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3-Fluoro-1-hydroxypropan-2-one (Fluorohydroxyacetone) and Some Esters. Syntheses and Effects in BDF_1 Mice[1]

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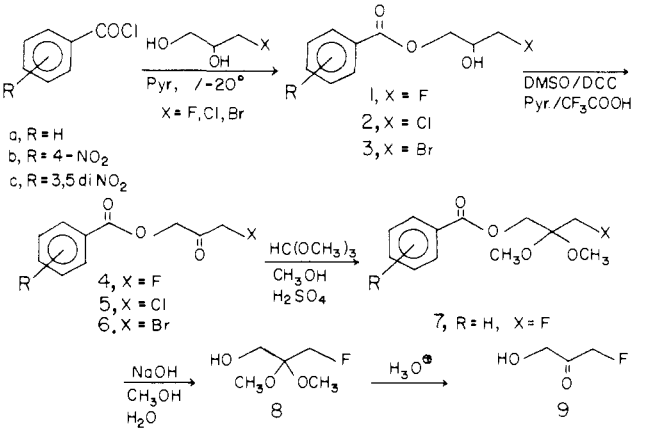
1-(Benzoyloxy), 1-(4-nitrobenzoyloxy), and 1-(3,5-dinitrobenzoyloxy) derivatives of 3-fluoro-, 3-chloro-, and 3-bromopropan-2-one were prepared by oxidation of the 1-benzoyloxy-3-halopropan-2-ols in turn prepared from the appropriate benzoyl chloride and 3-halo-1,2-propanediols. 1-Benzoyloxy-3-fluoropropan-2-one was allowed to react with acidic trimethyl orthoformate to yield 1-benzoyloxy-2,2-dimethoxy-3-fluoropropane which upon basic hydrolysis afforded 2,2-dimethoxy-3-fluoropropan-1-ol (fluorohydroxyacetone dimethyl ketal). This was deketalized with aqueous HCl to afford 3-fluoro-1-hydroxypropan-2-one (fluorohydroxyacetone), the title compound. By reacting 1-chloro-3-fluoropropan-2-one and 1,3-dichloropropan-2-one with potassium acetate, 1-acetoxy-3-fluoropropan-2-one and 1-acetoxy-3-chloropropan-2-one (fluoro- and chlorohydroxyacetone acetate, respectively) were obtained. Similarly, sodium benzoate and 1-chloropropan-2-one produced 1-benzoyloxypropan-2-one. Structure–activity relationships are discussed which relate chemical structure, alkylating ability, toxicity, and antitumor effects. Comparative toxicities in mice showed decreasing toxicity, on a molar basis, in the 1-benzoyloxy-3-halopropan-2-one series of bromo > fluoro > chloro. Ketones were much more toxic than the corresponding alcohols. In general the phosphate and benzoyloxy derivatives are more toxic than acetoxy compounds, with nitro-substituted benzoyloxy derivatives being much less toxic.

Differences in glycerolipid metabolism between neoplastic and host normal cells may be exploitable for cancer chemotherapy. In one such chemotherapeutic approach, we have prepared 1-halo analogues of DL-,[3a] D-,[3b] and L-glycerol 3-phosphate[3c] and the corresponding glycerols as agents designed to exploit differences in levels of cytosolic NAD-linked glycerol-3-phosphate dehydrogenase in neoplastic compared to normal cells. We have also prepared 1-halo analogues of dihydroxyacetone 3-phosphate potentially to affect glycerol-3-phosphate dehydrogenase or the acyldihydroxyacetone phosphate alternative pathway to phosphatidic acid and ether lipids.[4]

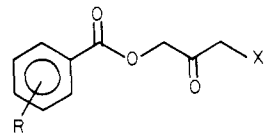
The use of phosphorylated analogues as chemotherapeutic agents is likely to be limited by transport restrictions in vivo, suggesting the use of deoxyfluoroketohexoses[5] as transportable precursors of the fluorotriose phosphates, or suggesting the use of nonphosphorylated derivatives of the fluorotrioses. Moreover, LaBelle and Hajra[6] have observed that monobenzoate esters of dihydroxyacetone inhibit the acyldihydroxyacetone phosphate pathway but that inhibition in vivo is limited by the activity of a kinase generating the phosphoryl ester of 1,3-dihydroxyacetone monobenzoate, which is noninhibitory.

