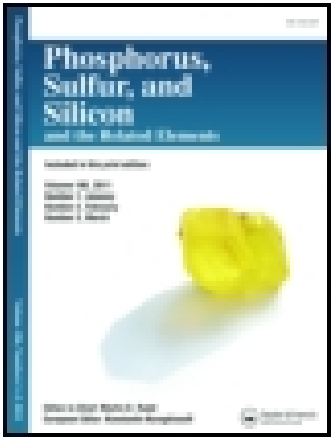

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THE NOVEL SYNTHESES OF α-TRIFLUOROMETHYLATED KETONES FROM β-BROMOENOL PHOSPHATES

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THE NOVEL SYNTHESES OF α-TRIFLUOROMETHYLATED KETONES FROM β-BROMOENOL PHOSPHATES

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A series of 1-aryl-3,3,3-trifluro-1-propanones have been synthesized from the reaction of $FO_2SCF_2CO_2Me$ with β-bromoenol phosphates in the presence of CuI in moderate yield. The reaction mechanism was discussion, the electron-withdrawing substituent at the β-position of the enol phosphates promoted the catalytic cleavage of the O-P bond in enol phosphates by fluoride ion.

Keywords: Trifluoromethylated ketones; β-bromoenol phosphates

INTRODUCTION

α-trifluoromethylated ketones would be very useful synthetic intermediates for the synthesis of a wide range of fluoride-containing organic compounds. The trifluoromethylating properties, of enamines[1] enol alkyl[2] silyl or germyl ethers[3] enol esters[4] or ketene silyl acetals[3] enol anion[5] etc are available methods currently. However, these methods are not always fuilly satisfactory and suffer from disadvantages such as lower yield, preparation of reagents. On the other hand methyl fluorosulphonyldifluoroacetate, $FO_2SCF_2CO_2Me$, has been proved to be a very useful, cheap and convenient trifluoromethylating agent[6] which can transform α-bromo-substituted alkenes, benzene and esters into trifluoromethylaled products. But our experiments showed that α-bromo or α-iodoketones did

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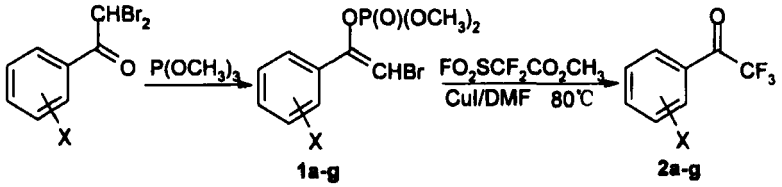
not yield the corresponding α-trifluoromethylated ketones under the conditions described in the literature.

Enol phosphates are versatile intermediates in organic synthesis[7–13]. In these examples the enol phosphates can be thought of as an active form of ketones. On the other hand, $FO_2SCF_2CO_2Me$ is more suitable for the trifluoromethylation of sp^2 carbon, so we imagine that β-haloenol phosphates may be a more reactive substrate than α-haloketones in trifluoromethylation. Here we wish to report its new application; β-haloenol phosphates reacted with the trifluoromethylating agent $FO_2SCF_2CO_2Me$ to provide α-trifluoromethylated ketones.



SCHEME 1

RESULTS AND DISCUSSION

In the presence of CuI, 1-aryl-2-bromoethenyl phosphates, which are easily prepared by the Atherton-Todd reaction[14] or Perkow[15], readily reacted with $FO_2SCF_2CO_2Me$ in DMF solution at 80°C, giving 1-aryl-3,3,3-trifluoro-1-propanones as shown in Scheme 1 and Table I. The moderate yields were comparable with other methods reported in the literature.

