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The interaction of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one with C-nucleophiles – organo-magnesium and -zinc compounds

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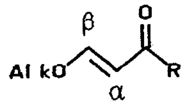
Abstract

4-Ethoxy-1,1,1-trifluoro-3-buten-2-one (**1**) reacts with phenylmagnesium bromide to give ethoxy group substitution products while the reaction of **1** with organozinc compounds gives products arising from 1,2-addition to the carbonyl group. Enone **1** reacts with electron-rich aromatic systems such as indole and *N*,*N*-dimethylaniline in the presence of a Lewis acid catalyst to give a β-arylvinyltrifluoromethylketone.

Introduction

We have reported previously [1, 2] that 1,1,1-trifluoro-4-ethoxy-3-buten-2-one (**1**) reacts readily with N-nucleophiles to give stable *N*-(β-trifluoroacetyl)vinyl amine derivatives. Compound **1** can be also used in peptide syntheses as a protection agent for amino groups. Kinetic investigations have shown that the reaction of enone **1** with diethylamine is 3–4-orders faster than that of the non-fluorinated analogue of **1**, i.e. compound **2**. The significant influence of the fluorine atoms on the electron-density distribution in α,β-unsaturated ketones was demonstrated by comparison of ^{13}C NMR spectra of enone **1** and enone **2** [3].



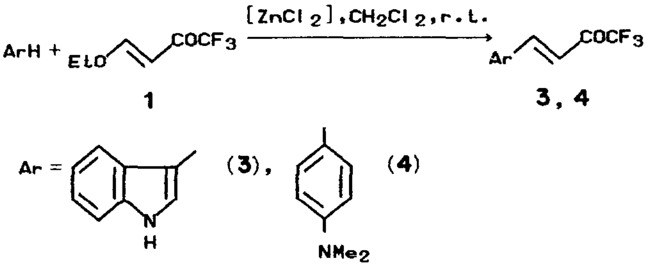
$R = CF_3$; Alk = Et (**1**)
$R = Me$; Alk = Me (**2**)

(**1**, **2**)

With the enone **1**, the ^{13}C NMR signal for the β-carbon atom shifts to lower field by 6.0 ppm relative to the position of the β-carbon atom for enone **2** (162.6 ppm). This indicates that the trifluoroacetyl group is more electron-withdrawing than the acetyl group. However, the regioselectivity N-nucleophilic reactions with enones **1** and **2** is the same, *N*-β-acetylvinyl compounds being formed in both cases. This paper deals with the behaviour of enone **1** in reactions with organo-magnesium and -zinc compounds, i.e. C-nucleophilic agents, as well as with electron-rich aromatic systems.

Results and discussion

Enone **1** reacts with indole and *N*,*N*-dimethylaniline in the presence of the Lewis acid catalyst $ZnCl_2$ to give β-arylvinyltrifluoromethylketones **3**, **4** because of the electron-deficiency of the β-carbon atom. In the case of indole, a few mole per cent of $ZnCl_2$ is sufficient to give a 60% yield of ketone **3**. The yield of the reaction product in the case of *N*,*N*-dimethylaniline, even in the presence of excess $ZnCl_2$, was not more than 20%. It is probable that the action of the catalyst consists in $ZnCl_2$–carbonyl group complex formation which results in a significant increase in the β-carbon atom electrophilicity.



The α,β-unsaturated ketones **3**, **4** are coloured crystalline substances; from the ^1H NMR spectra, the vinyl protons are in the *trans* configuration.

All our attempts to carry out the β-trifluoroacetylvinylation of anisole with enone **1** were unsuccessful. The reaction does not proceed in the presence of $ZnCl_2$. The application of stronger Lewis acids such as BF_3 or $TiCl_4$ at room temperature or on heating only led to the formation of tars. Probably activation of the

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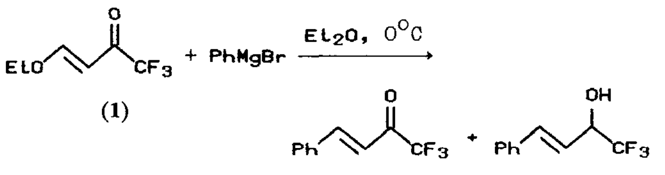
benzene ring by the methoxy group is insufficient in this case.