Scheme I



It is apparent that fluorohydroxyacetone and nonphosphorylated derivatives of it might serve both to avoid transport limitations and, in the case of the esters, to function as potential inhibitors of the acyldihydroxyacetone phosphate pathway incapable of deactivation by phosphorylation in vivo.

Table I. 1-Benzoyloxy-3-halopropan-2-ones



Compd	R	X	Mp or bp (mm), °C	Recrystn solvent[a]	Yield,[b] %
4a	H	F	64	Et_2O	45
4b	4-NO_2	F	110	Me_2CO-petr ether	25
5a	H	Cl	94[c]	C_6H_{12}	25
5b	4-NO_2	Cl	114-116	Me_2CO-petr ether	28
5c	3,5-$(NO_2)_2$	Cl	126	Et_2O	35
6a	H	Br	87-88[d]	C_6H_{12}	19
10	H	H	100 (0.01)[e]		95[f]

[a] All compounds required repeated crystallization and use of activated charcoal to be obtained in a pure state. [b] Yields are of purified product based on halopropanediol and have not been maximized. [c] Lit.[8] 93.5-95.5 °C. [d] Lit.[8] 84-86 °C. [e] Lit.[11] 116 °C (1.5 mm). [f] Yield based on 1-chloropropan-2-one.

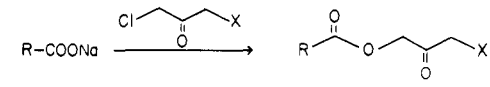
In this paper we present the synthesis of fluorohydroxyacetone, selected aliphatic and aromatic esters, and corresponding chloro and bromo esters. The in vivo effects of these analogues in BDF_1 mice have been determined since a number of important tumor model systems used for chemotherapeutic evaluation are carried in this hybrid.

Chemistry. The benzoate esters of 3-fluorohydroxypropan-2-one, 3-chlorohydroxypropan-2-one, and 3-bromohydroxypropan-2-one were prepared (Scheme I) by treating the requisite 3-halopropane-1,2-diol with benzoyl chloride to give the 1-benzoyloxy-3-halopropan-2-ols **1a,b**, **2a–c**, and **3a**. These were used without further purification in a Pfitzner–Moffatt oxidation[7] as modified by Hartman[8] to yield the ketones **4a,b**, **5a–c**, and **6a** (Table I). The 1-(4-nitro- and 3,5-dinitro)benzoyloxy-3-halopropan-2-ols **1b** and **2b,c** were prepared by dissolving the solid substituted benzoyl chlorides in THF and adding this to the cooled 3-halopropane-1,2-diol–pyridine solution. The oxidations of **1b**, **2b**, and **2c** were conducted in a THF–Et_2O mixture (1:1) because the halo esters were not soluble in Et_2O. In some cases, particularly that of 1-(3,5-dinitrobenzoyloxy)-3-chloropropan-2-one (**5c**), the product is only slightly soluble in Et_2O, so that large volumes were needed in the work-up and subsequent recrystallization.

