FLUORINATION OF METHYL 3-OXOPENTANOATE (MOP) USING DIFLUOROBIS(FLUOROXY)METHANE, BDM

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This paper is dedicated to the memory of Professor Miloš Hudlický who shall always be remembered as a kind gentleman and a skilled fluorine chemist.

Difluorobis(fluoroxy)methane, BDM, is an electrophilic fluorinating agent that is capable of affecting selective monofluorination of 1,3-dicarbonyls such as diketones and ketoesters with very high regioselectivity. For example, in highly acidic anhydrous HF (AHF) solvent, fluorination of methyl 3-oxopentanoate (MOP) with BDM provides methyl 2-fluoro-3-oxopentanoate (MFOP) with 100% conversion and 95% selectivity. In mixtures of HF and methanol, fluorination conversions and selectivity are markedly lower. In comparison, direct fluorination of MOP with dilute F_2 typically affords a fluorinated product that is less pure, being contaminated with radical fluorination byproducts that are difficult to separate. Fluorination of MOP with dilute mixtures of BDM and F_2 is generally more selective than using dilute F_2 alone.

Keywords: Electrophilic fluorination; Fluoroxy compounds; Dicarbonyl fluorination; Fluorinated compounds; Keto esters.

Difluorobis(fluoroxy)methane, BDM, $CF_2(OF)_2$, and to a much greater extent trifluoro(fluoroxy)methane, FTM, CF_3OF, have been used to carry out a number of electrophilic fluorinations; however, their use for the fluorination of 1,3-dicarbonyl compounds has not been previously reported[1–5]. Another O–F bond containing compound, acetyl hypofluorite, has been used successfully in the fluorination of ketoesters and their enolate salts, giving 70–80% of the desired monofluoro product[6,7]; however, there are safety concerns with the large-scale use of this reagent. Similarly, cesium fluoroxy sulfate, $CsSO_3(OF)$ gave a 44% yield of the desired monofluorinated product and 19% of the difluorinated product on reaction with the relatively nucleophilic substrate, 2,4-pentanedione[8].

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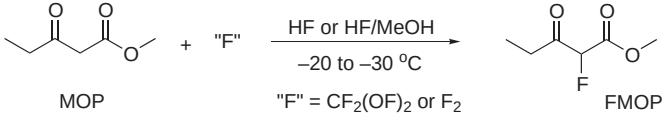
Previously, 1,3-dicarbonyls have been fluorinated directly with fluorine in acidic solvents or in polar solvents containing acidic, or weakly basic, polar additives[9–11]. While this fluorination methodology is reasonably selective, the desired 2-fluoro product still contains significant amounts of impurities, which most commonly result from radical fluorination of the pendant alkyl groups on the substrate, at substrate loadings of only 5–10 wt.%. Others have demonstrated that the substrate loading, in the specific case of methyl 3-oxopentanoate, can be substantially increased in very strong acids (up to 88 wt.% MOP in highly acidic triflic acid); however, the product still contained up to 16 wt.% fluorinated impurities, including the 2,2-difluoro derivative[12]. There are other methods for the preparation of fluorinated dicarbonyl compounds; however, these methods generally employ multiple steps. For example, the dicarbonyl compound is chlorinated and then fluorine introduced by halogen exchange[13]. Unfortunately, this method gives only moderate yields of fluorinated product, 30–80%, that must still be purified by fractional distillation[13]. Many popular methods for the selective fluorination of dicarbonyl compounds using reagent based chemistry have been developed, for example, in the work of Hara, Yoneda, and coworkers using (difluoro-λ^3-iodanyl)toluene and HF·pyridine complex[14], and in the work of Prof. E. Banks and coworkers using Selectfluor® fluorination agent[15]. A comprehensive review of electrophilic fluorination, which includes several examples of α-fluoro carbonyl compound formation, has recently been published[16].

Despite a significant amount of work reported in the literature, there remains the need for a selective method of fluorinating the important 1,3-dicarbonyl compound, MOP, that produces the monofluoro product, methyl 2-fluoro-3-oxopentanoate, MFOP, in high yield and without radical fluorination impurities that are troublesome, if not impossible, to separate.

RESULTS AND DISCUSSION

In the present work, depicted in Eq. (*1*), we have investigated fluorination of the 1,3-dicarbonyl compound, MOP, in HF, and in some cases HF/MeOH solvent at low temperatures, and compared results obtained using N_2-diluted BDM, BDM and F_2 mixtures, and F_2. The results are summarized in Table I.



