting ketone was recovered in 80%. [f] No reaction at −78 °C. [g] Only traces of the α-iodo derivatives. [h] The combined yield of the two possible α-iodo isomers.

able to observe $N_2$ evolvement and in addition could isolate 2,4-dinitroiodobenzene in higher than 90% yield (Scheme II).

Semicarbazones, are another well-known group of carbonyl derivatives. They too are easy to make and purify and have the advantage of being more soluble in the reaction solvent than the parallel DNP derivatives. This last feature makes it possible for aldehydes such as *p*-nitrobenzaldehyde semicarbazone to react with IF and produce the difluoro derivative **15** in 40% yield. This relatively low yield, however, is typical for all reactions we examined with semicarbazones (see Table I) and comparable with the DNPs yields. Another similarity is the fact that the reaction will start only at temperatures above 0 °C. The major byproduct of this family of hydrazones are the parent ketones, some times in yields higher than the expected $CF_2$ derivatives.

The next group of carbonyl derivatives examined were tosylhydrazones, which are similar to DNPs and semicarbazones in their ease of preparation, purification, and storage, but also similar in the low-yield formation of the $CF_2$-containing products averaging between 30 and 50%. Some examples can be found in the Experimental Section, Table I.

$$R_2C{=}O \longrightarrow R_2C{=}NNHR' \xrightarrow{IF} R_2CF_2$$

$$R' = CONH_2;\ SO_2Tol$$

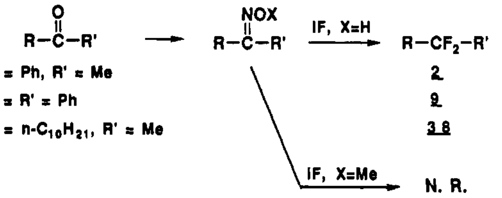
As for now, we have only preliminary results with yet another group of protected carbonyls, the oximes. Although they differ from all the previous derivatives discussed so far by their inability to form $N_2$, they too have been found to react with IF and in some cases do so better than the electron-withdrawing substituted hydrazones. Thus acetophenone and benzophenone oximes yielded the $CF_2$ derivatives **2** and **9** in yields of 80% each while the aliphatic 2-dodecane oxime gave **38** in only 40% yield but with no indication for the formation of the α-iododifluoro