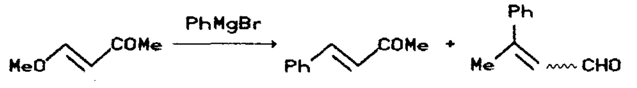
The reaction of phenylmagnesium bromide with enone **1** gives a mixture of two products, i.e. β-phenylvinyltrifluoromethylketone (**5**) and the allyl alcohol **6**. The total yield of the mixture was 40–60% (based on **1**).



(1) (5) (6)

Reaction time (h)	(5)		(6)
2	1	:	1
20	1	:	7

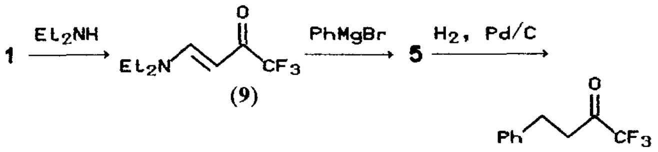
Compounds **5**, **6** are colourless liquids. According to the ^{1}H NMR spectra of **5** and **6**, the vinyl fragments of the molecules are in the *trans* configuration. For a reaction time of 1–2 h, the ratio of the products **5** and **6** obtained was almost unity; increasing the reaction time resulted in a substantial increase in the reduction product **6** (GLC methods). The composition of the mixture and the ratio of products does not depend upon the order of addition of the reagents. Thus, the phenyl anion attacks enone **1** only in the β-position with substitution of ethoxy group (product **5**) and alcohol **6** is formed by reduction of ketone **5** in the presence of organomagnesium compounds. However, the non-fluorinated ketone **2** reacts with phenylmagnesium bromide with attack on either the β-carbon atom or the carbonyl group to give a mixture of products **7** and **8** in a 1:2 ratio (GLC methods).



(2) (7) (8)

Compounds **7** and **8** were purified by column chromatography and identified by ^{1}H NMR spectroscopy. From the NMR spectra (which were identical to those quoted in the literature [4]), aldehyde **8** is a mixture of *E* and *Z* isomers (2:3).

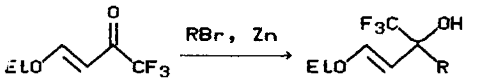
Although fluorine substitution into the molecule of ketone **2** (enone **1**) leads to anionic attack on the β-carbon atom alone, the formation of both **5** and **6** during this reaction makes it useless for the preparation of the pure ketone **5**. The latter is formed as the sole product of the reaction of phenylmagnesium bromide with β-(*N*,*N*-diethylamino)vinyltrifluoromethylketone (**9**) which can be obtained easily in high yield from diethylamine and enone **1** [1, 5].



(9) (10)

Ketone **5** was isolated with 55% yield in more than 99% purity (GLC methods). Hence, this reaction can be recommended as a simple and readily available method for the preparation of ketone **5** which was previously synthesized by the reaction of ω-styrylmagnesium bromide with trifluoroacetic acid [6] or by the condensation of benzaldehyde with trifluoroacetone [7]. Ketone **5** has been used for the synthesis of trifluoromethyl-containing retinoid [7] and studied as a murine hepatic cytosolic and microsomal epoxide hydrolase substrate [8]. Compound 5 may be reduced with hydrogen over palladium on carbon to give ketone **10** in high yield. According to the literature [9, 10], ketone **10** is a very effective carboxylesterase inhibitor.

In contrast to phenylmagnesium bromide, organozinc compounds formed *in situ* react with enone **1** only at the carbonyl group. Thus, under Reformatsky reaction conditions, enone **1** reacts with ethyl bromoacetate to give compound **11**, whilst allylation of enone **1** results in the formation of dienol **12**.