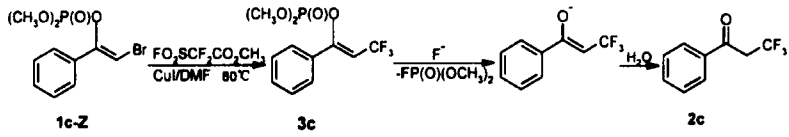
In order to explicate the reaction mechanism, The reaction of substrate **1c-Z** with $FO_2SCF_2CO_2Me$ was followed by ^{19}F-NMR spectroscopy. Two trifluoromethyl peaks existed during the reaction. Thus, after the reaction was stopped and worked-up two trifluoromethylated compounds were separated, 1-phenyl-3,3,3-trifluoropropenyl phosphate **3c** with a doublet CF_3 peak located at −20.3 ppm and α-trifluoromethylated ketone **2c** with a triplet CF_3 peak located at −15.6 ppm. ^{19}F-NMR spectrum also showed that the CF_3 signal of **3c** decreased as the reaction went on and only the CF_3 peak of **2c** was observed at the end of the reaction.

TABLE I The preparation of α-CF_3 ketones **2**

Entry	*Product*	*X*	*Yields*[a] *(%)*
1	**2a**	4-CH_3O	57
2	**2b**	4-CH_3	62
3	**2c**	H	56
4	**2d**	4-Cl	65
5	**2e**	3,4-Cl_2	58
6	**2f**	4-Br	55
7	**2g**	2,4-Cl_2	35

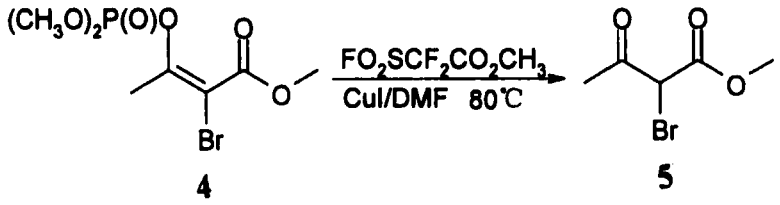
a. Isolated yields based on enol phosphates.

We also found other two signals in ^{19}F-NMR spectrum that were consistent with dimethyl phosphofluoride (^{19}F-NMR δ: 4.46, double peaks, J = 964Hz)[16]. So it was reasoned that **3c** was formed firstly and then transformed into **2c**. During the reaction partial fluoride ions produced from the decomposition of $FO_2SCF_2CO_2Me$ cleaved the O-P bond of the enolate before they combined with difluorocarbene to form the intermediate [CF_3CuI^-][6]. A possible mechanism of the present reaction is shown in scheme 2.



SCHEME 2

We attempted to prepare methyl 3-trifluoromethylacetoacetate by this method from 2-bromo-1-methyl-vinyl phosphate(**4**), but the product methyl 3-bromo-acetoacetate(**5**) was obtained without the trifluoromethylation product(Scheme 3). This result proves that the cleavage of O-P by the attack of fluoride ion is easier than trifluoromethylation. It is reasonable that electron-withdrawing substituents (carbonyl or trifluoromethyl groups) at the β-position of the enol phosphates will weaken the O-P bond and favour its cleavage, so β-bromoenol phosphate is trifluoromethylized firstly then the O-P bond is broken, while **4** lost the phosphoryl group directly.



SCHEME 3

The cleavage of the O-P bond of perfluoro-substituted enol phosphate accompanied with a loss of β-fluoride ion to form α,β-unsaturated ketone catalyzed by fuoride ion has be observed previously [17], the loss of β-fluoride ion may play an important role in bond cleavage. Recently Schmittel reported O-P bond cleavage in enol phosphates after one-electron oxidation[18]. The present example show a different mechanism, the electron-withdraw substituent at the β-position of enol phosphates promoted the decomposion of enol phosphates by fluoride ion.

In conclusion, by $FO_2SCF_2CO_2Me$, β-bromoenol phosphates were firstly transformed into β-trifluoromethylenol phosphates, the O-P linkages of which then underwent cleavage by the attack of fluoride ion. The β-trifluoromethylenol anion formed was quenched by water to give the ultimate products, α-trifluoromethylated ketones. The usefulness of readily available starting materials and reagent is the main advantage although the moderate yields were comparable with other methods reported in literature.

