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# A NOVEL ONE-POT FLUOROALKYLVINYLATION OF THIOPHENE

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## SUMMARY

A novel one-pot synthesis of fluoroalkylvinyl thiophenes using fluorinated β-ketophosphonium salts as a fluoroalkylvinylation reagent is described. In view of the fact that this one-pot reaction without isolation of intermediates and the total yield in 2 steps reaches 56-82%, the present method provides a convenient direct introduction of fluoroalkylvinyl group into the thiophene.

## INTRODUCTION

Organofluorine compounds have been shown to exhibit unique characters in pharmaceuticals, polymer sciences and other fields owing to characteristic features of the fluorine atom [1]. It is well known that fluorinated pyrimidines act as anti-cancer agents and much attention has been paid to the fluorination of heterocyclic compounds. To the best of our knowledge, only few reports have appeared in the literature concerning the fluoroalkylation of hete-

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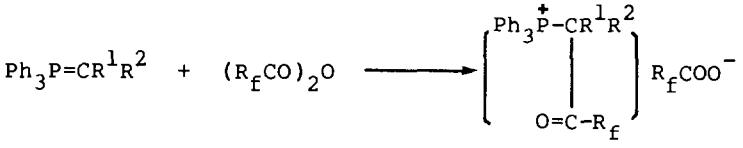
rocyclic rings [2] ; the fluoroalkylvinylation of heterocyclic compounds has not been reported previously. Therefore it is of much value to develop an effective method for direct fluoroalkylvinylation of heterocyclic compounds.

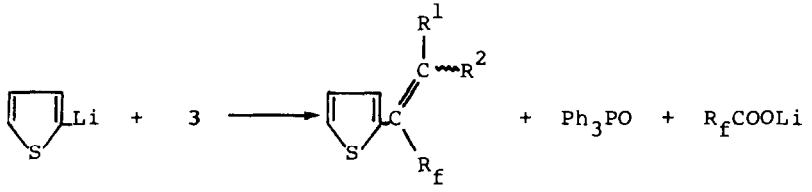
## RESULTS AND DISCUSSION

Recently we have found that fluorinated β-ketophosphonium salts reacted with nucleophiles to give fluoroalkenes [3] and fluoroenynes [4]. As an extension of this study we wish to report here the first example of direct introduction of a fluoroalkylvinyl group into the heterocyclic compound, thiophene.

The reaction sequence is as follows:



**1** **2** **3**



**4**

a $R^1,R^2$=-$(CH_2)_4$-;$R_f$=$CF_3$ e $R^1$=$CH_3$;$R^2$=Ph; $R_f$=$CF_3$

b $R^1,R^2$=-$(CH_2)_4$-;$R_f$=$C_2F_5$ f $R^1$=$CH_3$;$R_2$=$PhCH_2$; $R_f$=$CF_3$

c $R^1$=$R^2$=$CH_3$; $R_f$=$CF_3$ g $R^1$=$CH_3$;$R^2$=n-$C_3H_7$;$R_f$=$CF_3$

d $R^1$=$R^2$=$CH_3$; $R_f$=$C_2F_5$ h $R^1$=$CH_3$;$R^2$=n-$C_4H_9$;$R_f$=$CF_3$

Phosphoranes 1 were generated from the corresponding phosphonium salts and n-butyllithium in tetrahydrofuran and were acylated by the addition of perfluoroalkanoic anhydride to give fluorinated β-ketophosphonium salts 3 which in the reaction medium could be used as fluoroalkylvinylation reagents and were submitted to the reaction with thienyllithium to give fluoroalkylvinyl thiophenes **4** in 56-82% yields.
The results are shown in Table 1. All products exhibited NMR, IR, mass spectroscopic analysis and elemental analyses consistent with the assigned structures.

In the present reaction, the fluorinated β-ketophosphonium salts as electrophiles when attacking the thiophene anion, followed by elimination of triphenyl phosphine oxide to afford fluoroalkylvinyl thiophene. The characteristic feature of this new methodology is a one-pot synthesis leading to the direct introduction of fluoroalkylvinyl group into the heterocyclic compound, thiophene, and it should be useful for the synthesis of biologically active fluorine-containing compounds.

