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β-Ethoxyvinyl polyfluoroalkyl ketones — versatile synthones in fluoroorganic chemistry★

I.I. Gerus, M.G. Gorbunova*, V.P. Kukhar

Institute of Bioorganic and Petrochemistry, Ukrainian Academy of Sciences, Murmanskaya Str. 1, 253660, Kiev-94, Ukraine

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Abstract

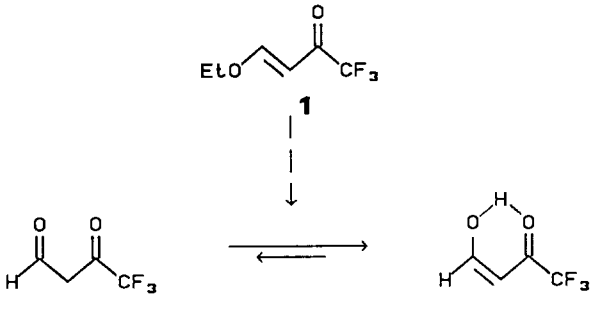
We have found readily available β-ethoxyvinyl trifluoromethyl ketone to be a convenient and comprehensive starting material for the synthesis of various fluoro-containing compounds such as heterocycles, enones, enaminones and chelate complexes. The 4,4,4-trifluoro-3-oxo-1-butenyl group formed by β-ethoxyvinyl trifluoromethyl ketone is a suitable protecting group for the N—H terminal of amino acids in peptide synthesis. The formation of peptides using these protected amino acids occurs without racemization.

Keywords: β-Ethoxyvinyl polyfluoroalkyl ketones; Synthones; Protecting group; Peptide synthesis; Reactions

1. Introduction

Polyfunctional compounds are of interest because of their properties and possible applications in organic synthesis. Enalkoxy- and enamino-carbonyl compounds have been extensively studied and have found a wide application in the synthesis of various heterocycles, dyes and drugs.

We have worked with β-ethoxyvinyl trifluoromethyl ketone or enone **1**. This is an α,β-unsaturated carbonyl compound with an alkoxy group in the β-position which is sensitive to nucleophilic attack. Enone **1** is also a fluorinated ketoaldehyde derivative and hence a potential 1,3-dicarbonyl compound. The chemical properties of enone **1** are very different from those of its non-fluorinated analogue and of the familiar fluorinated α,β-diketones (because of the absence of large substituents in the β-position). We have studied the chemical properties of enone **1** both to evaluate its use as a starting material for various syntheses and to estimate the influence of fluorine on its reactivity.



2. Results and discussion

Enone **1** was first synthesized by Gambaryan et al. in 1967 [1]. It was prepared in three steps from polyfluoroacetone and vinyl ether with an overall yield of 52%. In 1976, Japanese researchers found that trifluoroacetic anhydride reacts with ethyl vinyl ether in the presence of pyridine to give enone **1** in high yield [2]. Enone **1** is a stable substance.

We have found that ethyl vinyl ether can be acylated by different chloro anhydrides of polyfluorocarbonic acid. However, difluoroacetylation gave only 23% yield while monofluoroacetylation did not take place at all under these conditions [3].

★Dedicated to Professor L.M. Yagupolskii on the occasion of his 70th birthday.

*Corresponding author.

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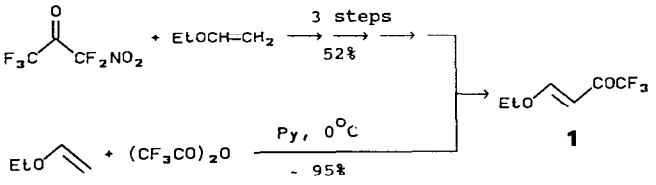
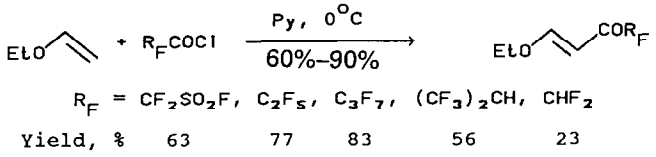
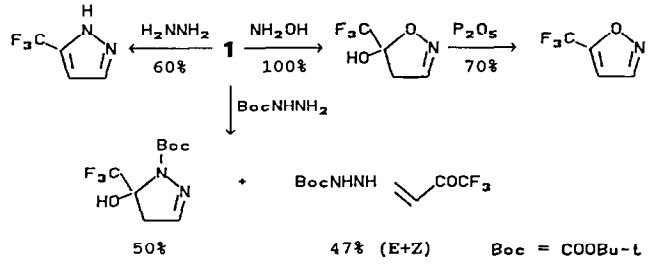