EXPERIMENTAL

All melting points were uncorrected. IR spectra were measured with a Shimadzu IR-440 spectrometer. ^{1}H-NMR spectra were recorded at 90 MHz using TMS as internal standard and CCl_4 as solvent. ^{31}P-NMR were recorded on a 300 MHz spectrometer at 161.97 MHz using $CDCl_3$ as solvent and 85% of H_3PO_4 as external standard. ^{19}F-NMR spectra were recorded on an EM-360L spectrometer at 56.4 MHz using TFA as the external standard with positive for upfield shifts and CCl_4 as solvent. Mass and HRMS spectra were taken on a Finnigan GC-MS-4021 spectrometer.

Elemental analyses were done by the Elemental Analyses Group of SIOC. The known compounds were identified in agreement with the literature data, and only the NMR data are reported here.

1-aryl-2,2-dibromo-ethanones were prepared from bromination of the corresponding 1-aryl-ethanones[19]. β-bromoenol phosphates **1a-g** were obtained by the Perkow reaction[15].

1a: oil, yield 80%, ^{1}H-NMR δ: 6.77–7.67(m, 4H), 6.40(s, 0.38H_E), 6.00(s, 0.62H_Z), 3.77(m, 9H); ^{31}P NMR δ –4.1713, –3.5413; IR(film) v: 3093, 2959, 1608, 1513, 1285, 1256, 1182, 1039 cm^{-1}; MS (m/z, %): 336(M^+, 6.76), 257(100.00), 229(9.85), 199(5.07), 132(7.95), 109(42.62), 93(21.73); anal. Calcd. for $C_{11}H_{14}BrO_5P$: C, 39.18; H, 4.19; found: C, 38.97; H, 4.25.

1b: oil, yield 82%, ^{1}H NMR δ: 7.20(m, 4H), 6.38(m, 0.2H_E), 6.08(s, 0.8H_Z), 3.74(d, J=10Hz, 6H), 2.38(s, 3H); ^{31}P NMR δ; –4.2095, –3.5928; IR(film) v: 3105, 2959, 1625, 1509, 1299, 1180, 1048, 906; MS (m/z, %): 320(M^+, 10.96), 241(100.00), 219(3.85), 195(2.56), 127(5.20), 109(9.48), 93(4.25); analy. Calcd. for $C_{11}H_{14}BrO_4P$: C, 41.14; H, 4.40; found: C, 40.87; H, 4.34.

1c[20]: ^{1}H-NMR δ: 7.40(m, 5H), 6.20(m, 1H), 3.75(d, J=10Hz, 6H).

1d[21]: ^{1}H NMR δ: 7.38(m, 4H), 6.20(s, 1H), 3.76(d, J=10Hz, 6H).

1e: oil, yield 75%, ^{1}H NMR δ: 7.52(m, 3H), 6.30(d, J=2Hz, 1H), 3.80(d, J=10Hz, 6H); ^{31}P-NMR δ: –4.170; IR(film) v: 3080, 1618, 1554, 1475, 1390, 1300, 1045, 933 cm^{-1}; MS (m/z, %): 374(M^+, 4.11), 294(100.00), 250(2.99), 235(41.35), 127(2.74), 109(53.40), 93(10.10); anal. calcd. for $C_{10}H_{10}BrCl_2O_4P$: C, 31.94; H, 2.68; found: C, 32.63; H, 2.65.

1f[22]: ^{1}H NMR δ: 7.35(m, 4H), 6.16(s, 1H), 3.70(d, J=10Hz, 6H).

1g[21]: ^{1}H NMR δ: 7.30(m, 3H), 5.93(s, 1H), 3.70(d, J=10Hz, 6H).

A general procedure for the preparation of 2a-g

A mixture of **1a-g**(1 mmol), $FO_2SCF_2CO_2Me$(1.5 mmol), CuI(1 mmol) and DMF(5 ml) was stirred at 80 °C for 10h under a nitrogen atmosphere. Then the reactionm mixture was cooled, filtered, poured into water and extracted with diethyl ether. The organic extracts were combined, washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by flash column chromatography using a mixture of petroleum ether (b.p. 60–90°C) and ethyl acetate (20~25:1) to give **2a-g, 2a-d** are known compounds.

