COMMUNICATION

A new and facile stereocontrolled synthesis of conjugated dienyl trifluoromethyl ketones †

Jingbo Xiao, Yanshu Feng and Chengye Yuan *

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

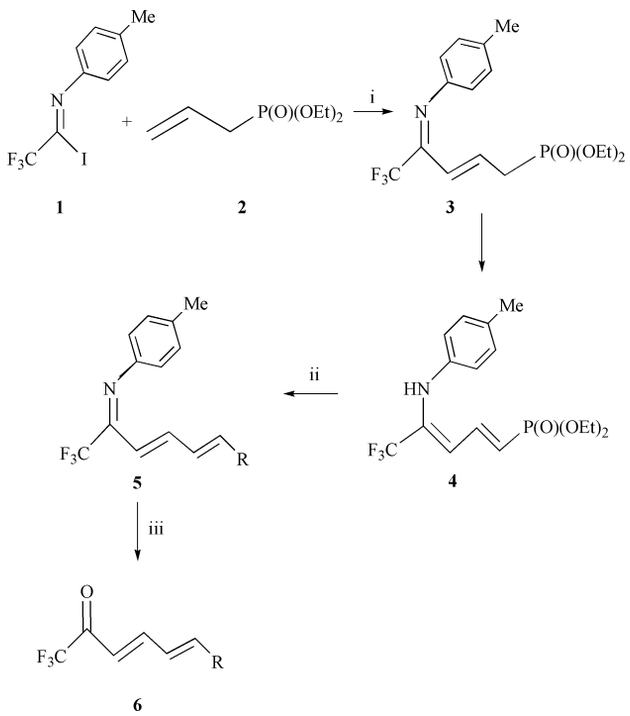
Received (in Cambridge, UK) 30th June 2000, Accepted 13th November 2000
First published as an Advance Article on the web 29th November 2000

The stereocontrolled synthesis of conjugated dienyl trifluoromethyl ketones has been achieved by a Horner–Wadsworth–Emmons reaction starting from the key trifluoromethylated building block *N*-(4-methylphenyl)-trifluoroacetimidoyl iodide.

Organofluorine compounds have gained considerable interest due to their possibly enhanced biological activities as compared to the nonfluorinated counterparts.[1] In particular, trifluoromethyl ketones are potential versatile synthetic precursors in the preparation of trifluoromethyl-containing compounds.[2] They can also serve as transition-state analogue inhibitors for a variety of hydrolytic enzymes.[3] For these reasons, the synthesis of trifluoromethyl ketones has received much attention and many synthetic routes have been developed in recent years.[4] However, unsaturated trifluoromethyl ketones, as functionalized trifluoromethyl ketones in general, are not very readily accessible,[5] because many procedures that are commonly employed in the synthesis of unsaturated ketones are not applicable to the preparation of the fluorinated counterparts. As an extension of our research on a one-pot synthesis of α,β-unsaturated trifluoromethyl ketones,[6] herein, we wish to present a new and facile stereocontrolled synthesis of conjugated dienyl trifluoromethyl ketones starting from the key trifluoromethylated building block *N*-(4-methylphenyl)-trifluoroacetimidoyl iodide, which has been widely used in the synthesis of trifluoromethyl-containing compounds.[6,7] Our synthetic route is based on the following sequence of reactions as shown in Scheme 1.

The key trifluoromethylated building block **1** was readily prepared by displacement of chlorine of the corresponding acetimidoyl chloride[7c,8] with iodine in the NaI–acetone system.[7a] We expected that *N*-(4-methylphenyl)trifluoroacetimidoyl iodide (**1**) would undergo a palladium-catalyzed reaction smoothly with diethyl allylphosphonate to afford diethyl *N*-(4-methylphenyl)imino-5,5,5-trifluoropent-2-enylphosphonate (**3**). But the ^{1}H NMR showed no signals corresponding to the P–CH_2 part, although the mass spectra and elemental analyses confirmed the molecular weight and atom components. So we deduced that compound **4** might easily isomerize to compound **3**. Thus we treated the important intermediates **4** with butyllithium at −78 °C which underwent a Horner–Wadsworth–Emmons reaction with aldehydes, followed by acid hydrolysis to provide moderate to good yield of the title products **6**. The stereochemistry of the two vinyl moieties in the products were both assigned as *E*-configuration on the basis of the vinylic H–H coupling constant (J = 15 Hz).

As demonstrated in Table 1, a variety of aromatic aldehydes can be converted into conjugated dienyl trifluoromethyl ketones. But the method was unsuccessful, when aromatic aldehydes were used instead of alkyl aldehydes and ketones. All the products showed a singlet in their ^{19}F NMR and the stereochemical features of the dienyl part were identified as *E*-isomers by ^{1}H NMR. The high stereoselectivity of the products is probably due to the less hindered *threo*-diastereoisomers of the oxyanion intermediates in the course of the Horner–Wadsworth–Emmons reaction.



