Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 6661–6664

TETRAHEDRON LETTERS

A highly efficient room temperature non-organometallic route for the synthesis of α,β,β-trifluorostyrenes by dehydrohalogenation

R. Anilkumar and Donald J. Burton*

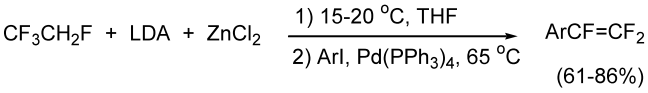
Department of Chemistry, The University of Iowa, Iowa City, IA 52242, USA

Received 11 June 2003; revised 1 July 2003; accepted 2 July 2003

Abstract—Various 1-aryl-1,2,2,2-tetrafluoroethanes ($ArCHFCF_3$, Ar = phenyl, substituted phenyl, naphthyl, heteroaryl) were synthesized by the fluorination of the corresponding alcohols with DAST. Dehydrofluorination of $ArCHFCF_3$ using lithium hexamethyldisilazide (LHMDS) base in THF at room temperature produced 1,2,2-trifluorostyrenes ($ArCF=CF_2$) in 61–91% isolated yields. This procedure provides an excellent non-organometallic alternative to the generally used metallation-Pd(0) coupling methods.

Among the fluorinated olefins 1,2,2-trifluorostyrene (TFS) has received increased attention as a monomer in recent years.[1] In particular, co-polymers have received interest as ion exchange membranes for fuel cell separators, dialysis membranes, and packing material for liquid chromatography columns.[2] The challenge in any applications of TFS has been its preparation; synthesizing TFS in good yield and purity has been a major task.[3] Formation of the styrene via organometallic reagents has received recent attention. One of the earlier methods was developed by Dixon,[4] wherein reaction of an aryl lithium reagent with tetrafluoroethylene generated the styrene in low isolated yields. Stilbene formation was the major side reaction in this process.[5] Synthesis of TFS via trifluovinylzinc and trifluorovinyltin was developed in the past two decades.[6] An excellent method for TFS and substituted TFS was developed in this laboratory where the trifluorovinylzinc reagent was generated by Zn(0) insertion into $CF_2=CFX$ (X = Br, I).[7] Subsequent Pd(0)-catalyzed cross coupling of the zinc reagent with aryl iodides generated TFS and substituted TFS in very good isolated yields. Although this method provided the first room temperature entry to TFS in high yield, it required $CF_2=CFX$, (X = Br, I), which although commercially available, are not cheap precursors—particularly for large scale or commercial preparation of TFS. Also, these gases are not environmentally friendly thus causing an important drawback in this preparation. Recently, Coe and co-workers[8] developed an excellent method for the generation of trifluovinyl lithium from a cheap, commercially available large volume precursor, 1,1,1,2-tetrafluoroethane (HFC-134a) at low temperature. With this background, we have very recently developed a remarkable room temperature preparation of 1,2,2-trifluorostyrene based on metallation—in situ transmetallation—coupling strategy starting from readily available HFC-134a (Scheme 1).[9]

As part of our ongoing efforts to develop synthetic methodologies for fluorinated styrenes we have explored non-organometallic routes for a highly efficient synthesis of 1,2,2-trifluorostyrenes. One such strategy was a dehydrofluorination method, where dehydrofluorination of the corresponding fluorinated precursor ($C_6H_5CHFCF_3$) was expected to produce TFS. Elimination of HF is a difficult process due to the high bond dissociation energy of the C–F bond especially from a CF_3 group.[10] But dehydrofluorination has been attempted with several derivatives of fluorinated compounds to produce the corresponding fluorinated olefins.[11] Unfortunately, the reaction conditions have involved high temperatures and afforded only modest



Scheme 1.

Keywords: HFC-134a; DAST; DBU; LHMDS; 1,2,2-trifluorostyrene; trifluoromethylketone; dehydrofluorination; dehydrochlorination; trifluoroethenylzinc; Pd(0) coupling.