Treatment of **4a** with trimethyl orthoformate and sulfuric acid in dry methanol afforded 1-benzoyloxy-2,2-dimethoxy-3-fluoropropane (**7**) in nearly quantitative yield. This was readily hydrolyzed by aqueous methanolic sodium hydroxide to afford 2,2-dimethoxy-3-fluoropropan-1-ol (fluorohydroxyacetone dimethyl ketal) (**8**), which upon treatment with aqueous acid yielded the free 3-fluoro-1-hydroxypropan-2-one (fluorohydroxyacetone) (**9**) in a reaction monitored by TLC. The ketal **8** does not reduce Fehling's solution even at elevated temperature, while **9** reacts readily with slight warming. This is in accord with the observations of Romo[9] on 2,2-diethoxypropane-1,3-diol (dihydroxyacetone diethyl ketal) and free 1,3-dihydroxypropan-2-one (dihydroxyacetone). Compound **9** was not isolated due to the well-known instability of free α-hydroxy ketones.[10]

1-Acetoxy-3-chloropropan-2-one[11] and 1-acetoxy-3-fluoropropan-2-one (**11** and **12**) were prepared (Scheme II) by treating 1,3-dichloropropan-2-one and 1-chloro-3-fluoropropan-2-one,[4] respectively, with KOAc. An analogous route[12] employing 1-chloropropan-2-one and sodium benzoate yielded 1-benzoyloxypropan-2-one (hydroxyacetone benzoate) (**10**).

Scheme II



R = C_6H_5, CH_3 X = H, F, Cl

10, R = C_6H_5; X = H
11, R = CH_3; X = Cl
12, R = CH_3; X = F

Table II. Toxicity in Female BDF_1 Mice[a]

Compd	LD_{50} (BDF_1 mice) mg/kg	mmol/kg
1a	45	0.23
2a	450	2.10
3a	355	1.37
4a	36	0.18
4b	90	0.37
5a	70	0.33
5b	170	0.66
5c	270	0.88
6a	30	0.12
7	57	0.23
8	28	0.20
9	18	0.22
10	1400	7.86
11	71	0.47
12	30	0.22
3-Fluoro-1,2-propanediol[b]	20	0.21
3-Chloro-1,2-propanediol[c]	200	1.80
3-Bromo-1,2-propanediol[d]	212	1.37
1,2-Diacetoxy-3-fluoropropane[e]	40	0.22
1,2-Diacetoxy-3-chloropropane[f]	340	1.74
1-FdG-3P DCHA[g]	110	0.30
3-Fluoro-1-hydroxypropan-2-one phosphate[h]	30	0.15
1-CldG-3P DCHA[i]	794	2.10
3-Chloro-1-hydroxypropan-2-one phosphate[j]	75	0.36

[a] See Experimental Section for general methods. [b] Fluorodeoxyglycerol. [c] Chlorodeoxyglycerol. [d] Bromodeoxyglycerol. [e] Fluorodeoxyglycerol diacetate, prepared by the general method of B. T. Golding, *J. Chem. Soc., Perkin Trans. 1*, 1214 (1973). [f] Chlorodeoxyglycerol diacetate. [g] 1-Fluorodeoxyglycerol 3-phosphate dicyclohexylammonium salt.[3] [h] Fluorohydroxyacetone phosphate.[4] [i] 1-Chlorodeoxyglycerol 3-phosphate dicyclohexylammonium salt.[3] [j] Chlorohydroxyacetone phosphate.[4]

Results and Discussion

Table II lists the toxicities of the esters of the 3-halo-1-hydroxypropan-2-ones and their precursors in a mouse strain used for chemotherapy testing. Several points of potential importance are apparent.

The toxicity of the fluoro compounds, on a molar basis, is relatively independent of molecular structure, ranging from 0.15 to 0.37 mmol/kg in both the glycerol and dihydroxyacetone analogue series.

In the case of the chloro and bromo compounds the keto analogues are significantly more toxic on a molar basis than the corresponding alcohols. Comparison of the alcohol, 1-benzoyloxy-3-chloropropan-2-ol (**2a**), with its corresponding ketone, 1-benzoyloxy-3-chloropropan-2-one (**5a**), shows a nearly sevenfold increase in toxicity. The phosphate esters of chlorodeoxyglycerol and chlorohydroxyacetone show a comparable relationship. The bromo compounds show an even more impressive increase in toxicity when **3a** is oxidized to **6a**, an increase of 11-fold. The greatest increase in toxicity in the fluoro analogue

series is that found in the phosphate esters of fluorodeoxyglycerol and fluorohydroxyacetone where toxicity just doubles.