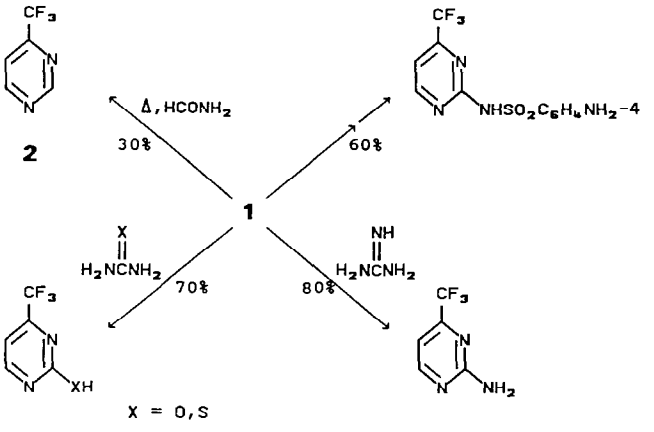


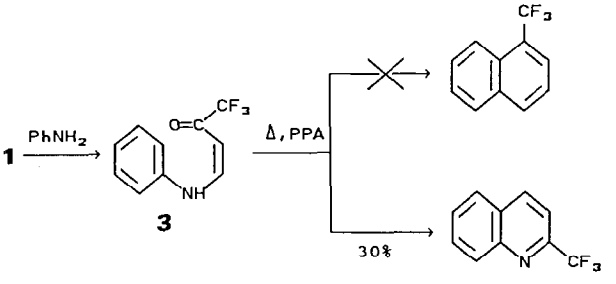
α,β-Dicarbonyl compounds are very important starting materials for various heterocyclic syntheses. The preparation of heterocycles containing only one trifluoromethyl substituent is often very difficult but such heterocycles can be obtained through the use of enone **1**. Thus, enone **1** reacts readily with hydrazine and hydroxylamine to give the corresponding trifluoromethyl-containing pyrazole and isoxazole [4].



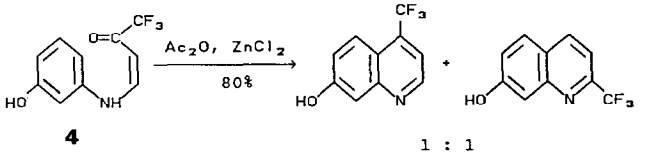
gem-Diamino substances such as urea, thiourea and guanidine react with enone **1** to give high yields of 4-trifluoromethylpyrimidines with functional substituents in the 2-position. For example, 4-trifluoromethylpyrimidine (**2**) was prepared by heating enone **1** with ammonium chloride in formamide. We have also studied the influence of the trifluoromethyl group on the electronic structure of the pyrimidine using IR and NMR spectroscopy [5].

Enone **1** reacts easily with different amines. Hence, it reacts with aniline to give enaminone **3**. We had expected enaminone **3** to condense intramolecularly with the formation of 4-trifluoromethylquinoline. However, 2-trifluoromethylquinoline was the sole product of heating enaminone **3** with PPA. The structure of this substance has been confirmed by NMR spectroscopy and by independent synthesis from quinaldic acid and sulphur tetrafluoride.

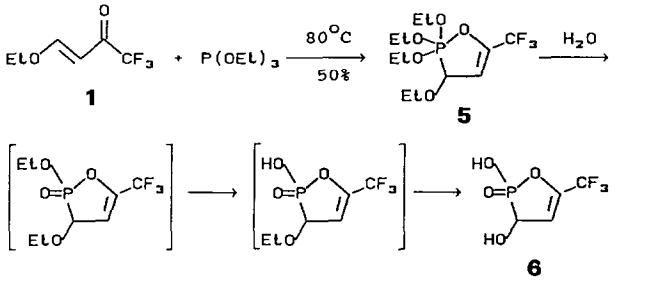




Hydroxy-substituted enaminone **4** undergoes intramolecular condensation, forming an aromatic ring and yielding a mixture of 4- and 2-trifluoromethylquinolines in almost equal quantities [6].