TABLE 1

Synthesis of Fluoroalkylvinyl Thiophenes **4**

| Compound | b.p. °C/mmHg | Yield[a] % | Z:E[b] |
|---|---|---|---|
| **4a** | 60-61/1.0 | 72 | |
| **4b** | 52-54/0.2 | 70 | |
| **4c** | 38-40/0.5 | 56 | |
| **4d** | 39-41/0.5 | 67 | |
| **4e** | 48-49[c] | 82 | 100:0 |
| **4f** | 82-84/0.3 | 60 | 71:29 |
| **4g** | 45-47/0.2 | 69 | 73:27 |
| **4h** | 50-52/0.7 | 80 | 67:33 |

[a] Isolated yields. Based on perfluoroalkanoic anhydride.

[b] The ratios of Z- and E- configurations in the vinyl group are estimated on the basis of NMR data.

[c] m.p. °C.

## EXPERIMENTAL

All boiling and melting points were uncorrected. Infrared spectra of solid products were obtained as KCl disks and of liquid products as films on a Shimadzu IR-440 Spectrometer. NMR spectra (chemical shifts in ppm from TMS for $^{1}H$ NMR and from external TFA for $^{19}F$ NMR, positive for up-

field shifts) were obtained on a Varian EM-360 Spectrometer at 60 MHz or a XL-200 Spectrometer at 200 MHz. Mass spectra were recorded on a Finnigan GC-MC 4021 Mass Spectrometer.

General procedure for preparation of fluoroalkylvinyl thiophenes **4**

Phosphorane **1** was generated from the corresponding phosphonium salt ( 3 mmol) and n-butyllithium ( 3 mmol) in tetrahydrofuran ( 30 ml) at 0°C under nitrogen. The reaction mixture was cooled to -78°C and perfluoroalkanoic anhydride(2.6 mmol) was slowly added until the disappearance of the ylidic color. After stirring at -78°C for 5 min, thienyllithium (3 mmol) was added. The mixture was allowed to warm to room temperature, stirred for a further 2 h and diluted with petroleum ether ( b.p. 30-60°C, 100 ml). The filtrate was collected and evaporation of the solvents gave a residue which was purified by column chromatography on silica gel eluting with petroleum ether (b.p. 30-60°C) to afford product **4**.

**4a**: 72% yield; b.p. 60-61°C/1mmHg; IR(film): 1660(m), 1110 (s), 700(s) $cm^{-1}$. $^{1}H$ NMR($CDCl_3$): $\delta$ 1.56-2.71(m,8H); 6.91 (dd,1H,J=3.6,1.1Hz); 7.02(dd,1H,J=5.1,3.6Hz); 7.32(dd,1H, J=5.1,1.1Hz); $^{19}F$ NMR($CDCl_3$): $\delta$ -17.0(s,3F)ppm; MS m/e: 232 ($M^+$), 163($M^+-CF_3$),69($CF_3^+$). Analysis: Calcd for $C_{11}H_{11}F_3S$: C,56.88, H,4.77, Found: C,57.16, H,4.86 %.

**4b**: 70% yield; b.p.52-54°C/0.2mmHg; IR(film): 1640(m),1130 (s), 700(s) $cm^{-1}$. $^{1}H$ NMR($CDCl_3$): $\delta$ 1.54-2.69(m,8H); 6.85 (dd,1H,J=3.5,1.1Hz); 7.00(dd,1H,J=5.2,3.5Hz); 7.33(dd,1H, J=5.2,1.1Hz); $^{19}F$ NMR($CDCl_3$): $\delta$ 6.7(s,3F); 33.0(s,2F)ppm; MS m/e: 282($M^+$), 263($M^+$-F), 69($CF_3^+$). Analysis: Calcd for $C_{12}H_{11}F_5S$: C,51.06, H, 3.93, Found: C,51.06, H,3.95 %.

4c: 56% yield; b.p.38-40°C/0.5mmHg; IR(film): 1660(m),1110 (s), 700(s) $cm^{-1}$. $^{1}H$ NMR($CDCl_3$): $\delta$ 1.75(q,3H,J=2.2Hz); 2.08 (q,3H,J=2.5Hz); 6.48(dd,1H,J=3.5,1.0Hz); 7.02(dd,1H,J=5.2, 3.5Hz); 7.34(dd,1H,J=5.2,1.0Hz); $^{19}F$ NMR($CDCl_3$): $\delta$-20.0 (s,3F)ppm; MS m/e: 206($M^+$), 191($M^+-CH_3$), 137($M^+-CF_3$), 69 ($CF_3^+$). Analysis: Calcd for $C_9H_9F_3S$: C,52.42, H,4.40, Found: C,52.40, H,4.42 %.

