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A CONVENIENT SYNTHESIS OF FLUORINATED α,β-UNSATURATED AMIDES

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SUMMARY

Pentafluorophenylated or p-chloro-tetrafluorophenylated α,β-unsaturated amides could be synthesized by the reaction of fluorinated arsorane, generated in situ from methylene-triphenylarsorane and hexafluorobenzene or chloro-pentafluorobenzene, with α-bromoacetamides in good yields giving E-isomer exclusively.

INTRODUCTION

α,β-Unsaturated amides constitute an important class of compounds occurring widely in a number of natural products which show biologically activities[1]. They are also capable of undergoing many useful organic transformations [2]. Therefore reactions leading to their formation especially fluorinated compounds, have attracted much attention. Ishihara et al. reported a fluoride ion-catalyzed reaction of 1-phosphonyloxy-F-1-alkenephosphonates with

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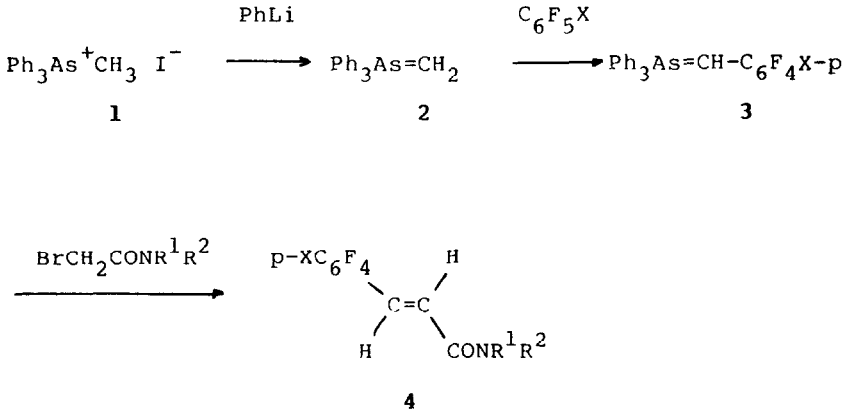
amines to give the perfluorinated α,β-unsaturated amides[3], but the method for their preparation is still limited.

Recently we found a facile synthesis of pentafluorophenyl olefines via arsonium ylides[4]. In our continuing investigation to exploit the synthetic utility of this reagent we now wish to report a convenient one-pot synthesis of fluorinated α,β-unsaturated amides by the reaction of pentafluorophenylated or chloro-tetrafluorophenylated arsorane with α-bromoacetamides.

RESULTS AND DISCUSSION

Pentafluorophenylmethylenetriphenylarsorane or p-chlorotetrafluorophenylmethylenetriphenylarsorane which was generated from methylenetriphenylarsorane and hexafluorobenzene or chloro-pentafluorobenzene, without isolation, reacted with α-bromoacetamides to give fluorinated products **4** in 52-80% yields(3 steps). The reaction sequence is shown in Scheme 1.



1 **2** **3** **4**

Scheme 1.

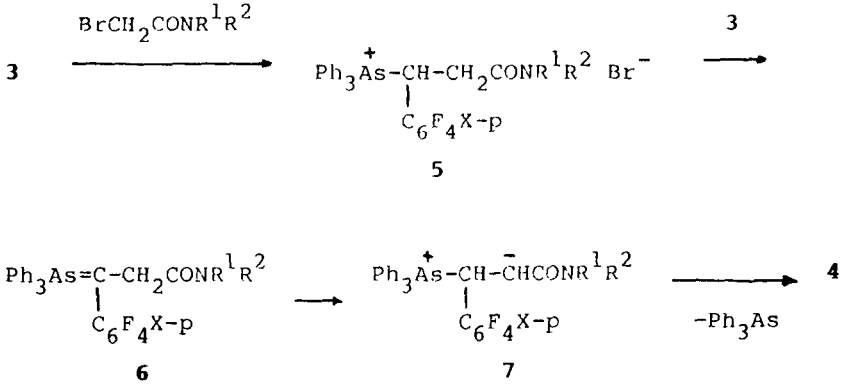
4a: X=F, $R^1=R^2=C_2H_5$ 4e: X=Cl; $R^1=R^2=C_2H_5$

4b: X=F; $R^1=R^2=C_3H_7$-i 4f: X=Cl; $R^1=R^2=C_3H_7$-i

4c: X=F; $R^1=R^2=C_4H_9$-n 4g: X=Cl; $R^1=R^2=C_4H_9$-n

4d: X=F; $R^1,R^2=-(CH_2)_5-$ 4h: X=Cl; $R^1,R^2=-(CH_2)_5-$

The mechanism of **3** to **4** may be rationalized in Scheme **2.** It is initiated by nucleophilic attack of fluorinated arsorane **3** on the α-carbon atom of bromoacetamide to give arsonium salt **5.** **5** reacted with another molecule of **3** to give **6** which converted to **7** via hydrogen transfer, followed by elimination of triphenylarsine affording product **4.** It **may be explained that 7 is more stable than 6 because the** negative charge can be stabilized by the $CONR^1R^2$ group.