* Corresponding author. Fax: 319-335-1270; e-mail: donald-burton@uiowa.edu

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01628-9

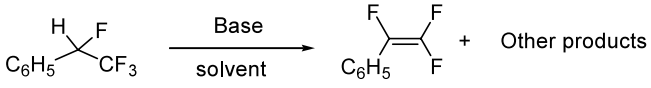
yields of dehydrofluorinated products. Mild bases did not effect the elimination; use of strong bases caused nucleophilic attack on the product olefin, thus leading to addition or addition–elimination products.[12] Insight into the mechanism of this base promoted dehydrohalogenation reaction was studied by various groups and it was proposed that the elimination proceeds through an intermediate carbanion mechanism rather than the normal E2 process.[10,13]

Despite the information concerning the difficulty in dehydrofluorination and formation of addition or addition–elimination side products, we felt that the preparation of the precursor, 1-phenyl-1,2,2,2-tetrafluoroethane ($C_6H_5CHFCF_3$), is trivial and an alternate base could be developed to effect the dehydrofluorination under mild reaction conditions without the consumption of the product olefin. The precursor 1-phenyl-1,2,2,2-tetrafluoroethane ($C_6H_5CHFCF_3$) was synthesized in 72% isolated yield from commercially available trifluoromethylphenylethanol by reaction with DAST in CH_2Cl_2.[14] Dehydrofluorination of 1-phenyl-1,2,2,2-tetrafluoroethane was attempted using various bases under different conditions and the results are summarized in Table 1.

Bases like DBU, NaOH and NaOMe did not effect the dehydrofluorination even under refluxing conditions; whereas lithium bases such as *n*-BuLi, *t*-BuLi, LDA, produced traces of TFS with significant amount of the addition–elimination product. A sterically hindered base lithium-2,2,6,6-tetramethyl-4-methoxy piperidine (4-methoxy LTMP), suppressed the addition–elimination process and produced TFS with traces of side products. Reaction with lithium hexamethyldisilazide (LHMDS) was then attempted; dehydrofluorination with almost complete conversion of $C_6H_5CHFCF_3$ to TFS was observed. No addition–elimination product was formed in this reaction. Simple acidic work-up followed by careful distillation under vacuum afforded the TFS in 74% isolated yield.

After standardizing the reaction conditions for the dehydrofluorination using the LHMDS, we have applied the same strategy for the synthesis of several aryl substituted 1,2,2-trifluorostyrenes. The corresponding starting materials, substituted trifluoromethylacetophenones [$ArC(O)CF_3$, Ar = *p*-ClC_6H_4-, *p*-MeC_6H_4-, *p*-$MeOC_6H_4$-, *m*-BrC_6H_4-, *m*-$CF_3C_6H_4$-, *m*-$NO_2C_6H_4$-, 1-naphthyl and 2-thienyl] were synthesized by the reaction of the corresponding Grignard reagent with either trifluoroacetic acid or its ethylester.[15] The ketones thus obtained were reduced in high yield (>90%) to the corresponding alcohol [$ArCH(OH)CF_3$] with sodium borohydride.[16] The direct synthesis of alcohols can also be achieved by the reaction of trifluoromethyltrimethylsilane and the corresponding aldehyde in the presence of a fluoride ion source.[17] The alcohols were then treated with DAST at −70°C, followed by warming to rt in CH_2Cl_2 medium (5–8 h), to obtain the corresponding aryl substituted tetrafluoroethanes ($ArCHFCF_3$) in good isolated yields (Table 2). Dehydrofluorination of the aryl substituted tetrafluoroethanes was then carried out using 1.1–1.2 equiv. of lithium hexamethyldisilazide in THF at 15°C.† The results of the dehyrofluorination

Table 1. Dehydrofluorination of $C_6H_5CHFCF_3$ using various bases

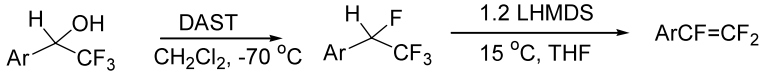


Entry	Base	Reaction conditions	Styrene[a]	Unreacted starting material[a]	Addition–elimination product[a]
1	DBU	DMF, 75°C, 12 h	0	100	0
2	NaOH	MeOH, heat, 12 h	0	100	0
3	NaOMe	MeOH, rt, then heat	0	100	0
4	*n*-BuLi	THF, 0°C, 1 h	2	35	33
5	LDA	THF, 0°C, 1 h	10	50	10
6	*t*-BuLi	THF, rt, 1 h	5	40	50
7	4-Methoxy LTMP	THF, 0°C, 12 h	82	3	10
8	LHMDS	THF, 0°C, 3 h	91	2	0

[a] ^{19}F NMR yield based on $PhCF_3$ as internal standard.

