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A CONVENIENT NEW SYNTHESIS OF α-FLUOROCARBONYL COMPOUNDS

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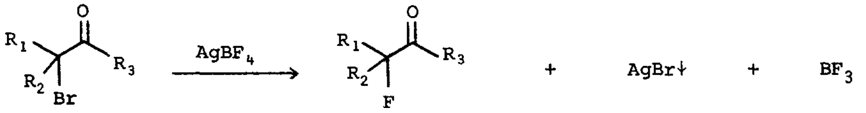
Abstract

The reaction between tertiary α-bromo ketones or aldehydes and silver tetrafluoroborate in ether affords α-fluorocarbonyl compounds. Neighboring group participation by the carbonyl oxygen is proposed to account for the products and by-products.

Published methods[1] for the synthesis of α-fluoro ketones or aldehydes (1) suffer from the disadvantages of requiring several steps and/or inconvenient reagents. Prompted by a recent report by Rozen and Menahem[2] concerning this problem we describe herein a convenient synthesis of α-fluorocarbonyl compounds, involving simply reaction of the corresponding α-bromo compound with silver tetrafluoroborate in ether (eq. 1). The reaction is mild and uses readily available materials. On the other hand, it is not applicable to primary ($R_1 = R_2 = H$) or chloro ketones (Table I). The observed dependence upon the degree of α-alkyl substitution permits selective exchange by one bromine of an unsymmetrical α,α'-dibromo ketone (entry 6, Table I). The only by-products in the reactions proceeding to α-fluoro ketones are the corresponding α,β-unsaturated ketones (3). Reactions carried out in nucleophilic solvents (CH_3OH or CH_3CO_2H) afford the corresponding α-methoxy or α-acetoxy ketones.



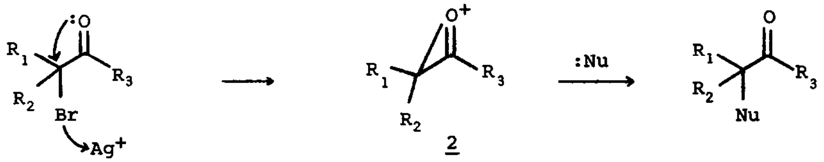
(1)

The fact that tertiary α-bromo ketones react, while primary bromo ketones do not, indicates the silver ion-assisted reaction is more accurately described as an ionization than as an S_N2 process (which would proceed more rapidly with primary bromo ketones). Because of the presumed difficulty of generating a positive charge adjacent to a carbonyl group, we believe that the reaction involves neighboring group participation by the carbonyl oxygen, i.e.,

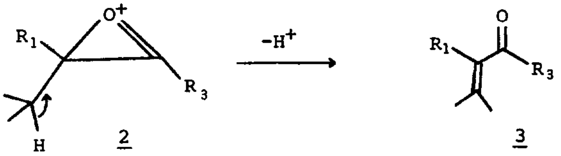
Table I. Reaction of α-Bromocarbonyl Compounds with Silver Tetrafluoroborate[a]

Entry	Halide	Solvent	Products[8]
1	$CH_3CO\underset{Br}{C}(CH_3)_2$	Et_2O	$CH_3CO\underset{F}{C}(CH_3)_2$,[1b] 87% $CH_3COC(CH_3){=}CH_2$,[9] 10%
2	$(CH_3)_2CHCO\underset{Br}{C}(CH_3)_2$ ($\underline{11}$)[10]	Et_2O	$(CH_3)_2CHCO\underset{F}{C}(CH_3)_2$ ($\underline{12}$),[11] 72% $(CH_3)_2CHCOC(CH_3){=}CH_2$ ($\underline{13}$),[12] 17%[b]
3	$BrCH_2CO\underset{Br}{C}(CH_3)_2$[13]	Et_2O	$BrCH_2CO\underset{F}{C}(CH_3)_2$,[11] 87% $BrCH_2COC(CH_3){=}CH_2$,[11] 9%[c]
4	$(CH_3)_2\underset{Br}{C}CO\underset{Br}{C}(CH_3)_2$	Et_2O[f]	$(CH_3)_2\underset{Br}{C}CO\underset{F}{C}(CH_3)_2$,[11] 30% $(CH_3)_2\underset{F}{C}COC(CH_3){=}CH_2$,[11] 60% $(CH_3)_2\underset{F}{C}CO\underset{F}{C}(CH_3)_2$,[11] trace
5	$(CH_3)_2\underset{Br}{C}CHO$ ($\underline{4}$)[14]	Et_2O	$(CH_3)_2\underset{F}{C}CHO$,[1b] 70% $(CH_3)_2CHCO_2H$, 15%
6	$\underline{11}$	CH_3OH	$(CH_3)_2CHCO\underset{OCH_3}{C}(CH_3)_2$,[10] 50% $\underline{13}$, 12%[d]
7	$\underline{11}$	AcOH	$\underline{12}$, 42% $\underline{13}$, 21% $(CH_3)_2CHCO\underset{OAc}{C}(CH_3)_2$,[15] 25%[e]
8	$\underline{4}$	CH_3OH	$(CH_3)_2CHCO_2CH_3$, 40% $(CH_3)_2\underset{OCH_3}{C}CH(OCH_3)_2$,[16] 40% $(CH_3)_2\underset{OH}{C}CH(OCH_3)_2$, 20%
9	$(CH_3)_3CCOCH_2Br$[17]	Et_2O	No reaction
10	$CH_3CO\underset{Cl}{C}(CH_3)_2$[18]	Et_2O	No reaction
11	$(CH_3)_2\underset{Cl}{C}CHO$[19]	Et_2O	No reaction