**Table II. Physical Data for the Products from the Reaction: $R_2C{=}NR' + IF$**

| entry | mp | $^1$H NMR | $^{19}$F NMR |
|---|---|---|---|
| **2** | oil[a] | 1.9 (3 H, t, $J = 18$ Hz) | −88.2 (q, $J = 18$ Hz) |
| **3**[b] | | 3.65 (2 H, t, $J = 15$ Hz) | −93 (t, $J = 15$ Hz) |
| **6** | oil[c] | 2.1 (2 H, octet, $J_1 = 15$, $J_2 = 7$ Hz), 0.98 (3 H, t, $J = 7$ Hz) | −98.4 (t, $J = 15$ Hz) |
| **7** | oil | 3.9 (2 H, t, $J = 16$ Hz) | −95.42 (t, $J = 16$ Hz) |
| **9** | oil | 8.43 (m) | −89.94 (s) |
| **11**[d] | 38[e] | 1.96 (3 H, t, $J = 18$ Hz) | −89.57 (q, $J = 18$ Hz) |
| **12**[f] | oil | 3.68 (2 H, t, $J = 15$ Hz) | −93.3 (t, $J = 15$ Hz) |
| **15**[g] | oil | 6.77 (1 H, t, $J = 56$ Hz) | −113.4 (d, $J = 56$ Hz) |
| **16** | oil[h] | 6.86 (1 H, t, $J = 57$ Hz) | −113.5 (d, $J = 57$ Hz) |
| **18**[i] | oil | 2.2–1.0 (9 H, m), 0.88 (9 H, s) | −92 (1 F, d, $J = 234$ Hz), −103.6 (1 F, ddt, $J_1 = 234$, $J_2 = 40$, $J_3 = 11$ Hz) |
| **19** | oil | 4.53 (1 H, m), 2.2–1.1 (7 H, m), 0.88 (9 H, s) | −88.9 (1 F, d, $J = 234$ Hz), −103.1 (1 F, ddm, $J_1 = 234$, $J_2 = 40$, $J_3$ ($W_{h/2}$) = 91 Hz) |
| **21**[j] | 34 | 2.2 (4 H, m), 1.33 (24 H, br m) | −91.5 (pentet, $J = 9$ Hz) |
| **23**[k] | oil[l] | 2.0 (4 H, m), 1.65–1.6 (14 H, br m) | −91.5 (hept, $J_1 = 32$, $J_2 = 16$ Hz) |
| **26** | 109[e] | | −89.6 (1 F, d, $J = 234$ Hz), −99.4 (1 F, dm, $J_1 = 234$, $J_2$ ($W_{h/2}$) = 110 Hz) |
| **27** | 135[e] | | −89.7 (1 F, d, $J = 234$ Hz), −98.4 (1 F, dm, $J_1 = 234$, $J_2$ ($W_{h/2}$) = 89 Hz) |
| **32** | oil | 3.07 (4 H, t, $J = 16$ Hz) | −95.3 (pentet, $J = 9$ Hz) |
| **37**[m] | oil | 1.9–1.7 (2 H, m), 1.57 (3 H, t, $J = 18$ Hz), 1.2 (12 H, m), 0.88 (3 H, t, $J = 7$ Hz) | −90.9 (sextet, $J = 18$ Hz) |
| **39** | oil | 3.4 (2 H, C*H*$_2$I, t, $J = 16$ Hz), 1.9–1.7 (2 H, C*H*$_2$CF$_2$, m) | −94.9 (pentet, $J = 16$ Hz) |
| **40** | oil | 4.06 (1 H, C*H*I, m), 1.57 (3 H, t, $J = 18$ Hz), 1.5–1.2 (12 H, m), 0.88 (3 H, t, $J = 7$ Hz) | −88.4 (1 F, dm, $J_1 = 255$, $J_2 = W_{h/2} = 48$ Hz), −92.8 (1 F, dm, $J_1 = 255$, $J_2 = W_{h/2} = 48$ Hz) |
| **38**[n] | oil | 1.9–1.7 (2 H, m), 1.57 (3 H, t, $J = 18$ Hz), 1.29 (16 H, m), 0.88 (3 H, t, $J = 7$ Hz) | −90.4 (sextet, $J = 18$ Hz) |
| **41** | oil | 3.4 (2 H, C*H*$_2$I, t, $J = 15$ Hz) | −94.9 (pentet, $J = 15$ Hz) |
| **42** | oil | 4.06 (1 H, C*H*I, m), 1.57 (3 H, t, $J = 18$ Hz), 1.5–1.2 (16 H, m), 0.88 (3 H, t, $J = 7$ Hz) | −88.4 (1 F, dm, $J_1 = 250$, $J_2 = W_{h/2} = 45$ Hz), −92.8 (1 F, dm, $J_1 = 250$, $J_2 = W_{h/2} = 45$ Hz) |
| **44** | oil | 5.78 (1 H, tt, $J_1 = 57$, $J_2 = 6$ Hz), 1.8 (2 H, bm), 1.27 (18 H, m), 0.9 (3 H, t, $J = 7$ Hz) | −116.24 (dt, $J_1 = 57$, $J_2 = 17$ Hz) |
| **46**[o] | oil | 7.2 (m) | −98 (s) |

