Pergamon

Tetrahedron Letters 40 (1999) 2985–2988

TETRAHEDRON LETTERS

Chemistry of Fluorinated Enamines. Novel Reaction of Trifluoromethylated Enamine with Grignard Reagents

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Received 28 September 1998; revised 12 February 1999; accepted 19 February 1999

Abstract: Trifluoromethylated enamine, *N*-(2,3,3,3-tetrafluoro-1-propenyl)dimethylamine (**1**), readily reacted with a variety of Grignard reagents **2** at room temperature to afford the trifluorovinyl compounds **3** in good yields.

Many kinds of enamines have been prepared and utilized as very important building blocks in organic synthesis and their chemistry has widely been documented.[1] Recently, the fluorine-containing analogues have also attracted much attention since they could serve as the fluorine-containing synthons both for the synthesis of various new fluorinated compounds and for the introduction of fluorine-substituent into natural products. As for the preparation of the fluorinated enamines, various new methods[2] have been developed in addition to classical methods based on the reactions of perfluoroalkenes[3] or 1*H*-perfluoroalkynes[4] with amines. Thus, Begue and his co-workers reported a new preparation of α-trifluoromethylated enamines by heating trifluoroacetamides with alkylidenetriphenylphosphoranes.[2j,k] Portella and Iznaden obtained perfluorinated enaminoesters in good yields by the reaction of α-*H*-perfluoroesters with secondary amines.[2l] We have also developed a new facile and stereoselective route to β-trifluoromethylated enamines through the reaction of *N*-(2,3,3,3-tetrafluoro-1-propenyl)trimethylammonium iodide with secondary amines.[5] It has been known that the reactivities of the fluorinated enamines differ profoundly from those of their hydrocarbon analogues. For example, the nitrogen atom of the enamines, $RfCF_2CH{=}CHNR_2$ (Rf; perfluoroalkyl, R; alkyl group), is so much less basic that neither N-alkylation nor acylation can take place.[6] Moreover, their double bond is less reactive towards electrophilic addition; no bromination occurs even at room temperature, whereas this addition proceeds readily at -78 °C with the hydrocarbon analogues.[7] As to the synthetic applications, to our best knowledge, there has been found only one report in the literature except acidic hydrolysis of partially fluorinated enamines to the corresponding ketones.[2f,4c,8] Bridge and O'Hagan synthesized a variety of substituted α-fluoroketones by 1,4-additions of α-monofluorinated enamines to Michael acceptors.[9] Herein, we wish to report the novel reaction of β-trifluoromethylated enamine with a variety of Grignard reagents, which provides a very simple and efficient route to the trifluorovinyl compounds.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00399-8

The reaction of the β-trifluoromethylated enamine, *N*-(2,3,3,3-tetrafluoro-1-propenyl)-dimethylamine (**1**), with 1.2 equiv. of phenylmagnesium bromide (**2a**) in anhydrous diethyl ether at room temperature for 10 h gave 1,1,2-trifluoro-3-(dimethylamino)-3-phenylprop-1-ene (**3a**)[10] in 25% yield together with recovery of **1** (62% yield). However, when the reaction was conducted at reflux in anhydrous tetrahydrofuran (THF) for 1 h, **3a** was obtained in 85% yield without recovery of **1**. The reaction with an excess amount (2.4 equiv.) of **2a** at room temperature in diethyl ether also proceeded completely within 6 h to give **3a** in high yield (87%). In these reactions, any substitution products arising from the displacement of the vinylic fluorine and/or dimethylamino groups of **1** by phenyl group of **2a** were not obtained. An elimination product (ynamine) formed in the reaction of **1** with butyllithium or lithium diisopropylamide[11] was also not produced.

The reactions with various Grignard reagents **2** (2.4 equiv.) were examined in diethyl ether at room temperature for 6-8 h (Scheme 1). The results are summarized in the Table 1 together with IR absorption bands ($\nu_{CF2=cF-}$), which appeared at high wave numbers by ca.100 relative to those of non-fluorinated double bond.[12]

Scheme 1

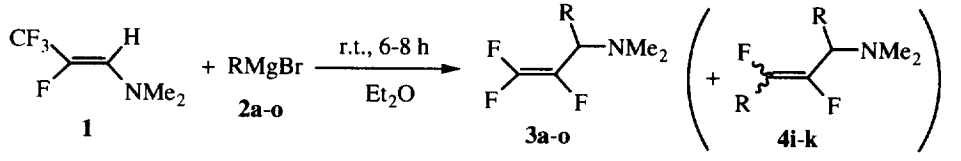


Table 1
Results of reaction of the enamine **1** with Grignard reagents **2** in diethyl ether at room temperature