2a[23]: ^{1}H NMR δ: 7.80(d, J=7Hz, 2H), 6.85(d, J=7Hz, 2H), 3.9(s, 3H), 3.6(q, J=10Hz, 2H).

2b[23]: ^{1}H-NMR δ: 7.75(d, J=7Hz, 2H), 7.20(d, J=7Hz, 2H), 3.65(q, J=9Hz, 2H), 2.45(s, 3H); ^{19}F-NMR δ: −16.0(t, J=9Hz).

2c[23]: ^{1}H NMR δ: 7.70 (m, 5H), 3.70(q, J=9Hz, 2H); ^{19}F-NMR δ: −15.6(t, J=9Hz).

2d[23]: ^{1}H NMR δ: 7.70 (m, 4H), 3.65(q, J=9Hz, 2H); ^{19}F-NMR δ: −16.0(t, J=9Hz).

2e: m.p. 61–62°C; ^{1}H NMR δ: 7.98(s, 1H), 7.65(dd, 2H), 3.72(q, J=9Hz, 2H); ^{19}F NMR δ:-15.8(t, J=9Hz); IR(KBr) v: 3084, 1694, 1585, 1371, 1221, 1139, 1108, 1026 cm^{-1}; MS (m/z, %): 256(M^+, 27.39), 173(100.00), 145(28.08), 109(9.64), 91(2.50), 83(3.07), 75(5.56); anal. calcd. for $C_9H_5Cl_2F_3O$: C, 42.05; H, 1.96; found: C, 42.04; H, 1.78.

2f: m.p. 68–70°C; ^{1}H NMR δ: 7.90(m, 4H), 3.85(q, J=9Hz, 2H); ^{19}F NMR δ: −16.4(t, J=9Hz); IR(KBr) v: 2958, 1701, 1587, 1373, 1267, 1225, 1130, 1102, 995 cm^{-1}; MS (m/z, %): 266(M^+, 19.69), 183(100.00), 161(16.95), 155(41.32), 104(6.67), 76(30.15); anal. calcd. for $C_9H_6BrF_3O$: C, 40.47; H, 2.27; found: C, 40.35; H, 2.25.

2g: oil, ^{1}H NMR δ: 7.40(m, 3H), 3.75(q, J=9Hz, 2H); ^{19}F NMR δ: −15.8(t, J=9Hz); IR(film) v: 3094, 1710, 1585, 1375, 1262, 1137, 1104 cm^{-1}; MS (m/z, %): 256(M^+, 15.95), 236(10.99), 173(100.00), 145(15.45), 109(5.85), 91(13.93); HRMS: calcd. for $C_9H_5Cl_2F_3O$: 255.9669; found 266.9664.

Seperation of compound 3

Following the procedure described above for **2**, a mixture of **1c-Z** (500 mg, 1.6 mmol), $FO_2SCF_2CO_2Me$(1.9 mmol), CuI(1.9 mmol) and DMF(5 ml) was stirred at 80 °C for 3 h under a nitrogen atmosphere. Then the mixture was cooled to stop the reaction. After work-up, **2c**(78 mg, 25%) and **3c**(95 mg, 20%) were obtained. **3c**: ^{1}H-NMR δ: 7.40(m, 5H), 5.55(q, J=7.5Hz, 1H), 3.70(d, J=12Hz, 6H); ^{31}P-NMR δ: −4.911; ^{19}F-NMR δ: −20.3(d, J=7.5Hz); IR(film) v: 3076, 2964, 1672, 1450, 1340, 1281, 1134, 1043, 934 cm^{-1}; MS (m/z, %): 296(M^+, 39.58), 256(5.12), 227(6.30), 184(8.16), 170(100.00), 151(19.09), 127(7.06); HRMS Calcd. for $C_{11}H_{12}F_3O_4P$: 296.0425; found 296.0425.

Acknowledgements

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