† Typical procedure for the dehydrofluorination using LHMDS: A 250 mL three-necked RB fitted with a nitrogen tee, septum and a thermometer was charged with THF (15.0 mL) and *p*-$MeC_6H_4CHFCF_3$ (5.0 g, 26.0 mmol). The solution was cooled to 15°C by an ice-water bath. A solution of LHMDS [pre-generated from hexamethyldisilazane (6.6 mL 31.3 mmol), and *n*-BuLi (12.6 mL, 2.5 M, 31.3 mmol) in THF (15.0 mL) at 0°C] was slowly added to the RB (~20 min) through a cannula. The mixture was stirred at that temperature for 1 h and then warmed to rt. The reaction progress was monitored via ^{19}F NMR, and after 3 h above 90% conversion to the styrene was observed. After complete conversion (8 h) the reaction mixture was quenched with water (35.0 mL) and pentane (40.0 mL) was added. The aqueous and organic layer was separated (emulsion formation could be broken with dil. HCl) and the aqueous layer extracted with pentane (2×25 mL). The combined organic extracts were washed with dil. HCl (4×40 mL) and then with water. The pentane extracts were dried over anhydrous Na_2SO_4 and evaporated under mild vacuum without the loss of the volatile styrene. The resulting solution on distillation through a 10 mm vigreux column under vacuum produced 3.64 g (21.6 mmol, 81%) of pure *p*-$MeC_6H_4CF{=}CF_2$. Bp: 45°C/8 mm ^{19}F NMR ($CDCl_3$): δ −101.5 (dd, J = 73.3, 31.0 Hz, 1F), −116.2 (dd, J = 110.5, 77.3 Hz, 1F), −177.0 (dd, J = 109.5, 31.8 Hz, 1F); ^1H NMR ($CDCl_3$): δ 7.33 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 155.6 (ddd, J = 291.5, 281.9, 50.6 Hz), 138.9 (s), 129.4 (s), 128.9 (ddd, J = 227.1, 46.6, 19.5 Hz), 124.4 (m), 21.2 (s); GC–MS: 172 (M^+) (100), 151 (68), 121 (55), 101 (38), 75 (28). HR-MS: calcd for $C_9H_7F_3$ 172.0500, found 172.0500.

Table 2. Preparation of 1,2,2-trifluorostyrenes by dehydrofluorination



Entry	Ar	Isolated yield of $ArCHFCF_3$	Reaction time (h)	NMR yield of styrene ($ArCF{=}CF_2$)	Isolated yield of styrene[a,b] ($ArCF{=}CF_2$)
1[c]	C_6H_5-	72	3	91	74
2[d]	*p*-ClC_6H_4-	84	1.5	84	72
3	*p*-MeC_6H_4-	83	8	93	81
4	*p*-$MeOC_6H_4$-	69	8	90	82
5[d,e]	*m*-BrC_6H_4-	76	0.5	79	69
6	*m*-$F_3CC_6H_4$-	63	1	90	61
7	*m*-$O_2NC_6H_4$-	78	1	88	83
8	1-Naphthyl-	72	1	95	91
9[c]	2-Thienyl-	69	1	89	69

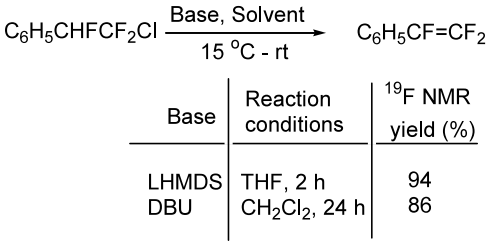
[a] Isolated yield of pure styrene after distillation under reduced pressure or column chromatography.
[b] All products gave satisfactory ^{19}F, ^{1}H, ^{13}C NMR and HRMS consistent with assigned structure and are in agreement with samples prepared in our laboratory by other methods.[7,9]
[c] The distilled styrene contaminated with 1–2% hexamethyldisilazane.
[d] 1.1 equiv. LHMDS used.
[e] Some cyclodimerization of the styrene observed when the reaction mixture kept for longer time.