Toxicity of the chloro- and bromoketo analogues is related to their alkylating ability[13] since the chloro ketones are almost as toxic as the fluoro ketones, even though the fluoro analogues are apparently being metabolized to highly toxic precursors of fluoroacetate.[14] In the case of the bromo analogues 1-benzoyloxy-3-bromopropan-2-one (**6a**) is more toxic than the corresponding chloro compound and even more toxic than the corresponding fluoro compound. In the alcohol series the chloro and bromo analogues are relatively nontoxic, while the fluoro analogues remain highly toxic. The toxicity of the chloro- and bromopropanediols and their benzoate esters, due to alkylation, apparently proceeds through the epoxide derivatives,[15] the formation of which is pH dependent. The ketones are already powerful alkylating agents and do not require transformation. Moreover, 1-benzoyloxypropan-2-one (**10**), which is not an alkylating agent, is also completely nontoxic even at 1 g/kg.

Toxicity of the esters of 3-chloro-1-hydroxypropan-2-one, on a molar basis, is in the series benzoate > phosphate > acetate > 4-NO_2^- benzoate > 3,5-dinitrobenzoate. With both the chloro and fluoro analogues of dihydroxyacetone, the toxicity is reduced by half in going from the benzoate ester to the 4-nitrobenzoate ester. A further reduction is produced by going to 1-(3,5-dinitrobenzoyloxy)-3-chloropropan-2-one (**5c**) which is nearly one-third the toxicity of the unsubstituted benzoate **5a**.

These same compounds have been examined for chemotherapeutic effects in vivo against L1210 mouse leukemia and Ehrlich ascites carcinoma (Babiarz-Tracy, Simon, Pero, and Fondy, unpublished results). The compounds in the chloro ketone series were much more active than the corresponding alcohol analogues and the esters of 3-fluoro-1-hydroxypropan-2-one were much less active than the 3-chloro-1-hydroxypropan-2-one esters. The benzoate and nitrobenzoate esters of 3-chloro-1-hydroxypropan-2-one (**5a,b**) completely cured (180-day survival) mice bearing Ehrlich ascites carcinoma when used at a dose which was well below the LD_{50}. The phosphate and benzoate esters of 3-fluoro-1-hydroxypropan-2-one inhibited Ehrlich carcinoma. However, the doses of these compounds which produced significant chemotherapeutic responses also showed delayed toxicity. Parallel studies with ascites L1210 cells treated in vitro with 1-benzoyloxy-3-chloropropan-2-one (**5a**) and reimplanted in vivo produced 85–100% 60-day survivors in immune competent BDF_1 mice but killed 85% of immunosuppressed animals (Rittmann, Roberts, and Fondy, unpublished results). This demonstrates that when L1210 cells are altered in vitro with **5a**, viable cells in the treated cell population do not retain their tumorigenicity. Since we have observed that the benzoates and nitrobenzoates are active against tumor model systems in vivo and in culture, the modulation of toxicity by introduction of nitro groups into the aromatic esters assumes considerable potential importance.

Experimental Section

General. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and were within ±0.4%. Melting points are uncorrected. IR spectra were obtained from a Beckman IR-33 grating infrared spectrophotometer and ^1H NMR spectra in $CDCl_3$ with a Varian Associates A-60 spectrometer using Me_4Si as internal standard; ^{13}C NMR spectra were obtained from a Varian Associates CFT-20 operating in the Fourier transform mode. Reduced pressure evaporations were done with a Buchler flash evapaorator and a bath temperature <40 °C. Animal temperatures were monitored as previously detailed.[3c,16] Toxicities (LD_{50}) were determined in female BDF_1 mice by intraperitoneal injection of the compound in 0.85% isotonic saline or 10% Tween 80 in 0.85% isotonic saline depending on solubility. TLC's were run on Eastman silica gel plates, using petroleum ether–ether (2:1) as solvent, and developing them with 2% 2,4-dinitrophenylhydrazine in methanol containing 4% H_2SO_4.