Scheme 2.

This one-pot synthesis of fluorinated α,β-unsaturated amides is quite convenient under mild conditions giving E-isomer exclusively **as judged on** the basis of NMR

TABLE 1

Synthesis of Fluorinated α,β-Unsaturated amides **4**

Compound	X	R^1	R^2	Yield(%)[a]
4a	F	C_2H_5	C_2H_5	65
4b	F	C_3H_7-i	C_3H_7-i	75
4c	F	C_4H_9-n	C_4H_9-n	80
4d	F	$-(CH_2)_5-$		62
4e	Cl	C_2H_5	C_2H_5	52
4f	Cl	C_3H_7-i	C_3H_7-i	74
4g	Cl	C_4H_9-n	C_4H_9-n	79
4h	Cl	$-(CH_2)_5-$		75

[a] Isolated yields.

spectroscopy and may be useful in the preparation of fluorinated natural products.

EXPERIMENTAL

All melting points and boiling points were uncorrected. Infrared spectra of solid products were obtained as KCl disks and of liquid products were as films on a Shimadzu IR-440 spectrometer. NMR spectra (chemical shifts in ppm from TMS for ^1H NMR and from external TFA for ^{19}F NMR, positive for **upfield** shifts) were obtained on a Varian EM-360 spectrometer at 60 MHz. Mass spectra were recorded on a Finnigan GC-MC-4021 Mass spectrometer.

General procedure for the preparation of fluorinated α,β-unsaturated amides **4**

Phenyllithium (4 mmol) in absolute diethyl ether (6 ml) was added dropwise to the suspension of methyltriphenyl arsonium iodide (4 mmol) in absolute Et_2O (25 ml) at 20°C under nitrogen. The mixture was stirred at 20°C for 1h and cooled to 0°C, the hexafluorobenzene or chloro-pentafluoro-benzene (2 mmol) was slowly added. After stirring for 15 min at 0°C, the mixture was warmed to 20°C and stirred for 30 min. Then α-bromoacetamide (1 mmol) was added and stirred at 20°C for 3h. The product 4 was isolated by column chromatography on silica gel with light petroleum (b.p. 60-90°C)-ethyl ether (8:2) as eluent.

4a: 65% yield; m.p. 46°C; IR(KCl): 1668(s), 1620(s) cm^{-1}; ^1H NMR(CCl_4/TMS): 1.02(6H,t,J=6Hz), 3.25(4H,q,J=6Hz), 6.85 (1H,d,J=16Hz), 7.37(1H,d,J=16Hz); ^{19}F NMR(CCl_4/TFA): 62.3-64.6(2F,m), 75.3-77.0(1F,m), 84.6-87.0(2F, m)ppm; MS m/z: 293(M^+,45%), 278(M^+-Me, 22%), 221(M^+-NEt_2, 100%); Analysis: Calcd for $C_{13}H_{12}F_5NO$: C, 53.26; H, 4.09; N, 4.78; Found: C, 53.24; H, 4.05; N, 4.45%.

4b: 75% yield; b.p. 105°C/2mmHg; IR(film): 1656(s), 1612(s) cm^{-1}; ^1H NMR(CCl_4/TMS): 1.28(12H,d,J=6Hz), 3.82(2H,hepta, J=6Hz), 6.87(1H,d,J=16Hz), 7.26(1H,d,J=16Hz); ^{19}F NMR(CCl_4/ TFA): 63.3-65.0(2F,m), 76.3-77.4(1F,m), 84.0-86.3(2F,m)ppm; MS m/z: 321(M+, 13%), 278(M^+-Pr, 12%), 221(M^+-NPr_2, 77%);

Analysis: Calcd for $C_{15}H_{16}F_5NO$: C, 56.10; H, 4.98; N, 4.36; Found: C, 56.33; H, 4.88; N, 4.02%.