(1) (11, 12)

R = CH_2COOEt (**11**); R = $CH_2CH{=}CH_2$ (**12**)

Compounds **11** and **12** are colourless viscous liquids. Even after thorough washing, enol **12** contains *c.* 5–10% of DMF. Ester **11** decomposes on vacuum distillation and hence was purified by column chromatography. The ^{1}H NMR spectra of compounds **11** and **12** are in complete agreement with the structures depicted. The vinyl fragment of enone **1** retains its *trans* configuration in the products of its reaction with organozinc compounds. Compounds **11** and **12** are β-trifluoromethyl-β-hydroxy-aldehyde derivatives and can be used as intermediates in the synthesis of biologically active fluorine-containing compounds.

Experimental

NMR spectra were determined on Bruker WP-200 and Varian Gemini-200 instruments using TMS and CCl_3F as internal references for ^{1}H and ^{19}F respectively (positive sign corresponds to low field). UV spectra were measured on a Specord M-40 spectrophotometer. IR spectra were obtained on a Specord M-80 spectrometer. GLC analyses were undertaken using a Chrom-5 gas chromatograph equipped with an FID detector, thermostat temperature 100–150 °C with He as the carrier gas at a flow rate of 20–30 ml min^{-1}, the column being of stainless steel 3 min × 240 mm, packed with SE-30 (5%) on Chromosorb N-AW-DMCS. Silica gel L 40/100 Lachema was used for column chromatography.

The starting materials were synthesized according to literature methods – enone **1** [1], enaminone **9** [5].

trans-*1,1,1-Trifluoro-4-(3-indolyl)-3-buten-2-one (3)*

To a solution of indole (0.82 g, 7 mmol) and enone **1** (1.2 g, 7 mmol) in CH_2Cl_2 (5 ml) was added $ZnCl_2$ (0.01 g, 1 mol%). The reaction mixture was stirred for 3 h at 22 °C. The resulting precipitate was filtered, washed with CH_2Cl_2 (2 × 10 ml) and dried. Yield 1.03 g (60.6%), m.p. 164 °C. UV (CH_2Cl_2) (λ_{max}): 379 nm. ^{1}H NMR (CD_3CN) δ: 8.2 (d, 1H, H_4, $J = 15.4$ Hz); 7.9 (m, 2H, H_{indole}); 7.83 (d, 1H, $H_{2\text{-}indole}$, $J = 2.8$ Hz); 7.5 (m, 1H, H_{indole}); 7.25 (m, 2H, H_{indole}), 6.95 (d, 1H, H_3, $J = 15.4$ Hz) ppm. ^{18}F NMR (CD_3CN) δ: −76.6 (s) ppm. IR (CH_2Cl_2) (cm^{-1}): 3430 (m) (NH); 1690 (m) (C=O); 1575 (vs) (C=C). Analysis: Found: C, 60.58; H, 3.14; F, 23.42%. $C_{12}H_8F_3NO$ requires: C, 60.25; H, 3.35; F, 23.44%.

trans-*1,1,1-Trifluoro-4-(4-dimethylaminophenyl)-3-buten-2-one (4)*

To a solution of *N*,*N*-dimethylaniline (0.88 g, 7 mmol) and enone **1** (1.2 g, 7 mmol) in CH_2Cl_2 (5 ml) was added $ZnCl_2$ (0.2 g, 20 mol%). The reaction mixture was stirred for 14 h at 20 °C. It was then washed, extracted with diethyl ether (3 × 40 ml) and dried with $MgSO_4$. The solvent was evaporated and the product **4** recrystallized from hexane. Yield 0.34 g (19.5%), m.p. 118–119 °C. UV (CH_2Cl_2) (λ_{max}): 437 nm. ^{1}H NMR (CD_3CN) δ: 7.86 (d, 1H, H_4, $J = 15.4$ Hz); 7.5 (d, 2H, C_6H_4, $J = 8.8$ Hz); 6.7 (d, 1H, H_3, $J = 15.4$ Hz); 6.6 (d, 2H, C_6H_4, $J = 8.8$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: −77.6 (s) ppm. IR (CH_2Cl_2) (cm^{-1}): 1685 (m) (C=O); 1560 (vs) (C=C). Analysis: Found: C, 59.35; H, 5.02; F, 24.04%. $C_{10}H_{12}F_3NO$ requires: C, 59.27; H, 5.02; F, 23.85%.