Epichlorohydrin, epibromohydrin, solketal (acetone ketal of glycerine), and more common reagents were obtained from Aldrich Chemical Co. 3-Bromo-1,2-propanediol was prepared from epibromohydrin by the method of Winstein and Goodman.[17] 3-Chloro-1,2-propanediol, 1-chloropropan-2-one, and 1,3-dichloropropan-2-one were products of Eastman Kodak. 1,3-Difluoropropan-2-ol, 1-chloro-3-fluoropropan-2-ol, and 1-chloro-3-fluoropropan-2-one were prepared as previously described.[4,18] Epifluorohydrin was prepared by the method of Rozen.[19] 3-Fluoro-1,2-propanediol was prepared by acid-catalyzed ring opening of epifluorohydrin[3a,20] or from solketal via its tosylate.[3b]

Synthesis. 1-Benzoyloxy-3-chloropropan-2-one (chlorohydroxyacetone benzoate) (5a) was prepared from 3-chloro-1,2-propanediol via 1-benzoyloxy-3-chloropropan-2-ol (**2a**) by the method of Hartman:[8] mp 94 °C (lit.[8] 93.5–95.5 °C); IR (Nujol) 1740, 1760 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.2–7.3 (m, 5 H, aromatic), 5.1 (s, 2 H, $OCH_2C{=}O$), 4.21 (s, 2 H, $ClCH_2$).

1-Benzoyloxy-3-bromopropan-2-one (bromohydroxyacetone benzoate) (6a) was prepared from 3-bromo-1,2-propanediol[17] via 1-benzoyloxy-3-bromopropan-2-ol (**3a**) using Hartman's[8] method: mp 87–88 °C (lit.[8] 84–86 °C); IR (Nujol) 1750, 1770 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.2–7.3 (m, 5 H, aromatic), 5.10 (s, 2 H, $OCH_2C{=}O$), 4.0 (s, 2 H, $BrCH_2$).

1-Benzoyloxy-3-fluoropropan-2-ol (1a) was prepared by adding 68 g (0.49 mol) of benzoyl chloride, slowly and with good stirring, to 45.3 g (0.48 mol) of 3-fluoro-1,2-propanediol in 300 mL of pyridine, cooled to −15 °C. Addition required 2.25 h after which the mixture was kept at 4 °C for 4 h. About 200 mL of pyridine was removed at reduced pressure; the residue was taken up in 500 mL of $CHCl_3$, washed with 1 N H_2SO_4 (3 × 250 mL) and saturated aqueous $NaHCO_3$ (2 × 250 mL) (all wash solutions were at 4 °C), and dried over Na_2SO_4. Removal of the $CHCl_3$ gave 83 g (88%) of a thick oil used without further purification: IR (neat) 3530 (OH), 1750 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.1–7.2 (m, 5 H, aromatic), 4.1 (dd, 2 H, FCH_2, J_{HF} = 48 Hz, J_{HH} = 4.5 Hz), 3.96 (d, 2 H, OCH_2CH, J_{HF} = 3 Hz, J_{HH} = 3.4 Hz), 3.9 (m, 1 H, CHOH, J_{HF} = 7 Hz, J_{HH} = 3.5 Hz).

