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A remarkable room temperature preparation of the trifluorovinylzinc reagent from HFC-134a. A cost-effective, high yield synthesis of α,β,β-trifluorostyrenes

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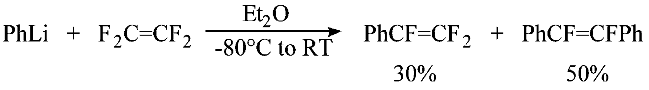
Abstract—The reaction of LDA (2.0 equiv.) with a THF solution of $ZnCl_2$ (1.0 equiv.) and CF_3CFH_2 (HFC-134a) (1.2 equiv.) at 15–20°C gives a 73% yield of [F_2C=CFZnCl]. Addition of R-C_6H_4I and $Pd(PPh_3)_4$ at rt to 65°C gives 61–86% yield of R-C_6H_4CF=CF_2. © 2002 Elsevier Science Ltd. All rights reserved.

Interest in α,β,β-trifluorostyrene (TFS) as a monomer has received increased attention in recent years. In particular, co-polymers have received interest as ion-exchange membranes for fuel cell separators, dialysis membranes, and packing materials for liquid chromatography columns.[1] The challenge in the applications of TFS has been the preparation of TFS itself. Numerous strategies have been employed to prepare this monomer in an efficient and cost-effective manner.[2] Acylation methodology[3] and dehydrohalogenation of fluorine-containing ethyl benzene derivatives[4] gave low overall yields (<20%) of TFS. Dixon reacted aryllithium reagents with tetrafluoroethylene (TFE) to give TFS, but the styrene product reacted rapidly with a second equivalent of PhLi—thus reducing the overall yield of TFS (Scheme 1).[5] Even with excess TFE, the disubstituted product was favored.[6]

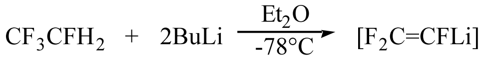
Substituted TFS derivatives were also prepared by this route.[7] Organometallics, such as PhLnI, PhYbI and PhNa, with TFE gave similar results.[8] Pyrolytic routes have been patented, but they generally provided only low yields of TFS.[9] Trifluorovinylzinc derivatives with R-C_6H_4I in the presence of $Pd(PPh_3)_4$ gave improved yields of TFS derivatives; however, the trifluorovinylzinc intermediate was prepared at low temperature (−120°C) via reaction of trifluorovinyllithium with zinc halides.[10] Recently, we developed a room temperature preparation of trifluorovinylzinc derivatives via direct insertion of Zn(0) into F_2C=CFX (X = Br, I).[11] Subsequent coupling of the trifluorovinylzinc reagent with R-C_6H_4I in the presence of $Pd(PPh_3)_4$ provided excellent isolated yields of substituted TFS derivatives via a one-pot procedure,[12] and this route has become the method of choice by the chemical community. Although this methodology provided the first room temperature entry to TFS in high yield, it required the use of F_2C=CFX (X = Br,I); which, although commercially available, are not necessarily cheap precursors—particularly for commercial preparation of TFS. In addition, the lack of large volume availability of F_2C=CFX also limited the commercial application of this methodology.



$$\mathrm{PhLi} + \mathrm{F_2C{=}CF_2} \xrightarrow[\text{-80°C to RT}]{\mathrm{Et_2O}} \underset{30\%}{\mathrm{PhCF{=}CF_2}} + \underset{50\%}{\mathrm{PhCF{=}CFPh}}$$

Scheme 1.

The only viable cheap, large volume, commercially available precursor for the introduction of a trifluorovinyl group is 1,1,1,2-tetrafluoroethane (HFC-134a). Coe and co-workers recognized the potential of HFC-134a as a trifluorovinyl synthon in 1999.[13] They generated trifluorovinyllithium from HFC-134a at −78°C by a sequence of dehydrofluorination and metallation reactions and carried out low temperature functionalization reactions with various electrophiles (Scheme 2).[13,14] When zinc halides were utilized as the



$$\mathrm{CF_3CFH_2} + 2\mathrm{BuLi} \xrightarrow[\text{-78°C}]{\mathrm{Et_2O}} [\mathrm{F_2C{=}CFLi}]$$

Scheme 2.

Keywords: 1,1,1,2-tetrafluoroethane; HFC-134a; trifluorovinylzinc; trifluorovinyllithium; trifluorostyrenes; Pd(0) coupling.

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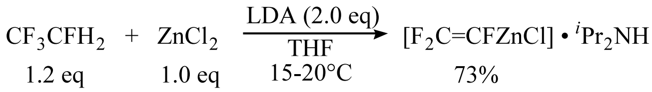

$$\underset{1.2\ \text{eq}}{CF_3CFH_2} + \underset{1.0\ \text{eq}}{ZnCl_2} \xrightarrow[\substack{\text{THF}\\ \text{15-20°C}}]{\text{LDA (2.0 eq)}} \underset{73\%}{[F_2C{=}CFZnCl] \bullet {}^iPr_2NH}$$

Scheme 3.

electrophile, $F_2C{=}CFZnX$ was formed and subsequently coupled with $R\text{-}C_6H_4I$ in the presence of Pd(0).[13,15] This route offered a solution to the cost-effectiveness problem, but the use of low temperature (−78°C) precluded scale-up for any commercial application. One needs to form $[F_2C{=}CFZnX]$ at temperatures compatible with scale-up (0°C–rt). In addition, since $[F_2C{=}CFLi]$ readily decomposes[13] to difluoroacetylene at temperature >−70°C, the formation of the zinc reagent must be accomplished in situ at these higher temperatures.

