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THE PREPARATION OF ALPHA-HALO-BETA, BETA-DIFLUOROSTYRENES

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SUMMARY

Halogenation of β,β-difluorostyrene gave excellent yields of $PhCHXCF_2X$ (X=Cl, Br). Li_2CO_3/DMF, NaOEt/EtOH, and KOBu/hexane promoted dehydrohalogenation of $PhCHXCF_2X$ (X=Cl, Br) gave reasonably good isolated yields of the titled olefins.

INTRODUCTION

The synthesis of gem-difluoromethylene olefins is of interest because of the reactivity of this functional group with a wide variety of nucleophilic reagents. General syntheses of $R_2C{=}CF_2$, where R can be alkyl, aryl, perfluoroalkyl, perfluoroaryl, or hydrogen, have been reported via Wittig type of reactions [1], but this approach is not adaptable to the preparation of $RCX{=}CF_2$, where X=Cl or Br [2]. Alternatively, this type of olefin could be prepared via Grignard or organolithium reaction with fluoroolefin. However such attack on $CF_2{=}CFX$ gives RCF=CFX, and thus provides the undesired isomeric olefin, or exchange occurs to give the trifluorovinyl organometallic compound [3].

These olefins were of interest to us for the preparation of vinyl phosphoranes and vinyl phosphonium salts [4]. This paper describes our approach to their preparation on a synthetically useful scale. Hopefully, other workers will find additional utility of these compounds and they will become useful additions to the arsenal of gem-difluoromethylene model olefins.

RESULTS AND DISCUSSION

The easiest route to achieve these compounds would be the addition of halogen to $RCH{=}CF_2$ followed by base-promoted dehydrohalogenation:

$$RCH{=}CF_2 + X_2 \longrightarrow RCHXCF_2X \xrightarrow{\text{base}} RCX{=}CF_2$$

$R = C_6H_5$	X = Cl, I	X = Cl, III
	X = Br, II	X = Br, IV

The major difficulty with this simple scheme is that the base employed in the second step can also potentially act as a good nucleophile toward the reactive alkene (III and IV), thus leading to the formation of undesirable secondary products and lower yields of the desired olefins [5].

Our initial approach to circumvent this problem was to employ Li_2CO_3, a weak base and poor nucleophile, in DMF. Results were modestly satisfactory and an overall in-hand yield, based on the initial $PhCH{=}CF_2$ precursor, of 50% (IV) and 41% (III) was realized. The yields of (III) and (IV) were somewhat dependent on the reflux time in the Li_2CO_3 reaction. Longer reflux times decreased the yield of product olefins, presumably ue to reaction of (III) and (IV) with decomposition products of DMF.

$$PhCH{=}CF_2 + X_2 \longrightarrow PhCHXCF_2X \xrightarrow[\text{reflux, 2-4 hrs.}]{Li_2CO_3/DMF} PhCX{=}CF_2$$

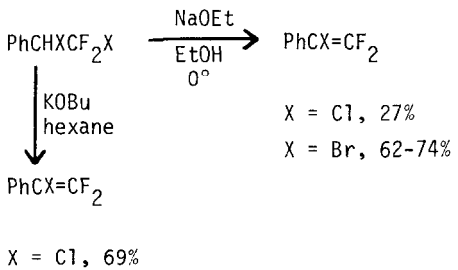
X = Cl, 81%	X = Cl, 50%
X = Br, 91%	X = Br, 55%