trans-*1,1,1-Trifluoro-4-phenyl-3-buten-2-ol (6)*

To a solution of PhMgBr [prepared from 0.88 g (37 mmol) of Mg and 4.9 g (37 mmol) of PhBr in diethyl ether (30 ml)] was added a solution of enone **1** (5 g, 29.7 mmol) in diethyl ether (10 ml) with stirring in an argon atmosphere at −10 °C. The mixture was warmed to 20 °C and stirred for 20 h. The resulting mixture was then poured into water, acidified with 1 N HCl to a pH value of 4–5, extracted with diethyl ether (3 × 20 ml) and dried with $MgSO_4$. The solvent was evaporated. Distillation of the residue gave alcohol **6**. Yield 2.46 g (42.5%), b.p. 88–90 °C/10 mmHg, m.p. 42–43 °C (recrystallized from pentane). Lit. value [11], b.p. 76–77 °C/1 mmHg. ^{1}H NMR ($CDCl_3$) δ: 7.4–7.2 (m, 5H, C_6H_5); 6.8 (d, 1H, H_4, $J = 15.6$ Hz); 6.1 (dd, 1H, H_3, $J = 15.6$, 6.3 Hz); 4.55 (ddq, 1H, H_2, $J = 6.3$, 5.8, 6.4 Hz); 2.27 (d, 1H, OH, $J = 5.8$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: −79.7 (d, $J = 6.4$ Hz) ppm.

Interaction of PhMgBr with trans-*4-methoxy-3-buten-2-one (2)*

To a solution of PhMgBr [prepared from 2.48 g (18 mmol) of PhBr and 0.45 g (18 mmol) of Mg in diethyl ether (30 ml)] was added *trans*-4-methoxy-3-buten-2-one (**2**) (1.5 g, 15 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 10 h. It was then made up with a saturated solution of NH_4Cl (40 ml), extracted with diethyl ether (3 × 20 ml) and dried with $MgSO_4$. The solvent was evaporated. A mixture of benzalacetone **7** and aldehyde **8** was separated by column chromatography using silica gel and chloroform/hexane (1:1) as eluent. Yield 0.35 g (15.8%) of aldehyde **8** ($R_f = 0.46$) and 0.16 g (7.2%) of benzalacetone **7** ($R_f = 0.26$). The ^{1}H NMR spectra of compounds **7** and **8** were in accordance with those reported in the literature [4].

trans-*1,1,1-Trifluoro-4-phenyl-3-buten-2-one (5)*

To a solution of PhMgBr [prepared from 0.62 g (26 mmol) of Mg and 3.38 g (26 mmol) of PhBr in diethyl ether (30 ml)] was added a solution of enaminone **9** (4 g, 20.5 mmol) in diethyl ether (10 ml) at 0 °C. The reaction mixture was stirred for 20 h at 20 °C. The mixture was then poured into water, acidified with 6 N HCl to a pH value of 4–5, extracted with diethyl ether, dried with $MgSO_4$ and the solvent evaporated. Distillation of the residue gave ketone 5. Yield 2.16 g (52.7%), b.p. 79–80 °C/10 mmHg. Lit. value [6], b.p. 57 °C/0.3 mmHg. ^{1}H NMR ($CDCl_3$) δ: 7.9 (d, 1H, H_4, $J = 15.5$ Hz); 7.5 (m) and 7.4 (m, 5H, C_6H_5); 6.95 (dq, 1H, H_3, $J = 15.5$, 0.8 Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: −78.2 (d, $J = 0.8$ Hz) ppm. IR (CH_2Cl_2) (cm^{-1}): 1730 (s) (C=O); 1618 (vs) (C=C).