Entry	RMgX (**2**)	Product (**3**)	Yield/%[a]	IR (cm^{-1})
1	PhMgBr (**2a**)	CF_2=CF-CH(Ph)NMe_2 (**3a**)	87 (91)	1786
2	*p*-AnisMgBr (**2b**)	CF_2=CF-CH(*p*-Anis)NMe_2 (**3b**)	85	1786
3	*p*-TolMgBr (**2c**)	CF_2=CF-CH(*p*-Tol)NMe_2 (**3c**)	92	1788
4	*p*-F-PhMgBr (**2d**)	CF_2=CF-CH(*p*-F-Ph)NMe_2 (**3d**)	77	1790
5	PrMgBr (**2e**)	CF_2=CF-CH(Pr)NMe_2 (**3e**)	55 (75)	1778
6	ButMgBr (**2f**)	CF_2=CF-CH(But)NMe_2 (**3f**)	78 (81)	1778
7	HexMgBr (**2g**)	CF_2=CF-CH(Hex)NMe_2 (**3g**)	81	1778
8	OctMgBr (**2h**)	CF_2=CF-CH(Oct)NMe_2 (**3h**)	91	1778
9	*i*-PrMgBr (**2i**)	CF_2=CF-CH(*i*-Pr)NMe_2 (**3i**)	21[b]	1778
10	*s*-ButMgBr (**2j**)	CF_2=CF-CH(*s*-But)NMe_2 (**3j**)	25[c]	1778
11	*c*-HexMgBr (**2k**)	CF_2=CF-CH(*c*-Hex)NMe_2 (**3k**)	22[d]	1778
12	α-NaphMgBr (**2l**)	CF_2=CF-CH(α-Naph)NMe_2 (**3l**)	69	1786
13	PhCH=CHMgBr (**2m**)	CF_2=CF-CH(CH=CHPh)NMe_2 (**3m**)	76	1786
14	PhC≡CMgBr (**2n**)	CF_2=CF-CH(C≡CPh)NMe_2 (**3n**)	78	1790
15	 (**2o**)	CF_2=CF-CH(2-thienyl)NMe_2 (**3o**)	75	1789

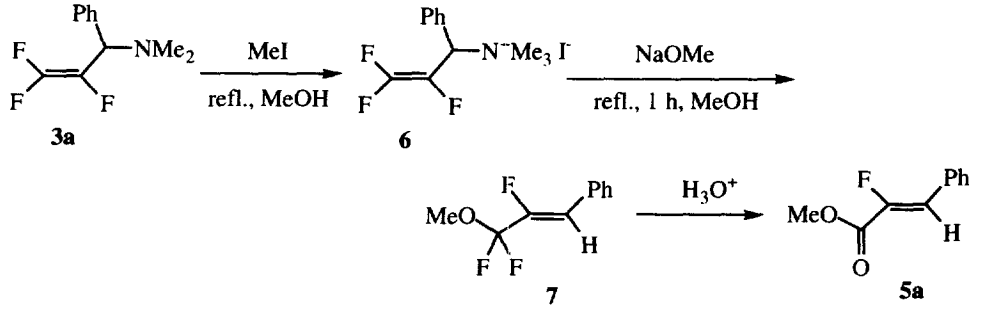
[a]Isolated yields. Values in parentheses are the yields determined by ^{19}F NMR. [b]Byproduct **4i** was obtained in 55% yield. [c]Byproduct **4j** was obtained in 36% yield. [d]Byproduct **4k** was obtained in 39% yield.

Thus, all arylmagnesium bromides **2a-d** reacted cleanly to afford the corresponding trifluorovinyl compounds **3a-d**[13] as a sole product in high yields (77-92%) (Entries 1-4). Similarly, primary alkyl Grignard reagents **2e-h** also gave the vinyl compounds **3e-h** in good yields (Entries 5-8). However, isopropylmagnesium bromide (**2i**) produced a mixture of stereoisomers (E/Z=7:3) of 1,2-difluoro-1,3-diisopropyl-3-(dimethylamino)prop-1-ene (**4i**)[13] in 55% yield together with **3i** (21% yield) (Entry 9). The formation of the byproduct corresponding to **4i** was common in the reaction with secondary Grignard reagents such as *sec*-butyl- (**2j**) and cyclohexylmagnesium bromide (**2k**) (Entries 10 and 11). Other Grignard reagents such as α-naphthyl- (**2l**), β-styryl- (**2m**), phenylethynyl- (**2n**), and 2-thienyl-magnesium bromide (**2o**) also nicely underwent the reaction to give the corresponding vinyl compounds in good yields (Entries 12-15).