Kinetic studies of both the elimination reactions of (I) and (II) and the nucleophilic reactions of (III) and (IV) with alkoxide suggested that alkoxide might be useful in the dehydrohalogenation step. The alkenes (III) and (IV) react at similar rates with ethanolic sodium ethoxide (NaOEt) at 0°: (IV), $k = 1.38 \times 10^{-2} M^{-1} s^{-1}$; (III), $k = 1.14 \times 10^{-2} M^{-1} s^{-1}$. Methanolic sodium methoxide (NaOMe) reacted slightly slower with (III), $k = 8.06 \times 10^{-3} M^{-1} s^{-1}$ at 0°. Alkoxide promoted dehydrochlorination of (I) gave rate constants of $1.10 \times 10^{-2} M^{-1} s^{-1}$ (NaOEt) and $6.87 \times 10^{-4} M^{-1} s^{-1}$ (NaOMe) at 0°. Thus, the rate ratio for NaOEt/NaOMe is only 1.4 for the reaction with the alkenes but 16 for the elimination reaction. Thus, the NaOEt system would appear to be the better choice for the overall synthetic conversion. Experimentally, mixed success has been obtained.

Dehydrochlorination of (I) with ethoxide gave only a 27% isolated yield of (III). GLPC indicated the presence of significant amounts of higher boiling products, attributed to further reaction with ethoxide. Therefore, the NaOEt route is inferior to the Li_2CO_3/DMF route to (III).

Dehydrobromination of (II) is too rapid to measure with standard kinetic techniques using NaOEt. However, a rate constant of 6.00×10^{-2} $M^{-1}s^{-1}$ has been measured at 0° with NaOMe. So, (II) is 87 times more reactive than (I) with NaOMe, and we would expect a similar discrimination in rates of elimination with NaOEt. Consequently, one might anticipate that under the proper conditions (II) might be converted to (IV) without concomitant destruction of (IV). Indeed, when (II) is treated with ethanolic NaOEt, (IV) is obtained in 62-74% isolated yield (a 56-67% overall yield from $PhCH{=}CF_2$). The reaction is rapid and is over as fast as it take to mix the reagents. The overall yield is similar to the Li_2CO_3/DMF sequence, but the ease and rapidity of reaction may make this method the one of choice for the conversion of (II) to (IV).

The use of potassium t-butoxide (KOBu) in t-butanol has given substantial rate increases for elimination reactions from highly halogenated compounds. For example, we have observed a KOBu/NaOEt rate ratio of 400 for dehydrochlorination of $PhCH_2CF_2Cl$ [6]. One difficulty with the use of KOBu in t-butanol is that removal of the solvent, t-butanol, can present isolation problems. This difficulty can be avoided by use of solid KOBu in hexane as the solvent [7]. Thus, when (I) was treated with KOBu in hexane, a 69% isolated yield of (III) was obtained (56% overall from $PhCH{=}CF_2$). Again, reaction is rapid (10-15 minutes) and an improved yield (relative to Li_2CO_3/DMF) is obtained.



CONCLUSIONS

The preparation of α-chloro and α-bromo-β,β-difluorostyrenes can be accomplished in good overall yield from $PhCH{=}CF_2$ *via* a simple two step

process; addition of halogen followed by base-promoted dehydrohalogenation. For $PhCCl{=}CF_2$, KOBu in hexane was found to be the best reagent for the elimination step. For $PhCBr{=}CF_2$, NaOEt in ethanol or Li_2CO_3/DMF gave comparable yields with the NaOEt route being the faster method.

EXPERIMENTAL

All boiling points are uncorrected and were obtained during fractional distillation. β,β-difluorostyrene was prepared by literature routes[1]. ^{19}F NMR spectra were recorded on a Varian HA-100 spectrometer operating at 94.075 MHz, and the chemical shifts are reported in ø* values upfield from external (capillary) $CFCl_3$ reference. All ^{13}C NMR spectra were recorded on a Bruker HX-90E NMR operating at 22.635 MHz. The ^{13}C chemical shifts are reported with respect to internal TMS with downfield shifts reported as positive. ^1H NMR (Varian A-60) chemical shifts are reported relative to internal TMS.