of various 1-aryl-1,2,2,2-tetrafluoethanes are summarized in Table 2. The reaction proceeded very smoothly and rapidly to produce 1,2,2-trifluorostyrenes in excellent yield (even for the *p*-methyl and *p*-methoxy derivatives the reaction was more than 90% complete in 3 h, entries 3 and 4). Longer reaction time (24 h) resulted in traces ($\sim$2%) of the addition–elimination product (^{19}F NMR). The product olefins were extracted with pentane and purified either by column chromatography or by careful vacuum distillation through a 10 cm vigreux column. 4-Methoxy substituted 1,2,2-trifluorostyrene partially dimerized during distillation and was purified by column chromatography.

After successfully synthesizing 1,2,2-trifluorostyrenes by dehydrofluorination, we attempted to generate TFS by dehydrochlorination of the chlorinated precursor 2-chloro-1-phenyl-1,2,2-trifluoroethane ($C_6H_5CHFCF_2Cl$). Dehydrohalogenation of fluorinated phenylethanes to the corresponding fluorinated olefins using mild bases is well known in the literature.[18] Dehydrochlorination is expected to proceed easier than dehydrofluorination due to the better leaving group ability of Cl^- compared to F^-. Substitution of CF_3 group of $C_6H_5CHFCF_3$ by CF_2Cl does not significantly change the acidity of the benzilic hydrogen or stabilize the intermediate carbanion,[10,12a,19] but studies have shown that the better leaving group at the 2-position significantly alters the reaction progress.[13b,c] Consequently, we prepared the analogous chloro derivative to determine if a weaker base could be utilized in this reaction.

The precursor ketone [$C_6H_5C(O)CF_2Cl$] was obtained by the reaction of chlorodifluoroacetic acid with excess phenylmagnesium bromide.[15a] An alternative facile method of preparation of α-halodifluoromethylketones from trifluoromethylketones has recently been reported.[20] $NaBH_4$ reduction of the ketone, followed by reaction of the alcohol with DAST in CH_2Cl_2 produced the precursor, $C_6H_5CHFCF_2Cl$ in 71% isolated yield. Dehydrochlorination of $C_6H_5CHFCF_2Cl$ was attempted at rt with LHMDS in THF solvent, and the reaction proceeded smoothly in 2 h to produce the TFS in 94% (by ^{19}F NMR) yield. Dehydrochlorination of $C_6H_5CHFCF_2Cl$ was also attempted in CH_2Cl_2 using DBU as a base at room temperature, and by 24 h most of the starting material has been transformed to product in 86% (by ^{19}F NMR) yield (Scheme 2). The pK_a of the benzilic hydrogen in $C_6H_5CHFCF_3$ is estimated to be $\sim$30.0,[12a] and a mild base like DBU (pK_a = 23.9)[21] did not effect the dehydrofluorination (cf. also Table 1). Stronger bases, like LHMDS (pK_a = 29.5),[22] were required to effect the dehydrofluorination. The fact that DBU was efficient to perform the dehydrochlorination of $C_6H_5CHFCF_2Cl$, even though its pK_a is not significantly different from $C_6H_5CHFCF_3$ confirm the above argument about the leaving group ability of the chloride ion.

In conclusion, a highly efficient synthesis of various 1,2,2-trifluorostyrenes was achieved by a room temperature dehydrohalogenation methodology where the reactive olefinic species survived under the reaction conditions without undergoing an addition–elimination reaction with the base. Various bases were scanned to



Scheme 2.

effect this conversion and lithium hexamethyldisilazide was found to be the best choice. Overall, this methodology provides an excellent non-organometallic alternative route for the synthesis of 1,2,2-trifluorostyrenes in high yield and purity. We are currently extending this methodology to the synthesis of other α-halo-β,β-difluorostyrenes, as well as investigating the selectivity in this elimination to achieve the stereospecific preparation of $C_6H_5CF{=}CFR_F$ type olefins starting from $C_6H_5CHFCF_2R_F$ precursors.

