

## A NOVEL SYNTHESIS OF TRANS- $\gamma,\delta$ -UNSATURATED TRIFLUOROMETHYL KETONES

Yanchang Shen\*, Tielin Wang

Shanghai Institute of Organic Chemistry, Academia Sinica  
 345 Lingling Lu, Shanghai 200032, China

**Summary :** A novel  $\gamma$ -trifluoroacetylation and a novel ylide-anion formation via conjugated nucleophilic addition and their application to the synthesis of trans- $\gamma,\delta$ -unsaturated trifluoromethyl ketones are described.

Syntheses of trifluoromethyl ketones are of current interest because of their ability as potential enzyme inhibitors<sup>1, 2</sup> and insect juvenile pheromone esterase inhibitors.<sup>3</sup> Shimizu et al.<sup>4</sup> reported a facile synthesis of  $\gamma,\delta$ -unsaturated trifluoromethyl ketone by palladium-catalyzed Carroll type reaction, but the method for their preparations is still limited. Recently, we reported a novel ylide-anion formation which resulted from the nucleophilic addition to the carbonyl group in trifluoroacetylmethylenetriphenylphosphorane and its application to the synthesis of trans- $\alpha$ -trifluoromethyl allylic alcohols.<sup>5</sup> Alternatively, we wish to report a novel ylide-anion which is formed from the nucleophilic addition to the double bond conjugated to the trifluoroacetyl group in (3-trifluoroacetyl)-allylidetriphenylphosphorane (3) and its application to the synthesis of trans- $\gamma,\delta$ -unsaturated trifluoromethyl ketones.

We found allylidetriphenylphosphorane (2) could react with ethyl trifluoroacetate to give ylide 3 exclusively as a cis isomer based on its <sup>1</sup>H NMR spectrum (Eq. 1).<sup>6</sup> The ylide 3 was very stable and unable to react with aldehyde due to the strong electron-withdrawing effect of trifluoroacetyl group. Use of n-butyllithium or phenyllithium to activate ylide 3 resulted in a different reaction from the previous case.<sup>5</sup> Thus, the nucleophiles attacked in a conjugate manner to give ylide-anion 4, which reacted with aldehydes or ketones, after hydrolysis, to afford trans- $\gamma,\delta$ -unsaturated trifluoromethyl ketones 5 in 46-92% yields (Eq. 2).

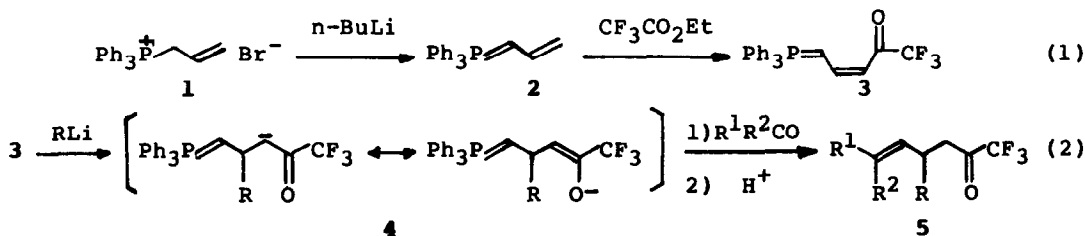


Table 1, Reaction of Ylide-Anion 4 with Carbonyl Compounds (Eq.2)

5	R <sup>1</sup>	R <sup>2</sup>	R	Time(h)	Yields(%) <sup>a)</sup>	B.P.(°C/mm)
a	C <sub>6</sub> H <sub>5</sub>	H	n-C <sub>4</sub> H <sub>9</sub>	4	63 <sup>b)</sup>	130/0.5
b	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	n-C <sub>4</sub> H <sub>9</sub>	14	46	147/0.5
c	c-C <sub>6</sub> H <sub>11</sub>	H	C <sub>6</sub> H <sub>5</sub>	4	82 <sup>b)</sup>	110/0.5
d	C <sub>6</sub> H <sub>5</sub>	H	C <sub>6</sub> H <sub>5</sub>	4	92 <sup>b)</sup>	152/0.5
e	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	14	66	160/0.5
f	4-ClC <sub>6</sub> H <sub>4</sub>	H	C <sub>6</sub> H <sub>5</sub>	4	85 <sup>b)</sup>	150/0.5
g	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	C <sub>6</sub> H <sub>5</sub>	4	90 <sup>b)</sup>	145/0.5
h	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	4	83 <sup>b)</sup>	165/0.5

a) Isolated yields. b) Exclusively trans isomers based on <sup>1</sup>H NMR.

In a general procedure lithium reagent (6 mmol) was added dropwise with stirring to a solution of 3 (6 mmol) in THF (24 ml) at -78 °C under nitrogen. The reaction mixture was stirred for 1 h at -78 -- -60 °C and an aldehyde or ketone (3 mmol) was slowly added. The mixture was then warmed to 20 °C, stirred for several hours and hydrolyzed by adding 2N HCl (2 drops) and diethyl ether (40 ml). The organic layer was washed with water to neutral and dried. Evaporation of the solvent gave a residue which was purified by column chromatography on silica gel eluting with petroleum ether (bp 60-90 °C)/ethyl acetate (95/5) to afford product 5.

The results are shown in Table 1. All products were new and characterized by microanalyses, IR, <sup>1</sup>H, <sup>19</sup>F NMR spectra and MS.

The one-pot synthesis of  $\gamma,\delta$ -unsaturated trifluoromethyl ketones was quite convenient, giving trans isomers exclusively in the case with aldehydes and should be useful for the synthesis of biologically active compounds.

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#### References and Notes

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6. CF<sub>3</sub>CO<sub>2</sub>Et (40 mmol) was added dropwise with stirring to a solution of 2 [from the reaction of 1 (40 mmol) with n-BuLi (40 mmol) in Et<sub>2</sub>O (150 ml) for 0.5 h at 0 °C] at -78 °C under nitrogen. The mixture was stirred for 0.5 h at -78 °C and 2 h at 20 °C. After filtration and recrystallization from CHCl<sub>3</sub>-AcOEt, 3 was obtained in 91% yield. Mp 185-186 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 60 MHz): 7.48-8.00(m, 17H), 6.73 ppm(d, J=7.2Hz, 1H).