1,2-Dichloro-1,1-difluoro-2-phenylethane, $PhCHClCF_2Cl$ (I)

A 250 ml flask fitted with a Teflon magnetic stir bar and a Dry-Ice condenser was charged with 28.0 g (0.200 mole) of β,β-difluorostyrene and 80 ml of CCl_4. Chlorine gas was added to the solution of the olefin at a rate to control the exothermic reaction, until the yellow-green color of the excess Cl_2 persisted. After removal of excess Cl_2 and CCl_4 *via* simple distillation, the residual yellow liquid was distilled through a six-inch Vigreux column to give 34.3 g (81%) of (I), bp 53-54° (3 mm) n_D^{20} 1.4956. Reported [8]: bp 200° (atm), n_D^{25} 1.4930.

^1H NMR: phenyl multiplet at 7.21 ppm and the methine hydrogen at 5.01 ppm (overlapping doublet of doublets), J_{H,F_a} 10.6 Hz and J_{H,F_b} 7.4 Hz.

^{19}F NMR: ø* 58.2 ppm (F_a), J_{F_a,F_b} 164 Hz; ø* 61.3 ppm (F_b).

Anal: Calcd for $C_8H_6Cl_2F_2$: C, 45.53; H, 2.86. Found: C, 45.61; H, 3.01.

1,2-Dibromo-1,1-difluoro-2-phenylethane, $PhCHBrCF_2Br$ (II)

A 500 ml three-necked flask was fitted with a Teflon magnetic stir bar, constant addition funnel, and a reflux condenser topped with a $CaSO_4$ drying tube. The flask was charged with 28.0 g (0.20 mole) of β,β-difluorostyrene and 250 ml CCl_4. A solution of 32 g (0.20 mole) of Br_2 in 10 ml CCl_4 was added dropwise over 20 minutes. After removal of the CCl_4 by simple distillation, the residual yellow liquid was distilled through a

six-inch Vigreux column to give 55.0 g (91%) of (II), bp 75-76 (2 mm), n_D^{20} 1.5476.
Reported [8]: bp 64-65° (0.4 mm), n_D^{20} 1.5448.
^{1}H NMR: phenyl multiplet at 7.25 ppm and the methine hydrogen at 5.20 ppm (overlapping doublet of doublets), J_{H,F_a} 5.5 Hz and J_{H,F_b} 17 Hz.
^{19}F NMR: Ø* 46.6 ppm (d,d) J_{F_a,F_b} 157 Hz; Ø* 55.2 ppm (d,d).
Anal: Calcd for $C_8H_6F_2Br_2$: C, 32.03; H, 2.02. Found: C, 32.02; H, 1.79.

(I) + Li_2CO_3 in DMF

A 250 ml flask equipped with a Teflon magnetic stir bar and reflux condenser was charged with 21.1 g (0.10 mole) of (I), 22.2 g (0.30 mole) Li_2CO_3 and 100 ml of dry DMF. The heterogeneous reaction mixture was heated at reflux for 4 hours, cooled, filtered, and the filtrate poured into 1 liter of ice water. Extraction of the aqueous solution with 3 x 150 ml portions of ether was followed by 3 x 100 ml washes of the combined ether extracts and subsequent drying of the ether solution over anhydrous $MgSO_4$. Distillation through a six-inch Vigreux column gave 8.8 g (50%) of (III), α-chloro-β,β-difluorostyrene; bp 90-92° (55 mm), n_D^{20} 1.5060.
Reported [9]: bp 100-100.5° (100 mm), n_D^{20} 1.5080.
^{1}H NMR: phenyl multiplet at 7.16 ppm.
^{19}F NMR: Ø* 83.7 ppm (d) and Ø* 89.2 ppm, $J_{F,F}$ 35 Hz.
IR: strong band at 5.77 μ (=CF_2).
Anal: Calcd for $C_8H_5ClF_2$: C, 55.04; H, 2.89. Found: C, 54.20; H, 2.90.