Scheme 1 *Reaction conditions and reagents*: i $Pd_2(dba)_3CH_3Cl$, K_2CO_3, 75 °C; ii n-BuLi, RCHO, −78 °C; iii 2 mol dm^{-3} HCl, room temp.

In conclusion, we have described the utility of *N*-(4-methylphenyl)trifluoroacetimidoyl iodide (**1**) as the key trifluoromethylated building block for the *stereocontrolled* synthesis of a series of conjugated dienyl trifluoromethyl ketones *via* a Horner–Wadsworth–Emmons reaction. Compared with some other synthesis of these compounds such as by a Claisen rearrangement,[9] our method is simpler and more convenient.

Experimental

1.1 Synthesis of compound 4

To a 25 cm^3 flask purged with N_2, was added K_2CO_3 (4.09 mmol, 564 mg), $Pd_2(dba)_3CHCl_3$ (0.115 mmol, 119 mg) and dried toluene (1 cm^3). A solution of *N*-(4-methylphenyl)-trifluoroacetimidoyl iodide (**1**) (1.955 mmol, 612 mg) and dried toluene (0.5 cm^3) was added dropwise to the mixture. After 30 min diethyl allylphosphonate (**2**) (5.87 mmol, 1.044 g) was added. Stirring was continued at 75 °C for 9 h. Completion of the reaction was monitored by TLC. The mixture was filtered

† Experimental data for compounds **6b**–**6g** are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b005250g/

 DOI: 10.1039/b005250g

Table 1 Conjugated dienyl trifluoromethyl ketones[a]

	R	Yield (%)[b]		R	Yield (%)[b]
6a	Phenyl	67	**6e**	4-Chlorophenyl	60
6b	4-Methylphenyl	61	**6f**	4-Bromophenyl	71
6c	4-Methoxyphenyl	43	**6g**	4-Nitrophenyl	47
6d	4-Fluorophenyl	41			

[a] Satisfactory spectral and microanalytical data were obtained for all new compounds. [b] Isolated yields.

and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel to give compound **4** (0.365 g, 51%) as a yellow solid, mp 66–68 °C (Found: C, 52.70; H, 5.83; N, 3.78. $C_{16}H_{21}F_3NO_3P$ requires C, 52.89; H, 5.83; N, 3.86%); IR: ν/cm^{-1} 3252, 2986, 1515, 1248, 1188, 1026; δ_H (300 MHz; C_6D_6; Me_4Si) 7.31 (1H, m), 6.87 (2H, d, J 8, Ph-H), 6.84 (1H, s, NH_2), 6.77 (2H, d, J 8, Ph-H), 5.96 (1H, d, J 11), 5.57 (1H, dd, $J_1 = J_2$ 18), 3.78 (4H, q, J 8, 2 × CH_2), 2.10 (3H, s, CH_3), 1.02 (6H, t, J 8, 2 × CH_2CH_3); δ_F (56.4 MHz; C_6D_6; TFA) −9.3(s); m/z 363 (M^+, 19.45%), 364 ($M^+ + 1$, 12.80%), 225 (base).

1.2 Synthesis of compound 6a, typical procedure

To a 25 cm^3 flask purged with N_2, was added dried THF (2 cm^3) and butyllithium (2.0 mol dm^{-3} in hexane; 0.396 mmol, 0.198 cm^3). After 10 min, the solution was cooled to −78 °C and a solution of compound **4** (0.265 mmol, 96 mg) in dried THF (2 cm^3) was added dropwise. After the mixture had been stirred for 3 h at −78 °C, the freshly distilled phenylaldehyde (0.317 mmol, 33.6 mg) in dried THF (2 cm^3) was gradually added at the same temperature. The mixture was stirred continuously at −78 °C for another 1 h and then warmed to room temperature over 2 h and stirred overnight. After addition of 2 mol dm^{-3} aq. HCl to the mixture, it was stirred at room temperature for 5 h and then extracted with diethyl ether (3 × 20 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Isolation of the product by column chromatography on silica gel (EtOAc : Petroleum ether = 50 : 1) gave compound **6a** (40 mg, 67%) as a yellow oil (Found: 226.06094; $C_{12}H_9F_3O$ requires 226.06055); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.74 (1H, dd, J_1 15, J_2 11), 7.52 (2H, m, ArH), 7.39 (3H, m, ArH), 7.16 (1H, d, J 15), 6.98 (1H, dd, J_1 15, J_2 11), 6.56 (1H, d, J 15); δ_F (56.4 MHz; $CDCl_3$; TFA) −0.42 (s); m/z 226 (M^+, base), 157 (67.11%), 129 (36.58%), 180 (29.06%).

Acknowledgements

We gratefully acknowledge the financial support of National Natural Sciences Foundation of China (NNSFC), Number 29832050.

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