1-Benzoyloxy-3-fluoropropan-2-one (Fluorohydroxyacetone Benzoate) (4a). Alcohol **1a** (45 g, 0.23 mol), DCC (90 g, 0.43 mol), 20 mL of Me_2SO, and 3 mL of pyridine were dissolved in 400 mL of dry Et_2O and cooled to 4 °C. To the above well-stirred solution 3 mL of CF_3COOH was added, and the ice bath was removed. Within 10 min vigorous refluxing ensued requiring ice cooling, for a short time. The mixture was stirred at ambient temperature for an additional 45 min. The ice bath was replaced and 25 g of oxalic acid in 50 mL of MeOH was added slowly to destroy excess DCC. After stirring for 30 min the DCU was filtered off and washed with 300 mL of Et_2O. The combined Et_2O solutions were washed with H_2O (1 × 250 mL) and saturated aqueous $NaHCO_3$ (3 × 250 mL) and dried over Na_2SO_4. Removal of Et_2O yielded a thick yellow oil which was stored at 4 °C and repeatedly triturated with C_6H_{12} to afford several crops of crystals. These crystals were taken up in the minimum amount of Et_2O at ambient temperature, treated with decolorizing carbon, filtered, and chilled in a dry ice–MeOH bath. Filtration afforded 22.5 g (45% based on 3-fluoro-1,2-propanediol): mp 64 °C; IR (Nujol) 1740, 1760 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.1–7.2 (m, 5 H, aromatic), 5.1 (d, 2 H, $OCH_2C{=}O$, J_{HF} = 3 Hz), 4.95 (d, 2 H, FCH_2, J_{HF} = 48 Hz). Anal. ($C_{10}H_9O_3F$) C, H, F.

1-Benzoyloxy-2,2-dimethoxy-3-fluoropropane (fluorohydroxyacetone dimethyl ketal benzoate) (7) was prepared by treating 12 g (0.06 mol) of **4a** with 95 g (0.9 mol) of trimethyl orthoformate and 500 mg of concentrated H_2SO_4 in 100 mL of MeOH. After 36 h, TLC showed complete disappearance of **4a** (R_f 0.60) and a new spot at R_f 0.79. The H_2SO_4 was neutralized with solid K_2CO_3 and the solution worked up to afford 14 g of cloudy oil. Upon standing at −20 °C for several days this produced large crystals and yielded 13 g (90%) of product containing some methyl benzoate, which was extremely difficult to remove at this point. It was readily removed at the next step so rigorous pu-

rification was not attempted. A sample purified by high-vacuum sublimation had mp 57–58 °C: IR (Nujol) 1755 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.2–7.25 (m, 5 H, aromatic), 4.5 (d, 2 H, FCH_2, J_{HF} = 48 Hz), 4.5 (d, 2 H, OCH_2–, J_{HF} = 3 Hz), 3.35 (s, 6 H, $2OCH_3$).

2,2-Dimethoxy-3-fluoropropan-1-ol (Fluorohydroxyacetone Dimethyl Ketal) (8). Compound **7** (1.8 g, 0.013 mol) was stirred with 10 mL of MeOH and 4 N NaOH (aqueous, 2 mL), while the reaction was monitored by TLC. The starting material (R_f 0.79) disappeared and **8** (R_f 0.53) appeared, with the reaction complete in 12 h. Removal of solvent and extraction with Et_2O, drying over K_2CO_3, and removal of solvent gave crude product containing quantities of methyl benzoate. It was purified by high-vacuum microdistillation (0.25 mm, bath 35 °C), taken up in 3 mL of H_2O, and extracted with hexane, and the H_2O was removed to yield 780 mg (70%): IR (neat) 3450 cm^{-1} (OH), no carbonyl present at 1750 cm^{-1}; NMR ($CDCl_3$) δ 4.42 (d, 2 H, FCH_2, J_{HF} = 48 Hz), 3.7 (d, 2 H, OCH_2, J_{HF} = 3 Hz), 3.35 (s, 6 H, 2 OCH_3), 2.0 (s, br, 1 H, OH); ^{13}C NMR ($CDCl_3$) shows three doublets ($^1J_{CF}$ = 173 Hz, $^2J_{CF}$ = 20.4 Hz, $^3J_{CF}$ = 1.3 Hz) and a singlet due to the dimethyl ketal carbons. The ^{13}C–^{19}F coupling constants are in accord with literature values[21] and those of 3-fluoro-1,2-propanediol ($^1J_{CF}$ = 166 Hz, $^2J_{CF}$ = 19 Hz, and $^3J_{CF}$ = 8.5 Hz). Anal. ($C_5H_{11}O_3F$) C, H, F.