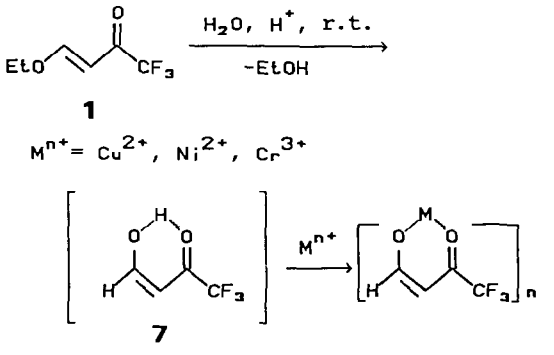


On heating with triethylphosphite, enone **1** reacts as a heterodiene to give phosphorane **5**, which is sensitive to moisture and loses its ethoxy groups (as monitoring by ^{31}P NMR spectroscopy). The final product of the hydrolysis of phosphorane **5** is compound **6** [7].

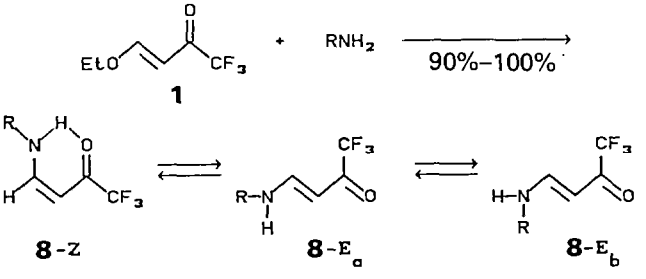


Enone **1** hydrolyzes easily in dilute acids to give ethanol and trifluoroacetylacetaldehyde (**7**) (GLC monitoring). Transition metal ions react with a solution of

7 to give the corresponding chelate complexes which are of interest in analytical chemistry [8].



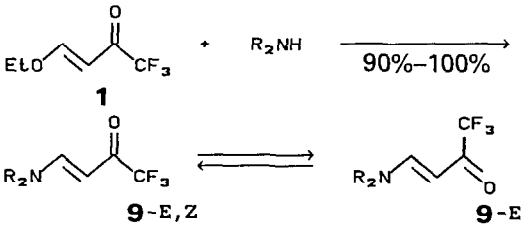
Enone **1** reacts readily with the N–H bonds of amines to give the corresponding enamines **8** in almost quantitative yield. Such reactions take place under various conditions. If there is a proton near the nitrogen atom, the intramolecular hydrogen bond causes the predominant existence of the *Z* configuration in non-polar solvents. The appearance of two *E* forms of enaminones **8** which differ in terms of their N-substituent arrangement is connected with an increase in solvent polarity. The quantitative composition of the isomeric mixture depends on the nature of the N-substituent and the polarity of the solvent. This dependence has been studied by NMR and IR spectroscopies. The NMR spectra of the enaminones **8** are easy to interpret because of the vicinal olefin protons [4,9].



for R=Me (by PMR)			
CCl_4	100%	–	–
CH_2Cl_2	95%	5%	–
DMSO	22%	58%	20%

R = H, Me, Et, i-Pr, t-Bu, $PhCH_2$, Ph, 3-HOC_6H_4, 2-Py

Enaminones **9** exist exclusively in the *E* configuration if there are two N-substituents and neither of them is hydrogen. We have studied the dynamic equilibrium between the *E,Z* and *E,E* conformers of enaminones **9** by IR spectroscopy and found that the tautomeric equilibrium depends on the N-substituent, the concentration, the temperature and solvent polarity [9].

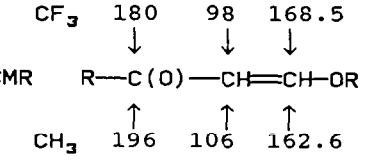


for R=Me (by IR)	n-C_7H_{16}	CCl_4	CH_2Cl_2	$CHCl_3$
E,Z/E,E	64/36	50/50	12/99	1/99

(c=0.05M, 20 °C)

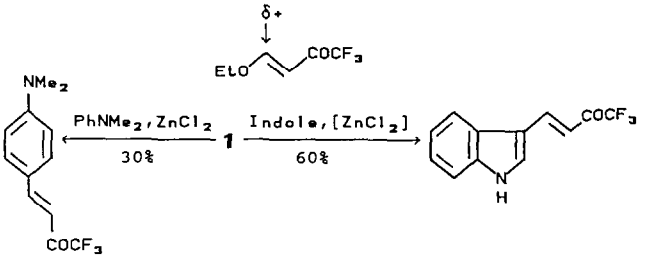
R = Me, Et, i-Pr

The β-carbon atom of enone **1** exhibits a chemical shift at a much lower field than its non-fluorinated



analogue. We have thus suggested that the exchange of a methyl group for a trifluoromethyl makes the β-carbon atom more electropositive and enone **1** more sensitive towards nucleophilic attack. On studying the kinetics of the reaction of diethylamine with methyl- and trifluoromethyl-containing enones by UV methods, we found that the reaction rate depends strongly on the solvent polarity. The introduction of three fluorine atoms increases the reaction rate about 10000 times [10], i.e. $k_{CF_3}/k_{CH_3} \approx 10^4$–$10^5$ (see Table 1).