(II) + Li_2CO_3 in DMF

To a 250 ml three-necked flask equipped with a Teflon magnetic stir bar and a reflux condenser was charged 30.0 g (0.10 mole) of (II), 22.2 g (0.30 mole) Li_2CO_3 and 100 ml of dry DMF. The heterogeneous reaction mixture was heated at reflux for 2 hours, cooled, filtered, and the filtrate poured into 1 liter of ice water. The aqueous solution was washed with 1 x 300 ml ether and 2 x 100 ml ether. The combined ether extracts were washed with 3 x 100 ml water and dried over anhydrous $MgSO_4$. After removal of ether by simple distillation, fractionation of the residual high boiling liquid through a six-inch Vigreux column gave 12.0 g (55%) of (IV), α-bromo-β,β-difluorostyrene (nc); bp 52-54° (12 mm), n_D^{20} 1.5530 [10].
^{1}H NMR: phenyl multiplet at 7.15 ppm.
^{19}F NMR: Ø* 78.9 ppm (d) and Ø* 85.2 ppm (d), $J_{F,F}$ = 30 Hz.

^{13}C NMR: $\underline{C}F_2$: δ 153.3 ppm (d,d) J_{C,F_a} 294.2 Hz and J_{C,F_b} 285.3 Hz

$\underline{C}Br$: δ 80.2 ppm (d,d) J_{C,F_a} 30.3 Hz and J_{C,F_b} 26.5 Hz

IR: intense band at 5.80 μ (=CF_2).

Mass Spectrum: parent ion at m/e 218 and 220 (1:1 ratio).

Anal: Calcd for $C_8H_5BrF_2$: C, 43.86; H, 2.30: Found: C, 43.65; H, 2.53.

(I) + NaOEt in ethanol

To a 100 ml three-necked flask equipped with a Teflon magnetic stir bar, an addition funnel, a reflux condenser, and a thermometer was charged 11.8 g (0.056 mole) (I) and 31 ml ethanol. The reaction flask was heated to 75°. The addition funnel was charged with 31.5 ml 1.4 M ethanolic sodium ethoxide (0.044 mole) which was slowly added to the reaction mixture (Ca. 10 min.). The reaction was exothermic and the temperature of the reaction mixture rose to about 85° during the course of the addition. The reaction mixture was poured into 400 ml 3 M HCl and extracted twice with 20 ml CH_2Cl_2. GLPC analysis of the methylene chloride extract gave: 67% (III), 10% (I), and 23% higher boiling products. After removal of CH_2Cl_2 by simple distillation, the residual high boiling liquid was fractionated through a six-inch Vigreux column to give 2.6 g (27%) of (III), bp 45-50° (6 mm). A second cut of 0.4 g, bp 55-70°, was shown by GLPC to be 86% (III). Repetition of this reaction using 10.3 g (I) gave 2.3 g (27%) (III).

(II) + NaOEt in ethanol

To a 100 ml three-necked flask equipped with a Teflon magnetic stir bar, an addition funnel, a reflux condenser, and a thermometer was charged 20 g (0.066 mole) (II) and 30 ml ethanol. The addition funnel was charged with 50 ml 1.35 M ethanolic sodium ethoxide (0.067 mole), which was slowly added to the reaction mixture (Ca. 10 min.). The reaction was exothermic and the temperature of the reaction mixture rose from 27° to 38° during the course of the addition. The reaction mixture was poured into 400 ml 3 M HCl and extracted twice with 20 ml CH_2Cl_2. After removal of CH_2Cl_2 by simple distillation, the residual high boiling liquid was distilled through a six-inch Vigreux column to give 10.7 g (74%) of (IV), bp 64-66° (10 mm). Repetition of this reaction with the same quantities of reagents gave 9.1 g (62%) (IV).

(I) + KOBu in hexane

To a 100 ml creased three-necked flask equipped with a Trubore[R] stirrer and a reflux condenser was charged approximately 13 g solid potassium t-butoxide, 40 ml hexane, and 12.9 g (0.061 mole) (I). A septum closed the third opening, and the mixture was vigorously stirred for 10-15 minutes. The contents of the reaction flask were filtered to remove solids, and the clear liquid was subjected to rotary evaporation to remove the hexane. The residual liquid was distilled through a six-inch Vigreux column to give 7.4 g (69%) (III), bp 46-48° (6 mm).

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