The dimethyl ketal **8** is stable for long periods of time when stored at −20 °C, showing no sign of dimerization, and in neutral aqueous solutions shows no loss of methanol over several days. It does not reduce Fehling's solution; however, after brief treatment with 0.1 N HCl it readily affords the deketalized product **9** which reacts rapidly. Free **9** does not react as readily with Fehling's solution as dihydroxyacetone.

3-Fluoro-1-hydroxypropan-2-one (fluorohydroxyacetone) (9) was prepared by the deketalization of **8**. A solution of 50 mg (0.36 mmol) of 3-fluoro-2,2-dimethoxypropan-1-ol in 1.0 mL of H_2O was brought to pH 1–2 with concentrated HCl and then allowed to stand at 37 °C for several hours. During that time 20-μL aliquots were taken and run in the above TLC system along with an aqueous neutral solution of **8** as control, until the acidic solution showed no starting material (R_f 0.53) but only very slowly migrating material (R_f 0.15). The solution was neutralized with solid $NaHCO_3$ and the volume then adjusted with saline solution for pharmacological studies.

1-Benzoyloxypropan-2-one (hydroxyacetone benzoate) (10) was prepared by a modification of the method of Graham.[12] Sodium benzoate (54 g, 0.4 mol), 1-chloropropan-2-one (18 g, 0.2 mol), and NaI (1.5 g, 0.01 mol) were refluxed in Me_2CO (300 mL) for 8 h, yielding 34 g (95%) of product: bp 100 °C (0.1 mm) [lit.[11] bp 116 °C (1.5 mm)]; IR 1750 cm^{-1} (C=O); NMR ($CDCl_3$) δ 8.1–7.2 (m, 5 H, aromatic), 4.81 (s, 2 H, OCH_2C=O), 2.10 (s, 3 H, CH_3).

1-Acetoxy-3-chloropropan-2-one (chlorohydroxyacetone acetate) (11) was prepared by the method of Hess and Fink[10] as modified by Clark and Howes[22] and purified by a second fractional distillation to remove traces of 1,3-diacetoxypropan-2-one: bp 60–63 °C (0.20–0.30 nm) [lit.[18] bp 112–114 °C (16 mm)]; IR 1765 cm^{-1} (C=O); NMR ($CDCl_3$) δ 4.88 (s, 2 H, OCH_2C=O), 4.26 (s, 2 H, CH_2Cl), 2.15 (s, 3 H, CH_3).

1-Acetoxy-3-fluoropropan-2-one (fluorohydroxyacetone acetate) (12) was prepared as 11 using 1-chloro-3-fluoropropan-2-one (19 g, 0.17 mol) and KOAc (29 g, 0.35 mol) which were refluxed 6 h in 150 mL of AcOH. Filtration and stripping of solvents afforded 14 g of dark brown oil. Repeated fractional distillation gave 5 g (21%) of a bright yellow oil: bp 38 °C (0.1 mm); IR (neat) 1775 cm^{-1} (br, C=O); NMR ($CDCl_3$) δ 4.95 (d, 2 H, FCH_2, J_{HF} = 47 Hz), 4.85 (d, 2 H, CH_2C=O, J_{HF} = 2 Hz), 2.15 (s, 3 H, CH_3). Anal. ($C_5H_7O_3F$) H; C: calcd, 44.78; found, 43.58; F: calcd, 14.16; found, 15.44. The differences between calculated and found values in the analysis are due to traces of 1,3-difluoropropan-2-one present in the starting material. This codistills with the product, and it is not detectable by NMR.

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References and Notes

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