[a] Bp: 58 °C (35 mm). MS: *m/e* 142 (M)$^+$. [b] $^{13}$C NMR: 134.5 (*C*F$_2$, t, $J = 192$ Hz), 6.5 (*C*H$_2$I, t, $J = 32$ Hz). MS: *m/e* 268 (M)$^+$. [c] Bp: 25 °C (2 mm). [d] MS: *m/e* 187 (M)$^+$. [e] From EtOH. [f] $^{13}$C NMR: 140.3 ($C_1$-arom, t, $J_{CF} = 23$ Hz), 113.4 (*C*F$_2$, t, 240 Hz). [g] MS: *m/e* 313 (M)$^+$. [h] Bp: 80–90 °C (20 mm). [i] $^{13}$C NMR: 123.34 (*C*F$_2$, t, $J = 241$ Hz), 46.78 (*C*Me$_3$), 34.36 (*C*H$_2$CF$_2$, t, $J = 20$ Hz), 27.64 (*C*H$_3$), 23.94, 23.84 (2 *C*H$_2$). [j] Anal. Calcd for $C_{15}H_{28}F_2$: C, 73.17; H, 11.38. Found: C, 72.81; H, 10.95. [k] $^{13}$C NMR: 126.4 (t, $J = 236$ Hz), 33.8 (t, $J = 26$ Hz), 27.5, 24.1, 20.9 (5 *C*H$_2$). [l] Bp: 25 °C (0.5 mm). [m] Anal. Calcd for $C_{10}H_{20}F_2$: C, 67.41; H, 11.24. Found: C, 68.00; H, 10.75. $^{13}$C NMR: 124.3 (*C*F$_2$, t, $J = 202$ Hz), 38.12 ($C_3$, t, $J = 21$ Hz), 29.44 ($C_1$, t, $J = 21$ Hz), 31.91, 23.56, 23.24, 22.83, 22.66, 21.95 (7 *C*H$_2$ groups), 14.02 (*C*H$_3$). [n] Anal. Calcd for $C_{12}H_{24}F_2$: C, 69.90; H, 11.65. Found: C, 69.67; H, 11.75. $^{13}$C NMR: 124.5 (*C*F$_2$, t, $J = 237$ Hz), 38.17 ($C_3$, t, $J = 25$ Hz), 29.62 ($C_1$, t, $J = 21$ Hz), 32.04, 29.70, 29.44, 29.33, 23.31, 22.89, 22.80 (rest of *C*H$_2$ groups), 14.16 (*C*H$_3$). [o] IR: 1692 cm$^{-1}$.

byproducts. In contrast to the hydroxylamine derivatives, *O*-alkyl oximes whose nitrogen basicity is very low[28] do not react with IF at all, even at room temperature, supporting the notion that the first step of the reaction is the IF attack on the most basic nitrogen atom.



We can conclude that at this stage, the most promising route for the CO → $CF_2$ transformation using IF passes through hydrazones or *N*-alkylhydrazones, but if the preparation of these intermediates poses some problems one can always turn to the easier to make derivatives such as DNP, although probably at the expense of somewhat lower yields of the desired $CF_2$ compound. Another important point of this work is the source of the fluorine atoms being $F_2$ itself. Most reactions described here are fairly fast and can be accomplished within a half-life time of the positron emitting isotope $^{18}$F. This isotope can be made in the form of $^{18}$F–F from neon, a fact that makes this works suitable for constructing $C^{18}F_2$ derivatives for use in the rapidly developing PET tomography.

## Experimental Section

$^1$H NMR spectra were recorded with a Bruker AM-360 WB at 360 MHz with $CDCl_3$ as solvent and $Me_4Si$ as internal standard. The $^{19}$F NMR spectra were measured at 338.8 MHz and are reported in parts per million upfield from $CFCl_3$, which also served as internal standard. The proton broad band decoupled $^{13}$C NMR spectra were recorded at 90.5 MHz and only the C–F couplings were observed. Here too $CDCl_3$ served as a solvent and TMS as internal standard. Mass spectra were measured with a DuPont 21-491B instrument, and IR spectra were recorded on a Perkin-Elmer 177 spectrometer.

