Novel One-Pot Synthesis of 4-Trifluoromethyl-2,4-dienamides

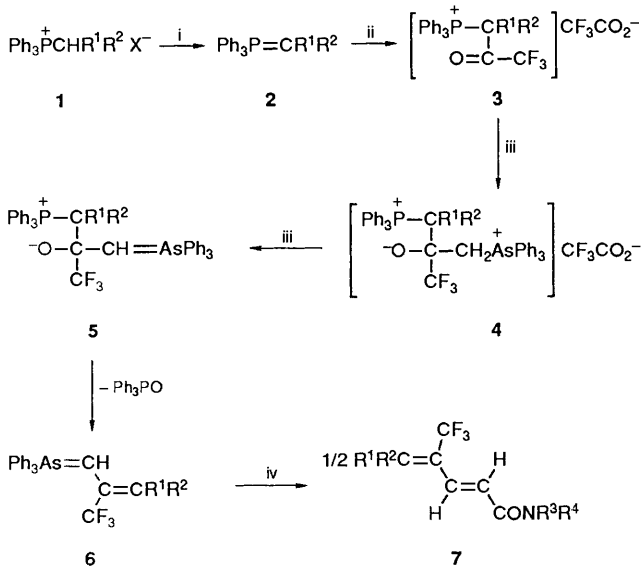
Yanchang Shen * and Yuejun Xiang
Shanghai Institute of Organic Chemistry, Academia Sinica, 345 Lingling Lu, Shanghai 200032, China

4-Trifluoromethyl-2,4-dienamides can be successfully synthesized by the reaction of trifluoromethylated arsoranes, generated from the transylidation between fluorinated β-oxoalkylphosphonium salts and methylenetriphenylarsorane, with α-bromoacetamides.

Synthesis of 2,4-dienamides is attracting much interest since such compounds are an important structural feature of a number of naturally occurring compounds which have been reported to be active both physiologically and insecticidally.[1] Several synthetic methods have been reported for their preparation.[1,2] However, the methods for the preparation of trifluoromethyl analogues are still limited. The synthesis of 3-trifluoromethyl analogues from trifluoromethylated allylic alcohols and a (phenylthio)ynamine in several steps was reported by Kobayashi and co-workers.[3] They would be expected to possess some biological activity and an effective method for their synthesis would be valuable.

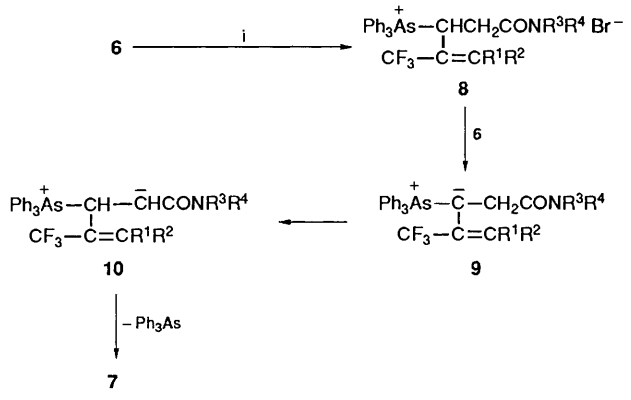
Results and Discussion

Recently we found a novel double elimination of arsonium salts and its application to the synthesis of 4-trifluoromethyl-2,4-dienyl carboxylates.[4] In our continuing investigation into the exploitation of the synthetic utility of this reaction in organic synthesis we report a novel one-pot synthesis of 4-trifluoromethyl-2,4-dienamides by the reaction of trifluoromethylated arsoranes with α-bromoacetamides. The reaction sequence is shown in Scheme 1.



Scheme 1 *Reagents:* i, PhLi; ii, $(CF_3CO)_2O$; iii, $Ph_3As=CH_2$; iv, $\frac{1}{2}$ $BrCH_2CONR^3R^4$

The phosphoranes **2** generated from the corresponding phosphonium salts **1** and phenyllithium in tetrahydrofuran (THF) were acylated by the addition of trifluoroacetic anhydride (TFAA) to give the fluorinated β-oxophosphonium salts **3**, which in the reaction medium were attacked by methylenetriphenylarsorane to give intermediates **4**, followed by deprotonation (to species **5**) and elimination of triphenylphosphine oxide to afford compounds **6**.[5] Without isolation, compounds **6** reacted with α-bromoacetamides to give 4-trifluoromethyl-2,4-dienamides in 45–85% yield (3 steps). The mechanism of the reaction **6** ⟶ **7** may be rationalized as in Scheme 2. The reaction is initiated by nucleophilic attack of



Scheme 2 *Reagent:* i, $BrCH_2CONR^3R^4$

trifluoromethylated arsoranes **6** on the α-carbon atom of the bromoacetamide to give arsonium salts **8**, which then react with another molecule of arsorane **6** to give the ylides **9**, which are in turn converted into the isomeric internal salts **10** *via* hydrogen transfer; this is then followed by elimination of triphenylarsine to afford products **7**. It may be that the internal salts **10** are more stable than the isomeric ylides **9** since the negative charge in species **10** can be stabilized by the $CONR^3R^4$ group.