The trifluorovinyl compounds **3** may be formed by *SN2'* type reaction where Grignard reagent attacks the α carbon of **1** followed by elimination of fluoride ion from the trifluoromethyl group.[14] Mechanism of the formation of byproduct **4** in the reaction with sterically bulky secondary Grignard reagents is not clear at present. The formed **3** could not further be attacked with another Grignard reagent existing in the reaction system. This was confirmed by the control experiment using the isolated **3i**. Thus, the reaction of **3i** with **2c** or **2k** did not occur, **3i** being recovered unchanged.

The trifluorovinyl compounds **3** thus obtained were useful precursor of α-fluoro-α,β-unsaturated esters **5**, which are versatile intermediates to synthesize various fluorinated compounds. Thus, the trifluorovinyl compound **3a** was easily methylated with methyl iodide to give the ammonium salt **6**, which was subsequently treated with sodium methylate in methanol at refluxing temperature for 1 h to afford an allyl ether **7**[16] in a 76% yield. The acidic hydration of **7** gave methyl α-fluorocinnamate **5a**[16] in an 85% yield (Scheme 2).

Scheme 2



General procedure for the reaction of the enamine **1** with Grignard reagent is as follows: To Grignard reagent (2.4 mmol) freshly prepared in diethyl ether was added the enamine **1** (1.0 mmol) at 0 °C under an argon atmosphere. The mixture was stirred at room temperature for 6 or 8 h and then poured into water (30 mL). The aqueous layer was extracted with diethyl ether (30 mLx3) and the combined organic layers were dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue, which was purified by column chromatography (silica gel) eluting with benzene-hexane (1:1) to afford the product **3**.

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10. Compound **3a**: Liquid. IR 1786 cm^{-1}($\nu_{C=C}$); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.28 (s, 6H), 3.97 (ddd, *J*=30.7, 4.7, 2.6 Hz, 1H), 7.27-7.44 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.14, 66.42 (dd, *J*=17.7, 2.3 Hz), 125.47, 127.30 (ddd, *J*=244.9, 47.4, 13.6 Hz), 128.03, 128.57, 137.45, 154.06 (ddd, *J*=290.5, 275.9, 44.9 Hz); ^{19}F NMR ($CDCl_3$, $CFCl_3$, 84.71 MHz) δ -103.48 (ddd, *J*=81.6, 30.7, 2.6 Hz, 1F), -120.97 (ddd, *J*=114.6, 81.6, 4.7 Hz, 1F), -182.23 (ddd, *J*=114.6, 30.7, 30.7 Hz, 1F); MS (EI) m/z (rel. intensity, %) 215 (46.4), 171 (54.9), 151 (100), 138 (39.8); HRMS (EI) Calcd. for $C_{12}H_{14}F_3N$ 215.0922, Found 215.0902.
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12. Silverstein, R.M.; Bassler, G.C.; Morrill, T.C. *Spectrometric Identification of Organic Compounds*, Fifth eddition, New York: John Wiley & Sons, **1991**, Chapter 3.
13. All isolated products **3** and **4** exhibited spectroscopic (IR, ^1H, ^{13}C, and ^{19}F NMR, MS, HRMS) data which are in good accord with the assigned structures.
14. It has been known that the reaction of trifluoromethyl alkenes with organolithium reagents can result in the formation of difluoroalkenes through an addition of the organolithium reagent followed by the elimination of lithium fluoride.[15]
15. Begue, J.P.; Bonnet-Delpon, D.; Rock, M.H. *J. Chem. Soc., Perkin Trans. I*, **1996**, 1409-1413.
16. Compound **5a**: Liquid. IR 1736, 1659 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.88 (s, 3H), 6.93 (d, *J*=35.2 Hz, 1H), 7.37-7.65 (m, 5H); ^{19}F NMR ($CDCl_3$, $CFCl_3$, 84.71 MHz) δ -126.1 (d, *J*=35.2 Hz); HRMS (EI) Calcd. for $C_{10}H_9O_2F$ 180.0586, Found 180.0588. Compound **7**: Liquid. IR 1701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.70 (s, 3H), 6.29 (d, *J*=36.4 Hz, 1H), 7.30-7.56 (m, 5H); ^{19}F NMR ($CDCl_3$, $CFCl_3$, 84.71 MHz) δ -80.8 (d, *J*=15.4 Hz, 2F), -129.7 (dt, *J*=36.4, 15.4 Hz, 1F); HRMS (EI) Calcd. for $C_{10}H_9OF_3$ 202.0605, Found 202.0601.