**General Fluorination Procedure.** Fluorine is of course a strong oxidizer and a very corrosive material. An appropriate vacuum line made from copper or monel in a well-ventilated area should be constructed for working with this element. We usually use higher than 95% technical grade fluorine purchased from Air Products. The vacuum line is equipped with secondary containers of a known volume made also from copper or monel. Pressure gauges constructed especially for work with fluorine (Matheson or Air Products) are attached to the line. All possible outlets of the system, including the one connected to the oil pump, are guarded by soda-lime traps so no fluorine escapes to the atmosphere. Variations of such vacuum lines are illustrated in Matheson report No. G-115B or in Vyplel's review.[29] The secondary cylinders are first evacuated and then charged with nitrogen to a positive pressure of about 5 psi. The nitrogen flow is stopped and $F_2$ is allowed to pressurize the system to whatever the desired final concentration is (usually 1–20 psi of $F_2$). The system is then charged again with $N_2$ up to 60–90 psi. The main fluorine and nitrogen cylinders are then completely disconnected.

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[28] Smith, P. A. S. *Open Chain Nitrogen Compounds, Vol 2*; Benjamin: New York, 1966; p 40.

[29] Vyplel, H. *Chimia* **1985**, *39*, 305.

If so wished this mixture can be passed through a NaF trap (Matheson) in order to absorb part of the HF always found in some quantities in technical commercial fluorine. Prediluted mixtures of fluorine in inert gases are also commercially available (Air Products). The reactions themselves can be carried out in glass vessels whose outlets are connected to soda-lime traps. A simple gas bubbler fitted at the end of this trap can give a fair idea of the bubbling rate of the gas through the reaction mixture, although this can be accurately measured if needed. If elementary precautions are taken, work with fluorine is relatively simple and we have had no accidents with it in the last 15 years.

**Preparation of IF.**[11] Well-grounded iodine (25 g) was suspended in 500 mL of $CFCl_3$ and sonicated for about 30 min in order to improve dispersion. It seems that there is a direct correlation between the surface of the iodine and the efficiency of the IF formation. The reaction mixture was cooled to −78 °C and vigorously agitated with the aid of a vibromixer. Next, 1.1 mol/equiv of nitrogen-diluted $F_2$ (10% v/v) was bubbled through the suspension. The IF yield is practically quantitative in respect to both iodine and fluorine. The formed IF is a light brown suspension, and its amount can be determined by reacting aliquots with olefins such as 1-dodecene followed by quantitative GC determination of the resulting 1-iodo-2-fluorododecane.[11]

**Preparation of the Various Hydrazones.** These follow well-known literature preparation. Unsubstituted hydrazones for example, were obtained from the reaction of hydrazone hydrate and the corresponding carbonyl derivative according to the Sternhall and Pross procedure.[10] In a typical experiment a solution of 15 mL of EtOH and 5 g of the carbonyl derivative were added to a 10-g solution of hydrazine hydrate in 40 mL of EtOH, brought slowly to the reflux temperature (ca. 0.5 h) and kept there for another 0.5 h. The reaction mixture was then diluted with 50 mL of water and extracted with $CHCl_3$. The organic layer was washed with water, dried over $K_2CO_3$, and then evaporated under reduced pressure at temperatures not exceeding 40 °C. The hydrazones, which were usually obtained in near quantitative yields, were not subjected to further purification and were immediately reacted with IF.

**General Procedure for the Reaction of Hydrazones and IF.** Between 5 and 20 mmol of the substrate (for best results an excess of about 4 mol/equiv of IF was usually used) in 30 mL of cold (−78 °C) $CHCl_3$ solution was added to the cold (−78 °C) IF suspension with vigorous stirring using a vibromixer. The reaction was monitored by either GC or TLC after treating the aliquots with thiosulfate. Where necessary the reaction temperature was allowed to rise either by removing the cooling bath or replacing the acetone/dry ice with another appropriate cooling mixture. Upon completion the reaction was poured into 400 mL of 10% $Na_2S_2O_3$ solution and stirred until colorless, the organic layer was washed with sodium bicarbonate till neutral and dried over anhydrous $MgSO_4$, and the solvent was removed. The crude product was usually purified by vacuum flash chromatography using silica gel 60-H (Merck) and if needed also by HPLC (Waters) on Merck's LiChrosorb Si-100 with mixtures of petroleum ether/EtOAc as eluent. In most cases it was very difficult to separate the α-iododifluoro byproducts in analytical purity, and their yields are based on GC and spectral analysis of the crude reaction mixture. Tables I and II summarize the yields of the various reactions as well as the physical and the spectroscopic data of all described compounds.