1,1,1-Trifluoro-4-phenylbutan-2-one (10)

Hydrogen was bubbled through a mixture of ketone **5** (1.65 g, 8 mmol) and Pd/C (5%, 0.1 g) in dry ethyl acetate (6 ml) for 12 h. The catalyst was then filtered and the solvent evaporated. Distillation of the residue gave ketone **10**. Yield 1.02 g (61%), b.p. 97 °C/20 mmHg. Lit. value [12], b.p. 75–77 °C/4 mmHg. ^{1}H NMR ($CDCl_3$) δ: 7.3–7.1 (m, 5H, C_6H_5); 2.94 (m, 4H, $2CH_2$) ppm. ^{19}F NMR ($CDCl_3$) δ: −79.7 (s) ppm.

Ethyl trans-*5-ethoxy-3-hydroxy-3-trifluoromethyl-4-pentenoate (11)*

To a solution of ethyl bromoacetate (2.39 g, 20 mmol) and enone **1** (2.4 g, 14 mmol) in dry diethyl ether (15 ml) was added Zn powder (1.4 g, 21.5 mmol) and the reaction mixture refluxed for 3 h. It was then cooled to 20 °C and made up with a saturated solution of NH_4Cl (20 ml), extracted with diethyl ether (3×40 ml) and dried with $MgSO_4$. The solvent was evaporated and the residue separated by column chromatography using silica gel and chloroform/pentane (1:2) as the eluent. Yield 1.61 g (44%) ($R_f=0.4$). ^1H NMR ($CDCl_3$) δ: 6.76 (d, 1H, H_5, $J=12.6$ Hz); 4.9 (s, 1H, OH); 4.75 (d, 1H, H_4, $J=12.6$ Hz); 4.22 (q, 2H, 1-OCH_2, $J=7.2$ Hz); 3.78 (q, 2H, 5-OCH_2, $J=7$ Hz); 2.82 (d) and 2.64 (d, 2H, AB, 2-CH_2, $J=15.5$ Hz); 1.29 (br t, 6H, $2CH_3$, $J=7$ Hz) ppm. Analysis: Found: C, 46.73; H, 5.98; F, 22.10%. $C_{10}H_{15}F_3O_4$ requires: C, 46.90; H, 5.98; F, 22.26%.

trans-*1-Ethoxy-3-hydroxy-3-trifluoromethyl-1,5-hexadiene (12)*

To a solution of allyl bromide (1.3 g, 11 mmol) and enone **1** (1.2 g, 7 mmol) in DMF (5 ml) was added Zn powder (0.7 g, 11 mmol). The mixture was stirred for 1 h and then warmed to 50 °C. The mixture was then made up with a saturated solution of NH_4Cl (20 ml), extracted with diethyl ether (3×20 ml) and dried with $MgSO_4$. The solvent was evaporated and the residue distilled. Yield 1.2 g (80.5%), b.p. 83–86 °C/20 mmHg. ^1H NMR ($CDCl_3$) δ: 6.67 (d, 1H, H_5, $J=12.8$ Hz); 5.8 (m, 1H, H_5); 5.3–5.17 (m, 2H, $2H_6$); 4.8 (d, 1H, H_2, $J=12.8$ Hz); 3.8 (q, 2H, OCH_2, $J=7$ Hz); 2.51 (m, 2H, CH_2); 2.2 (s, 1H, OH); 1.3 (t, 3H, CH_3, $J=7$ Hz) ppm. Analysis: Found: C, 51.70; H, 6.39; F, 27.02%. $C_9H_{13}F_3O_2$ requires: C, 51.45; H, 6.19; F, 27.13%.

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