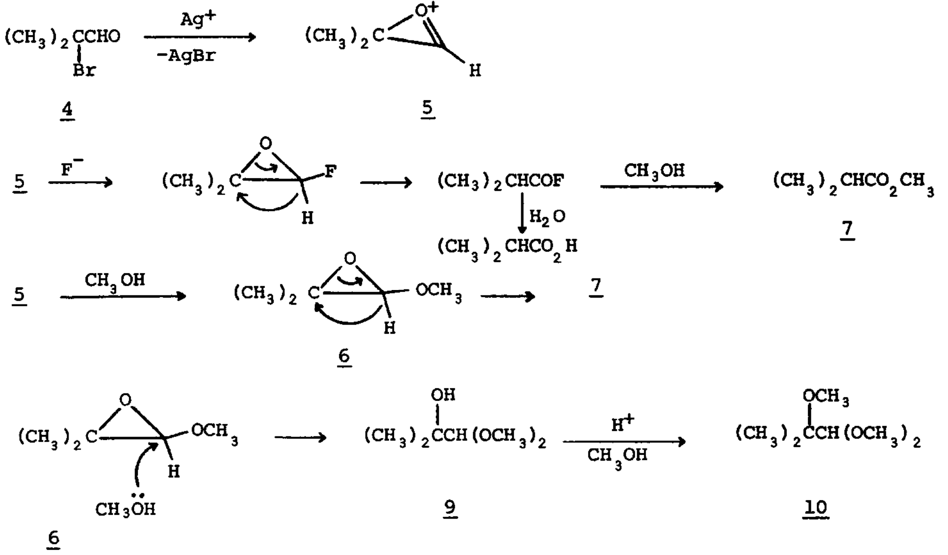
[a] The ratio of halide to $AgBF_4$ was 1:1 except where noted. Several reactions afforded some starting material; yields are uncorrected for this. [b] 4% starting material. [c] 2% starting material. [d] % starting material. [e] 8% starting material and 4% α-hydroxyketone also found. [f] 2:1 ratio of AgBF : bromide.



rather than formation of a free α-ketocarbonium ion. This mechanism is further supported by the observed by-products, e.g., unsaturated ketones 3:



and substances 7 - 10, formed from bromoaldehyde 4 in methanol:



(Compound 10 could arise by other routes, e.g., attack by methanol at the tetrahedral carbon of 5, with subsequent conversion of the resulting aldehyde to 10.) Epoxy ether 6 has previously been shown to afford 9 by reaction with methanol.[3] Cyclic oxonium ions have previously been invoked in the reactions of α-haloketones with $AgSbF_5$,[4] substitution on α-haloketones through oxirane mechanisms has been proposed,[5] and rearrangements of α-substituted oxiranes in acidic media are also well-known.[6] We have considered the possibility that ketenes are intermediates in the formation of 7 and 8, but are inclined to discount this possibility, since no diketenes or derived products are observed. The conversion of 2 to α-substituted carbonyl compounds might occur directly by attack at the α-carbon of species 2 (an S_N2-like process) (path A) or by attack at the carbonyl carbon of 2 to form intermediates similiar to 6, which subsequently rearrange (path B). Although route B appears attractive in view of the apparent involvement of oxirane intermediates in the case of bromoaldehyde 4 (formation of 7-10) and literature precedents, we cannot exclude the simpler route A.

Isolation of α-fluoroketone 12 in acetic acid (run 7) but not in methanol is interesting. It suggests that substitution in the less polar and less nucleophilic solvent acetic acid (and presumably also in ether) involves capture of fluoride ion in a tight ion pair. This is not unreasonable: even with assistance by silver ion and presumably also by the neighboring carbonyl group, ionization to 2 must be a marginal process, as shown by the facts that (a) replacement of bromine by chlorine causes the reaction to fail completely (runs 10 and 11) even though bromine is only 25-50 times better than chlorine as a leaving group,[7] and (b) primary α-bromo ketones also fail to react (runs 3 and 9).

Experimental. Run no. 1 is representative. 1.65 g (0.01 mol) of 2-bromo-2-methyl-3-butanone and 1.947 g (0.01 mol) of AgBF were allowed to react overnight at room temperature in 70 ml of dry ether. After filtration of silver bromide, washing of the filtrate with water, drying ($MgSO_4$), and careful removal of the solvent (Vigreux column), the residual liquid was separated by vpc (5% DEGS on Chromosorb P, 2.2 m x 6 mm column, 55°C); yields were determined by vpc. The products are 2-fluoro-2-methyl-3-butanone[1b] (87.5%) and 2-methyl-1-butenone-3[9] (12.5%).

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