Acknowledgements

We thank Dr. Charles Stone for stimulating discussions and insight into this project. We thank National Science Foundation for support of this research.

References

1. (a) Nikitina, T. S. *Usp. Khim.* **1990**, *59*, 995–1020 for a review of 1,2,2-trifluorostyrene and its polymers; (b) Narita, T.; Hagiwara, T.; Hamana, H.; Shibasaki, K.; Hiruta, I. *J. Fluorine Chem.* **1995**, *71*, 151–153; (c) Aoki, T.; Watanabe, J.; Ishimoto, Y.; Oikawa, E.; Hayakawa, Y.; Nishida, M. *J. Fluorine. Chem.* **1992**, *59*, 285–288.
2. (a) Stone, C.; Daynard, T. S.; Hu, L.-Q.; Mah, C.; Steck, A. E. *J. New Mater. Electrochem. Syst.* **2000**, *3*, 43–50; (b) Stone, C.; Steck; A. E. PCT Int. Appl. WO 2001058576; (c) Momose, T.; Kitazumi, T.; Ishigaki, I.; Okamoto, J. *J. Appl. Polym. Sci.* **1990**, *39*, 1221–1230; (d) Wodzki, R.; Narebska, A.; Ceynowa, J. *Angew. Makromol. Chem.* **1982**, *106*, 23–35; (e) Plummer, C. W.; Enos, J.; LaConti, A. B.; Boyack, J. R. *US Office Saline Water Res. Develop. Progr. Rep.*, 1969; (f) Kapustin, D. V.; Saburov, V. V.; Reznikova, O. A.; Kapustin, D. V.; Zubov, V. P. *J. Chromatogr. A.* **1994**, *660*, 131–136; (g) Shuyuan, L.; Mahamoud, A.; David, G. *Tetrahedron Lett.* **2000**, *41*, 4493–4497.
3. (a) Cohen, S. G.; Wolosinski, H. T.; Scheuer, P. J. *J. Am. Chem. Soc.* **1949**, *71*, 3439–3440; (b) Cohen, S. G.; Wolosinski, H. T.; Scheuer, P. J. *J. Am. Chem. Soc.* **1950**, *72*, 3952–3953; (c) Prober, M. *J. Am. Chem. Soc.* **1953**, *75*, 968–973; (d) Shingu, H.; Hisazumi, M. US Patent 3,489,807, 1970.
4. Dixon, S. *J. Org. Chem.* **1956**, *21*, 400–403.
5. McGrath, T. F.; Levine, R. *J. Am. Chem. Soc.* **1955**, *77*, 4168–4169.
6. (a) Sorokina, R. S.; Rybakova, L. F.; Kalinovskii, I. O.; Chernoplekova, V. A.; Beletskaya, I. P. *Zh. Org. Chim.* **1982**, *18*, 2458–2459; (b) Sorokina, R. S.; Rybakova, L. F.; Kalinovskii, I. O.; Beletskaya, I. P. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1985**, 1647–1649.
7. (a) Heinze, P. L.; Burton, D. J. *J. Fluorine Chem.* **1986**, *31*, 115–119; (b) Heinze, P. L.; Burton, D. J. *J. Org. Chem.* **1988**, *53*, 2714–2720.
8. (a) Burdon, J.; Coe, P. L.; Haslock, I. B.; Powell, R. L. *Chem. Commun.* **1996**, 49–50; (b) Burdon, J.; Coe, P. L.; Haslock, I. B.; Powell, R. L. *J. Fluorine Chem.* **1997**, *85*, 151–153.
9. Anilkumar, R.; Burton, D. J. *Tetrahedron Lett.* **2002**, *43*, 2731–2733.
10. Koch, H. F.; Dahlberg, D. B.; Toczko, A. G.; Solsky, R. L. *J. Am. Chem. Soc.* **1973**, *95*, 2029–2030.