4c: 80% yield; b.p. 122°C/2mmHg; IR(film): 1660(s), 1618(s) cm^{-1}; ^1H NMR(CCl_4/TMS): 0.95(6H,t,J=6Hz), 1.13-1.80(8H,m), 3.33(4H,t,J=6Hz), 7.06(1H,d,J=16Hz), 7.56(1H,d,J=16Hz); ^{19}F NMR(CCl_4/TFA): 62.3-64.7(2F,m). 75.7-77.2(1F,m), 84.4-86.3 (2F,m)ppm; MS m/z: 349(M^+,8%), 221(M^+-NBu_2,100%); Analysis: Calcd for $C_{17}H_{20}F_5NO$: C, 58.47; H, 5.73; N, 4.01; Found: C, 59.17; H, 5.91; N, 3.83%.

4d: 62% yield; m.p. 62°C; IR(KCl): 1660(s), 1620(s) cm^{-1}; ^1H NMR(CCl_4/TMS): 1.40-1.73(6H, m), 3.30-3.65(4H, m), 7.01 (1H,d,J=16Hz), 7.43(1H,d,J=16Hz); ^{19}F NMR(CCl_4/TFA): 62.6-64.6(2F, m), 75.8-77.2(1F,m), 84.0-86.4(2F, m)ppm; MS m/z: 306(M^++1,100%), 305(M^+,37%), 221(M^+-NC_5H_{10}, 13%); Analysis for $C_{14}H_{12}F_5NO$: C, 55.10; H, 3.93; N, 4.59; Found: C, 55.66; H, 3.61; N, 4.06%.

4e: 52% yield; b.p. 110°C/2mmHg; IR(film): 1660(s), 1622(s) cm^{-1}; ^1H NMR(CCl_4/TMS): 1.16(6H,t, J=6Hz), 3.30(4H,q, J=6 Hz); 7.00(1H,d, J=16Hz), 7.49(1H,d, J=16Hz); ^{19}F NMR(CCl_4/ TFA): 62.0-63.3(2F,m), 63.3-65.0(2F,m)ppm; MS m/z: 309(M^+, 42%), 237(M^+-NEt_2,100%); Analysis: Calcd for $C_{13}H_{12}ClF_4NO$: C, 50.43; H, 3.88; N, 4.52; Found: C, 50.38; H, 3.80; N, 4.34%.

4f: 74% yield; b.p. 108°C/2mmHg; IR(film): 1650(s), 1610(s) cm^{-1}; ^1H NMR(CCl_4/TMS): 1.32(12H,d, J=6Hz), 3.87(2H,hepta, J=6Hz), 6.94(1H,d,J=16Hz), 7.49(1H,d,J=16Hz); ^{19}F NMR(CCl_4/

TFA): 62.3-63.5(2F,m), 63.5-65.3(2F,m)ppm; MS m/z: 337(M^+, 15%), 237(M^+-NPr_2, 68%); Analysis: Calcd for $C_{15}H_{16}ClF_4NO$: C, 53.36; H, 4.74; N, 4.15; Found: C, 53.90; H, 4.78; N, 3.78%.

4g: 79% yield; b.p. 116°C/2mmHg; IR(film): 1660(s), 1618(s) cm^{-1}; ^1H NMR(CCl_4/TMS): 0.92(6H,t,J=6Hz), 1.12-1.75(8H,m), 3.30(4H,t,J=6Hz), 7.07(1H,d,J=16Hz), 7.50(1H,d,J=16Hz); ^{19}F NMR(CCl_4/TFA): 62.5-64.0(2F,m), 64.-65.0(2F,m)ppm; MS m/z: 365(M^+, 9%), 237(M^+-NBu_2, 100%); Analysis: Calcd for $C_{17}H_{20}ClF_4NO$: C, 55.84; H, 5.47; N, 3.83; Found: C, 55.87; H, 5.61 N, 3.78%.

4h: 75% yield; m.p. 60°C; IR(KCl): 1656(s), 1616(s) cm^{-1}; ^1H NMR(CCl_4/TMS): 1.40-1.80(6H, m), 3.40-3.70(4H, m), 7.17 (1H,d,J=16Hz), 7.59(1H,d,J=16Hz); ^{19}F NMR(CCl_4/TFA): 62.7-64.0(2F,m), 64.0-65.0(2F,m)ppm; MS m/z: 321(M^+, 74%), 320 (M^+-1, 100%), 237(M^+-NC_5H_{10}, 73%); Analysis: Calcd for $C_{14}H_{12}ClF_4NO$: C, 52,28; H, 3.73; N, 4.36; Found: C, 52.16; H, 3.42; N, 4.20.

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