We now wish to report that when a THF solution of HFC-134a and anhydrous zinc chloride is treated with LDA at 15–20°C, a 73% yield[16] of the trifluorovinylzinc reagent is formed (as detected by ^{19}F NMR analysis of the reaction mixture). Bases, such as *t*-BuLi, *s*-BuLi, *n*-BuLi, LHMDS and $t\text{-BuO}^-$ were significantly less effective under these reaction conditions. The diisopropylamine complexing agent, formed in situ in the LDA reaction outlined below, is necessary to obtain high yields of the zinc reagent (Scheme 3).

Addition of an aryl iodide and $Pd(PPh_3)_4$ to the solution of the complexed trifluorovinylzinc reagent and warming (rt–65°C) provided the TFS derivative in 61–86% isolated yields (based on aryl iodides). Table 1 summarizes the synthesis of several TFS derivatives prepared by this methodology.

In conclusion, a remarkable **room temperature** preparation of $[F_2C{=}CFZnCl]$ has been achieved from the cheap, commercially available HFC-134a via the in situ capture of $[F_2C{=}CFLi]$ with zinc halide, when LDA is utilized as the base. Subsequent Pd(0) coupling of the zinc reagent with aryl iodides gives the resultant TFS derivatives. Overall, this methodology provides the first room temperature preparation of a trifluorovinyl organometallic reagent by in situ capture of trifluorovinyllithium, and affords a new, cost-effective ambient temperature route to TFS and its derivatives. Work is in progress with other CF_3CH_2X ($X = Cl$, Br, I, CF_3) derivatives, as well as other metal halide trapping agents, to elucidate the generality of this new, in situ approach.

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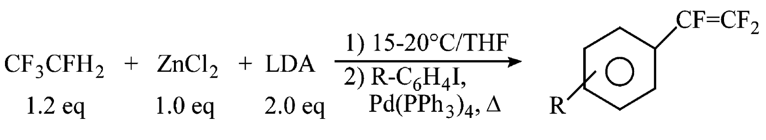
2. cf. Nikitina, T. S. *Usp. Khim.* **1990**, *59*, 995–1020 for a review of α,β,β-trifluorostyrene and its polymers.

Table 1. Preparation of α,β,β-Trifluorostyrenes from HFC-134a



Entry	R	Temp./time	Styrene	NMR yield (%)	Yield (%)[a,b]
1	H	65°C/3 h	$C_6H_5CF{=}CF_2$	99	69
2	*p*-F	65°C/4 h	$p\text{-}FC_6H_4CF{=}CF_2$	95	64
3	*m*-NO_2	rt/15 h	$m\text{-}NO_2C_6H_4CF{=}CF_2$	84	61
4	*p*-MeO	60°C/1 h	$p\text{-}MeOC_6H_4CF{=}CF_2$	94	82
5	*o*-$(CH_3)_2CH$	65°C/2 h	$o\text{-}(CH_3)_2CHC_6H_4CF{=}CF_2$	96	86
6	*p*-Br	rt/12 h	$p\text{-}BrC_6H_4CF{=}CF_2$	95	75[c]
7	*m*-CF_3	65°C/1 h	$m\text{-}CF_3C_6H_4CF{=}CF_2$	95	67
8	*o*-F	65°C/2 h	$o\text{-}FC_6H_4CF{=}CF_2$	98	74

[a] Isolated yield of pure styrene after column chromatography of the reaction mixture.

[b] All products gave satisfactory ^{19}F, ^{1}H, ^{13}C NMR and HRMS data consistent with the assigned structure.

[c] No bis-styrene detected after 12 h/rt; ~3% bis-styrene was formed after 24 h/rt.

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16. The yield may slightly vary from reaction to reaction; this yield was obtained in the typical experimental procedure described in Ref. 17.
17. Typical procedure: A 250 mL three-necked flask fitted with a dry ice/isopropanol condenser, septum and a low temperature thermometer was charged with anhydrous $ZnCl_2$ (3.42 g, 25 mmol) and THF (15 mL) under an N_2 atmosphere. The suspension was cooled to 15°C and HFC-134a (2.5 mL, 30 mmol) was condensed into the slurry. Then, an LDA [generated from diisopropylamine (7 mL, 50 mmol) and *n*-BuLi (20 mL, 2.5 M, 50 mmol) in THF (25 mL) at 0°C] solution was added slowly (~35 min) through a cannula to the HFC-134a/$ZnCl_2$ slurry while keeping the temperature at 15–20°C (the tip of the cannula was dipped into the THF to avoid decomposition of trifluorovinyllithium, formed by reaction of gaseous HFC-134a with LDA, at the tip). The pale yellow reaction mixture was stirred for 1 h and allowed to warm to rt. The ^{19}F NMR yield of the zinc reagent was 73%. The zinc reagent was concentrated to ~ half its volume (40 mL), then 3.51 g (15 mmol) of *p*-$MeOC_6H_4I$ and 0.28 g (1.5 mol%) $Pd(PPh_3)_4$ were added to the solution of the zinc reagent. The reaction mixture was heated at 60°C/1 h, cooled, triturated several times with hexanes, and the solvent was removed by rotoevaporation. Silica gel column chromatography gave 2.29 g (12.2 mmol, 82%) of pure *p*-$MeOC_6H_4CF{=}CF_2$. The spectroscopic data was in agreement with a sample prepared previously in this laboratory.[12b]