The high positive charge on the β-carbon atom allows direct β-trifluoroacetylvinylation of electron-rich aromatic systems such as indole and dimethylaniline [11].



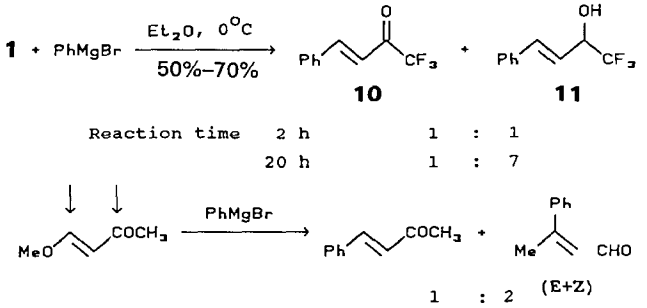
Enone **1** reacts with phenylmagnesium bromide to give ketone **10** (which arises as a result of β-carbon atom nucleophilic attack) together with its reduction

Table 1

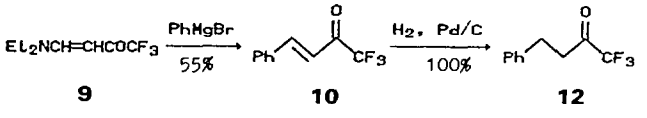
$RCOCH{=}CHOR \xrightarrow[-EtOH]{Et_2NH} RCOCH{=}CHNEt_2$

R	k (l mol^{-1} s^{-1})		
	c-C_6H_{12}	CH_2ClCH_2Cl	CH_3OH
CH_3	$\sim 4\times10^{-11}$	$\sim 1\times10^{-3}$	1.5×10^{-2}
CF_3	2.8	67	2.1×10^{2}

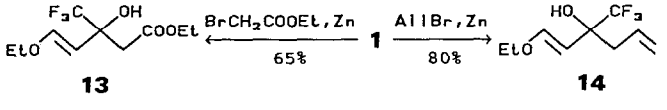
product, i.e. the allyl alcohol **11**. The products arising from reaction of the carbanion on the carbonyl group of enone **1** were not determined. However, the non-fluorinated analogue of enone **1** reacts with phenylmagnesium bromide to give a mixture of products in a 1:2 ratio. These products are the result of nucleophilic attack on the β-carbon atom or the carbonyl group [11].



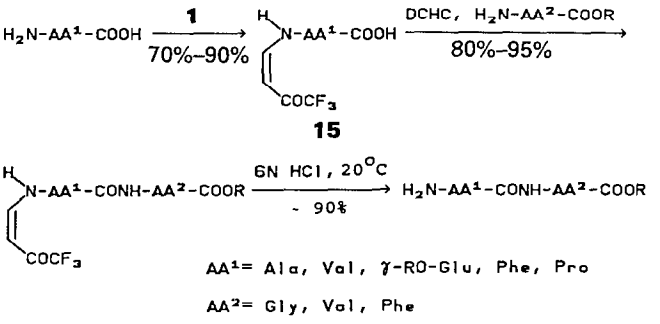
The α,β-unsaturated ketone **10** is the sole product of the reaction of enaminone **9** with phenylmagnesium bromide. Catalytic hydrogenation of enone **10** gives the corresponding fluorinated ketone **12** which is a strong enzyme inhibitor [11].



However, in contrast to phenylmagnesium bromide, enone **1** reacts with organozinc compounds (formed in situ) leading to addition on the carbonyl group. Compounds **13** and **14** are formed under Reformatsky and allylation reaction conditions. These compounds are β-hydroxy-β-trifluoromethyl-containing aldehyde derivatives which are available for the synthesis of the fluorinated analogues of bioactive substances [11].



Because of the simplicity of formation of enaminones **8** and **9** and their high stability, we have successfully used enone **1** for amino group protection. Various amino acids react easily with enone **1** in basic solution to yield stable *N*-β-trifluoroacetylvinyl derivatives **15** which were isolated after acidification of the reaction mixture. These compounds can be used in peptide synthesis.



The *N*-trifluoroacetylvinyl protective group is readily removed by acid solution at room temperature. Using HPLC control of the synthesized dipeptides, no racemization of the reaction products was observed. Hence, the protective group described here does not promote racemization during peptide bond formation [12].

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