**4d**: 67% yield; b.p.39-41°C/0.5mmHg; IR(film): 1650(m),1130 (s), 700(s) $cm^{-1}$. $^{1}H$ NMR($CDCl_3$): $\delta$ 1.74(t,3H,J=2.5Hz); 2.07 (t,3H,J=2.2Hz); 6.82(dd,J=3.5,1.2Hz); 7.00(dd,1H,J=5.2, 3.5Hz) 7.34(dd,1H,J=5.2,1.2Hz); $^{19}F$ NMR($CDCl_3$):$\delta$6.0(s,3F); 28.6(s,2F)ppm; MS m/e: 256($M^+$), 241($M^+-CH_3$), 187($M^+-CF_3$), 69($CF_3^+$). Analysis: Calcd for $C_{10}H_9F_5S$: C,46.88, H,3.54, Found: C,47.28,H,3.74 %.

**4e**: 82% yield; m.p. 48-49°C; IR(KCl): 1650(m), 1600(m), 1120(s), 700(s) $cm^{-1}$. $^{1}H$ NMR($CDCl_3$): $\delta$ 2.03(q,3H,J=2.1Hz); 7.03-7.43(m,8H); $^{19}F$ NMR($CDCl_3$): $\delta$ -20.0(s,3F)ppm; MS m/e:

268($M^+$), 253($M^+-CH_3$), 199($M^+-CF_3$), 69($CF_3^+$). Analysis: Calcd for $C_{14}H_{11}F_3S$: C,62.68, H,4.13, Found: C,63.07, H,4.17 %.

**4f**: 60% yield; b.p. 82-84°C/0.3mmHg; IR(film): 1640(m), 1600(m), 1110(s), 700(s) $cm^{-1}$. $^1H$ NMR($CDCl_3$): δ 1.55(E)+1.70(Z)(br.s,3H); 3.12(Z)+3.50(E)(br.s,2H); 6.66-7.05 (m,8H); $^{19}F$ NMR($CDCl_3$): δ [-20.0(Z)+(-21.6)(E)](s,3F)ppm; MS m/e: 282($M^+$), 263($M^+-F$), 213($M^+-CF_3$), 69($CF_3^+$). Analysis: Calcd for $C_{15}H_{13}F_3S$: C,63.82, H,4.64, Found: C,63.64, H,4.58 %.

**4g**: 69% yield; b.p. 45-47°C/0.2mmHg; IR(film): 1640(m), 1110(s), 700(s) $cm^{-1}$. $^1H$ NMR($CDCl_3$): δ 0.82(Z)+0.99(E) (t,3H,J=7.3Hz); 1.35-1.63(m,2H); 1.86(E)+2.05(Z)(q,3H, J=2.2Hz); 1.95-2.15(m,2H); 6.84(dd,1H,J=3.5,1.1Hz); 7.00 (dd,1H,J=5.1,3.5Hz); 7.32(dd,1H,J=3.5,1.1Hz); $^{19}F$ NMR ($CDCl_3$): δ [-19.5(Z)+(-20.2)(E)](s,3F); MS m/e: 234($M^+$), 165($M^+-CF_3$), 69($CF_3^+$). Analysis: Calcd for $C_{11}H_{13}F_3S$: C,56.40, H,5.59, Found: C,56.74, H,6.05 %.

**4h**: 80% yield, b.p. 50-52°C/0.7mmHg; IR(film): 1640(m), 1110(s), 700(m) $cm^{-1}$. $^1H$ NMR($CDCl_3$): δ 0.81(Z)+0.95(E) (t,3H,J=7.3Hz), 1.15-1.60(m,4H); 1.73(E)+2.04(Z)(q,3H, J=2.1Hz); 1.94-2.45(m,2H); 6.83(dd,1H,J=3.5,1.1Hz); 7.01 (dd,1H,J=5.1,3.5Hz); 7.32(dd,1H,J=5.1,1.1Hz); $^{19}F$ NMR ($CDCl_3$): δ [-20.0(Z)+(-20.6)(E)](s,3F); MS m/e: 248($M^+$),

233($M^+$-$CH_3$), 179($M^+$-$CF_3$), 69($CF_3^+$). Analysis: Calcd for $C_{12}H_{15}F_3S$: C,58.05, H,6.09, Found: C,57.99, H,6.25 %.

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