Experimental

All b.p.s are uncorrected. IR spectra of liquid products were obtained as films on a Shimadzu IR-440 spectrometer. ^1H and ^{19}F NMR spectra were recorded on a Varian EM-360 (60 MHz) or XL-200 (200 MHz) spectrometer with $SiMe_4$ or CF_3CO_2H (positive for upfield shifts) as external reference, respectively. *J*-Values are given in Hz. Mass spectra were measured on a GC-MS-4021 spectrometer.

General Procedure.—A solution of phenyllithium (3.0 mmol) in absolute diethyl ether (10 cm^3) was added dropwise to a stirred suspension of a phosphonium salt **1** (3.0 mmol) in absolute THF (30 cm^3) at −20 °C under nitrogen. The mixture was stirred for 30 min at −20 °C and was then cooled to −78 °C; TFAA (2.6 mmol) was slowly added until the characteristic colour of the phosphorane **2** had disappeared. After the mixture had been stirred at −78 °C for 15 min, a solution of methylenetriphenylarsorane [generated from methyltriphenylarsonium iodide (6 mmol) and phenyllithium (6 mmol) in diethyl ether (30 cm^3) at 20 °C for 1 h] was slowly added during 30 min. The mixture was then allowed to warm to 0 °C, stirred for further 30 min, recooled to −78 °C and the 2-bromoacetamide (1.3 mmol) was added. After the mixture had

Table 1 Preparation of 4-(trifluoromethyl)-2,4-dienamides

Compound	R^1	R^2	R^3	R^4	Yield (%)[a]
7a	Me	Me	Et	Et	59
7b	Me	Me	Pr^i	Pr^i	45
7c	Me	Me	Bu	Bu	75
7d	Me	Me	$-[CH_2]_5-$		57
7e	$-[CH_2]_4-$		Et	Et	55
7f	$-[CH_2]_4-$		Pr^i	Pr^i	51
7g	$-[CH_2]_4-$		Bu	Bu	85
7h	$-[CH_2]_4-$		$-[CH_2]_5-$		51

[a] Isolated yield. All products were characterized by microanalysis, and IR, NMR and mass spectroscopy.

been stirred at 20 °C for 2 h, the product **7** was isolated by column chromatography on silica gel with light petroleum (b.p. range 60–90 °C)–ethyl acetate (8:2) as eluent. The following dienamides were thus prepared (see Table 1 for definition of substituent groups).

N,N-*Diethyl*-5-*methyl*-4-(*trifluoromethyl*)*hexa*-2E,4-*dienamide* **7a** had b.p. 92 °C at 2 mmHg; δ_H 1.21 (6 H, t, *J* 6), 2.02 (3 H, s), 2.08 (3 H, s), 3.33 (4 H, q, *J* 6), 6.28 (1 H, d, *J* 16) and 7.36 (1 H, d, *J* 16); δ_F −20.7 (s); ν_{max}/cm^{-1} 1640s and 1600s; *m*/*z* 250 (M^+ + 1, 35%), 249 (M^+, 28), 234 (M^+ − Me, 31) and 177 (M^+ − NEt_2, 100) (Found: C, 58.2; H, 7.2; N, 5.3. $C_{12}H_{18}F_3NO$ requires C, 57.85; H, 7.22; N, 5.62%).

N,*N*-Diisopropyl-5-methyl-4-(trifluoromethyl)hexa-2*E*,4-dienamide **7b** had b.p. 90 °C at 2 mmHg; δ_H 1.10 (12 H, d, *J* 6), 1.85 (3 H, s), 1.90 (3 H, s), 3.70 (2 H, septet, *J* 6), 6.16 (1 H, d, *J* 16) and 7.13 (1 H, d, *J* 16); δ_F −21.1 (s); ν_{max}/cm^{-1} 1640s and 1600s; *m*/*z* 278 (M^+ + 1, 75%), 277 (M^+, 11), 262 (M^+ − Me, 11) and 177 (M^+ − NPr^i, 97) (Found: C, 59.9; H, 7.85; N, 4.7. $C_{14}H_{22}F_3NO$ requires C, 60.67; H, 7.94; N, 5.05%).