(*1*)

TABLE I
Experimental data for the low-temperature fluorination of MOP with BDM, F_2, or BDM/F_2 diluted with N_2

Entry	Substrate loading wt.%	Solvent	BDM, eq./ Concentration, vol.%	F_2, eq./ Concentration, vol.%	*T*, °C	Conversion %	Isolated purity[a,b] %	Radical byproducts wt.%
1	10	HF	1/5 in N_2	0	–20	83	82	< 0.5
2	20	1 HF/3 MeOH	0.9/3 in N_2	0	–25	80	72	5
3	10	1 HF/6 MeOH	1.1/3 in N_2	0	–25	40		
4	80	HF	1.1/5 in N_2	0	–20	100	95	4
5	80	HF	0.7/5 in N_2	0.6/4 in N_2	–25	100	68	30
6	50	HF	0.6/5 in N_2	0.5/4 in N_2	–25	95	91	3
7	85	HF	0.6/5 in N_2	0.5/4 in N_2	–25	91	81	7
8	38	HF	0	1.1/10 in 1 : 8 (v/v) O_2/N_2	–30	100	85	11
9	26	HF	0	1.1/10 in 1 : 8 (v/v) O_2/N_2	–30	100	92	5
10	28	HF	0	1.1/10 in N_2	–30	100	81	14–15

[a] Unfluorinated starting material, α,α-difluorinated material, as well as radical fluorination byproducts are included as impurities in calculation of the isolated purity. [b] Radical fluorination byproducts are identified by ^{19}F NMR ($CDCl_3$) and include methyl 2,2-difluoro-3-oxopentanoate: –115.1 s; methyl 2,4-difluoro-3-oxopentanoate: –190.5 dm and –202.0 dd; fluoromethyl 2-fluoro-3-oxopentanoate: –196.0 d and –221.0 m; fluoromethyl 3-oxopentanoate: –230.2 m.

In Table I, the first four entries represent experiments done using dilute (<5 vol.%) BDM for fluorination of MOP in either neat HF, or HF/MeOH mixtures. Comparing entries 1 and 4 that were done in strong acid solution, <1% radical fluorination impurities are observed at 10 wt.% MOP loading, however, just 83% conversion was obtained. On the other hand, 100% conversion of MOP was obtained at 80 wt.% loading, which essentially represents fluorination of the substrate in the absence of solvent but in the presence of a small amount of acid, and just 4% fluorination impurities (including 2,2-difluoro MOP) were obtained. Radical fluorination impurities are observed to increase if the acid solvent is diluted with methanol (entry 2), and at higher levels of methanol dilution (entry 3), the substrate becomes deactivated towards fluorination, with the result being lower conversion of MOP substrate.

If the dilute BDM stream contains some fluorine, selectivity of the fluorination reaction is reduced; however, BDM/F_2/N_2 mixtures (entries 5–7) still perform better than F_2/air or F_2/N_2 at relatively high substrate loadings. Thus, a 50 wt.% substrate solution in HF (entry 6) showed only 3 wt.% radical fluorination impurities when fluorinated with a 55 : 45 mixture of BDM/F_2 diluted with N_2, compared to 11wt. % radical fluorination impurities for a 38 wt.% substrate solution fluorinated with F_2/air (entry 8) and 14–15 wt.% radical fluorination impurities for a 26 wt.% solution fluorinated with F_2/N_2 (entry 10).

Finally, we found that by addition of oxygen to the diluting gas, the levels of radical fluorination impurities could be significantly reduced. Thus, comparing entries 9 and 10, just 5% radical impurities were obtained when a 26 wt.% MOP solution in HF was fluorinated at –30 °C with 10% F_2 diluted with O_2/N_2, whereas without O_2 in the diluent gas (entry 10), the amount of radical fluorination impurities was increased significantly to 14–15 wt.%.

A process is described wherein low temperature (–20 °C) selective fluorination of concentrated (80 wt.%) methyl 3-oxopentanoate in anhydrous HF with BDM provides methyl 2-fluoro-3-oxopentanoate with 100% conversion, 95% selectivity, and just 4% radical fluorination byproducts.

EXPERIMENTAL

BDM was produced in a flow system as previously described[5]. MOP (Wacker Chemical) and F_2 (Air Products) were used as received.

^{1}H and ^{19}F NMR spectra were recorded on a Bruker DMX-500 NMR spectrometer operating at 500.243 and 470.696 MHz, respectively. ^{1}H NMR spectra were referenced internally to the deuterated solvent and ^{19}F NMR spectra were referenced externally to $CFCl_3$. Chemical

shifts are reported in ppm (δ-scale), coupling constants (*J*) in Hz. A positive chemical shift denotes a resonance to low field of the reference.

Fluorination of MOP in HF with BDM

In a typical experiment, methyl-3-oxopentanoate is charged to a 100 ml FEP reactor equipped with a valve. The reactor and contents are externally cooled to *ca* –35 °C and the required amount of anhydrous HF is transferred in under static vacuum. Following this, BDM (≈1 eq.) as a 5% BDM/N_2 stream is delivered at 225 ml min^{-1} into the reactor at –20 °C, with the effluent from the reactor being directed through a soda-lime scrubber. When the BDM addition is complete, the HF solvent is pumped off through a soda-lime scrubber. The reactor is then opened and the contents poured into 30 ml H_2O. The resulting aqueous solution is neutralized with $NaHCO_3$ and the product extracted into diethyl ether. After removal of ether, a portion of the resulting yellow liquid product is dissolved in $CDCl_3$ solvent and subsequently analyzed by ^1H and ^{19}F NMR spectroscopy. The results are shown in Table I. NMR parameters are summarized below.

Methyl 2-fluoro-3-oxopentanoate. ^1H NMR ($CDCl_3$): 5.04 d, J = 48.5; 3.47 s; 2.35 m; 0.68 t, J = 7.4. ^{19}F NMR ($CDCl_3$): –197.2 d, J = 48.5.

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