11. (a) Leroy, J. *J. Org. Chem.* **1981**, *46*, 206–209; (b) Asai, N.; Neckers, D. C. *J. Org. Chem.* **1980**, *45*, 2903–2907; (c) Modarai, B. *J. Org. Chem.* **1976**, *41*, 1980–1983; (d) Sheppard, B. M.; Yosef, E. M. Eur. Pat. Appl, EP 90-112561, 1991; (e) Francis, H. W.; Pavlath, A. E. *J. Org. Chem.* **1965**, *30*, 3284–3285; (f) Kudryavtsev, Y. P.; Babaev, V. G. *Izv. Akad. Nauk. Ser. Khim.* **1992**, 1223–1225; (g) Apsey, C. G.; Chambers, R. D.; Odello, P. *J. Fluorine Chem.* **1996**, *77*, 127–132; (h) Pedler, A. E.; Smith, R. C.; Tatlow, J. C. *J. Fluorine Chem.* **1972**, *1*, 337–345; (i) Bailey, J.; Raymond, G.; Tatlow, J. C. *J. Fluorine Chem.* **1988**, *39*, 227–233.
12. (a) Koch, H. F.; Kielbania, A. *J. Am. Chem. Soc.* **1970**, *92*, 729–730; (b) Normant, J. F.; Sauvetre, R.; Villieras, J. *Tetrahedron* **1975**, *31*, 891–896; (c) cf. Chambers, R. D. *Fluorine in Organic Chemistry*; John Wiley and Sons Inc: New York, 1973; pp. 148–156.
13. (a) Koch, H. F.; Dahlberg, B. D.; Lodder, G.; Root, S. K.; Touchette, N. A.; Solsky, R. L.; Zuck, M. R.; Wagner, J.; Koch, H. N.; Kuzemko, M. A. *J. Am. Chem. Soc.* **1983**, *105*, 2394–2398; (b) Koch, H. F.; Lodder, G.; Koch, G. J.; Bogdan, J. D. H.; Brown, H. G.; Carlson, A. C.; Dean, B. A.; Hage, R.; Han, P.; Hopmann, C. P. J.; James, L. A.; Knape, P. M.; Roos, C. E.; Sardina, L. M.; Sawyer, A. R.; Scott, O. B.; Testa, A. C.; Wickham, D. S. *J. Am. Chem. Soc.* **1997**, *119*, 9965–9974; (c) Zuilhof, H.; Lodder, G.; Koch, H. F. *J. Org. Chem.* **1997**, *62*, 7457–7463; (d) Hudlicky, M. *J. Fluorine Chem.* **1984**, *25*, 353–361.
14. Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574–578.
15. (a) Dishart, K. T.; Levine, R. *J. Am. Chem. Soc.* **1956**, *78*, 2268–2270; (b) Creary, X. *J. Org. Chem.* **1987**, *52*, 5026–5030.
16. Stewart, R.; Teo, K. C. *Can. J. Chem.* **1980**, *58*, 2491–2496.
17. Ramesh, K.; Bellew, D. R.; Prakash, S. G. K. *J. Org. Chem.* **1991**, *56*, 984–989.
18. (a) Kuroboshi, M.; Hiyama, T. *Chem. Lett.* **1990**, 1607–1610; (b) Burton, D. J.; Anderson, A. L.; Takei, R.; Koch, H. F.; Shih, T. L. R. *J. Fluorine Chem.* **1980**, *16*, 229–235; (c) Kuruboshi, M.; Yamada, N.; Takebe, Y.; Hiyama, T. *Tetrahedron Lett.* **1995**, *36*, 6271–6274.
19. Sheppard, W. A. *Tetrahedron* **1971**, *27*, 945–951.
20. Prakash, S. G. K.; Hu, J.; Alauddin, M. M.; Conti, S. P.; Olah, G. A. *J. Fluorine Chem.* **2003**, *129*, 239–243.
21. Galezowski, W.; Jarczewski, A.; Stancyzk, M.; Brzezinski, B.; Bartl, F.; Zundel, G. *J. Chem. Soc., Faraday Trans.* **1997**, *93*, 2515–2518.
22. Fraser, R. R.; Mansour, S. T. *J. Org. Chem.* **1984**, *49*, 3442–3443.