N,*N*-Dibutyl-5-methyl-4-(trifluoromethyl)hexa-2*E*,4-dienamide **7c** had b.p. 92 °C at 2 mmHg; δ_H 0.95 (6 H, t, *J* 6), 1.20–1.60 (8 H, m), 2.07 (3 H, s), 2.10 (3 H, s), 3.30 (4 H, t, *J* 6), 6.33 (1 H, d, *J* 16) and 7.41 (1 H, d, *J* 16); δ_F −21.0 (s);; ν_{max}/cm^{-1} 1640s and 1600s; *m*/*z* 306 (M^+ + 1, 48%), 305 (M^+, 6), 262 (M^+ − Pr, 17) and 177 (M^+ − NBu_2, 100) (Found: C, 62.4; H, 8.7; N, 4.5. $C_{16}H_{26}F_3NO$ requires C, 62.97; H, 8.52; N, 4.59%).

N-[5-*Methyl*-4-(*trifluoromethyl*)*hexa*-2E,4-*dienaoyl*]*piperidine* **7d** had b.p. 106 °C at 2 mmHg; δ_H 1.50–1.70 (6 H, m), 1.99 (3 H, s), 2.04 (3 H, s), 3.50–3.64 (4 H, m), 6.16 (1 H, d, *J* 16) and 7.24 (1 H, d, *J* 16); δ_F −21.2 (s); ν_{max}/cm^{-1} 1640s and 1600s; *m*/*z* 262 (M^+ + 1, 80%), 261 (M^+, 26), 246 (M^+ − Me, 14), 177 (M^+ − NC_5H_{10}, 18) and 84 ($\dot{N}C_5H_{10}$, 100) (Found: C, 59.4; H, 7.2, N, 5.4. $C_{13}H_{18}F_3NO$ requires C, 59.79; H, 6.89; N, 5.36%).

4-*Cyclopentylidene*-N,N-*diethyl*-5,5,5-*trifluoropenta*-2E,4-*dienamide* **7e** had b.p. 102 °C at 2 mmHg; δ_H 1.05 (6 H, t, *J* 6), 1.50–1.70 (4 H, m), 2.23–2.73 (4 H, m), 3.25 (4 H, q, *J* 6), 6.16 (1 H, d, *J* 16) and 7.20 (1 H, d, *J* 16); δ_F −21.0 (s); ν_{max}/cm^{-1} 1640s and 1600s; *m*/*z* 276 (M^+ + 1, 100%), 275 (M^+, 36) and 203 (M^+ − NEt_2, 50) (Found: C, 61.3; H, 7.5; N, 5.1. $C_{14}H_{20}F_3NO$ requires C, 61.11; H, 7.27; N, 5.09%).

4-*Cyclopentylidene*-5,5,5-*trifluoro*-N,N-*diisopropylpenta*-2E,4-*dienamide* **7f** had b.p. 96 °C at 2 mmHg; δ_H 1.30 (12 H, d, *J* 6), 1.62–2.00 (4 H, m), 2.55–2.82 (4 H, m), 3.93 (2 H, septet, *J* 6), 6.39 (1 H, d, *J* 16) and 7.32 (1 H, d, *J* 16); δ_F −20.3 (s); ν_{max}/cm^{-1} 1640s and 1600s; *m*/*z* 304 (M^+ + 1, 45%), 303 (M^+, 14) and 203 (M^+ − NPr^i_2, 60) (Found: C, 64.1; H, 8.0; N, 4.55. $C_{16}H_{24}F_3NO$ requires C, 63.89; H, 7.92; N, 4.62%).

N,N-*Dibutyl*-4-*cyclopentylidene*-5,5,5-*trifluoropenta*-2E,4-*dienamide* **7g** had b.p. 102 °C at 2 mmHg; δ_H 0.95 (6 H, t, *J* 6), 1.20–1.94 (12 H, m), 2.54–2.87 (4 H, m), 3.00 (4 H, t, *J* 6), 6.37 (1 H, d, *J* 16) and 7.42 (1 H, d, *J* 16); δ_F −20.5 (s); ν_{max}/cm^{-1} 1640s and 1600s; *m*/*z* 332 (M^+ + 1, 83%), 331 (M^+, 11) and 203 (M^+ − NBu_2, 88) (Found: C, 64.9; H, 8.3; N, 4.2. $C_{18}H_{28}F_3NO$ requires C, 65.28; H, 8.45; N, 4.23%).

N-(4-*Cyclopentylidene*-5,5,5-*trifluoropenta*-2E,4-*dienoyl*)-*piperidine* **7h** had b.p. 108 °C at 2 mmHg; δ_H 1.50–1.90 (10 H, m), 2.55–2.90 (4 H, m), 3.50–3.65 (4 H, m), 6.44 (1 H, d, *J* 16) and 7.38 (1 H, d, *J* 16); δ_F −18.7 (s); ν_{max}/cm^{-1} 1640s and 1600s; *m*/*z* 288 (M^+ + 1, 24%), 287 (M^+, 26); 203 (M^+ − NC_5H_{10}, 6) and 84 ($\dot{N}C_5H_{10}$, 100) (Found: C, 62.9; H, 7.1; N, 4.4. $C_{15}H_{20}F_3NO$ requires C, 62.73; H, 6.96; N, 4.88%).

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