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**Registry No.** 1, 98-86-2; **1** (hydrazone), 13466-30-3; **1** (semicarbazone), 2492-30-0; **1** (oxime), 613-91-2; **2**, 657-35-2; **3**, 133932-40-8; **4**, 93-55-0; **4** (hydrazone), 32770-66-4; **4** (DNP hydrazone), 3375-37-9; **4** (semicarbazone), 5470-03-1; **5**, 451-40-1; **5** (hydrazone), 5171-96-0; **6**, 74185-83-4; **7**, 350-62-9; **8**, 119-61-9; **8** (hydrazone), 5350-57-2; **8** (DNP hydrazone), 1733-62-6; **8** (semicarbazone), 14066-73-0; **8** (tosylhydrazone), 4545-20-4; **8** (oxime), 574-66-3; **9**, 360-11-2; **10**, 100-19-6; **10** (hydrazone), 28153-22-2; **10** (*N*-methylhydrazone), 133932-54-4; **10** (semicarbazone), 52376-81-5; **11**, 32471-55-9; **12**, 133932-41-9; **13**, 555-16-8; **13** (hydrazone), 6310-10-7; **13** (semicarbazone), 5315-87-7; **14**, 105-07-7; **14** (hydrazone), 87829-00-3; **15**, 29848-57-5; **16**, 55805-10-2; **17**, 98-53-3; **17** (hydrazone), 62082-37-5; **17** (*N*-methylhydrazone), 133932-55-5; **17** (*N*,*N*-dimethylhydrazone), 58911-63-0; **17** (DNP hydrazone), 54532-12-6; **17** (tosylhydrazone), 41780-53-4; 18, 19422-34-5; 19, 133932-42-0; **20**, 878-13-7; **20** (hydrazone), 133932-51-1; **20** (*N*-methylhydrazone), 133932-56-6; **21**, 502-72-7; **22**, 502-49-8; **22** (hydrazone), 50533-93-2; **22** (semicarbazone), 40338-24-7; **23**, 23170-87-8; **24**, 127794-12-1; **24** (hydrazone), 133932-52-2; **25**, 1164-91-6; **26** (hydrazone), 19640-01-8; **26**, 133932-43-1; **27**, 1827-75-4; **28**, 102-04-5; **28** (hydrazone), 5171-98-2; **29**, 103-79-7; **29** (*N*-methylhydrazone), 16602-83-8; **30**, 693-54-9; **30** (hydrazone), 105232-57-3; **30** (*N*-methylhydrazone), 106094-58-0; **30** (*N*,*N*-dimethylhydrazone), 106094-59-1; **30** (DNP hydrazone), 2675-17-4; **30** (semicarbazone), 3622-72-8; **31**, 112-12-9; **31** (hydrazone), 133932-53-3; **31** (semicarbazone), 89863-30-9; **31** (oxime), 51903-32-3; **32**, 74185-84-5; **33**, 58325-18-1; **34**, 133932-44-2; **35**, 133932-45-3; **36**, 133932-46-4; **37**, 106094-57-9; **38**, 133932-47-5; **39**, 133932-48-6; **40**, 133932-49-7; **41**, 97211-56-8; **42**, 133932-50-0; **43**, 112-44-7; **43** (hydrazone), 84941-27-5; **44**, 62127-44-0; **45**, 134-81-6; **45** (hydrazone), 5344-88-7; **46**, 365-01-5; IF, 13873-84-2; $I_2$, 7553-56-2; $F_2$, 7782-41-4; 3-iodo-2-decanone hydrazone, 133932-57-7; 1-iodo-2-decanone hydrazone, 133932-58-8; 3-iodo-2-dodecanone hydrazone, 133932-59-9; 1-iodo-2-dodecanone hydrazone, 133932-60-2.