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PAPER

Reactions of β-alkoxyvinyl polyfluoroalkyl ketones with ethyl isocyanoacetate and its use for the synthesis of new polyfluoroalkyl pyrroles and pyrrolidines†‡

Ivan S. Kondratov,[a] Violetta G. Dolovanyuk,[a] Nataliya A. Tolmachova,[a] Igor I. Gerus,[a] Klaus Bergander,[b] Roland Fröhlich[b] and Günter Haufe*[b]

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The hitherto unreported reactions of β-alkoxyvinyl polyfluoroalkyl ketones with ethyl isocyanoacetate and equimolar amounts of potassium-*tert*-butoxide proceeded mainly in the β-position of the α,β-unsaturated ketones in cases of α-nonsubstituted **1a–e** and α-methyl substituted ketones **1g–j**. Other α- or β-substituted ketones **1f,k–o** gave mainly products **4** of initial attack at the carbonyl carbon. Depending on the solvent, the major products of β-attack do exist in different tautomeric forms. Generally the open-chain enol tautomers **5** predominate in the polar DMSO-d_6, while the cyclic γ-hemiaminals **8** are the major tautomers in the less polar $CDCl_3$. Acid treatment of the latter compounds **8** led to the hitherto unknown ethyl 5-polyfluoroalkyl-pyrrole-2-carboxylates **11** by elimination of formic acid. Catalytic hydrogenation of pyrrole **11a** was used for the synthesis of earlier unknown 5-trifluoromethyl proline **16**.

Introduction

Polyfluoroalkyl alkoxyenones **1** are readily available, versatile building blocks for the construction of different fluoroorganic compounds.[1] For instance, compounds **1** were applied to protect amino acids in peptide synthesis,[2] as starting materials for the synthesis of mevalonic acid analogs[3] and GABA-surrogates,[4] as well as for the preparation of different classes of fluoro-containing heterocycles and versatile fluorinated building blocks.[1]

Most applications of enones **1** as starting materials include reactions with nucleophiles, which can proceed both at the carbonyl group and in its β-position. During the last two decades numerous reactions of enones **1** with various C-, N-, O- and P-nucleophiles were investigated in order to disclose the particularities of reactivity of compounds **1** and regioselectivity of the transformations (Fig. 1).

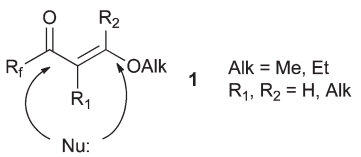


Fig. 1 Reactivity of β-alkoxyalkenyl polyfluoroalkyl ketones **1**.

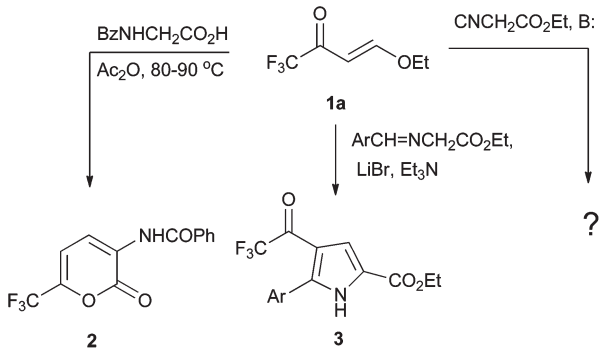
Most of the mentioned reactions of enone **1** are highly regioselective, but in some cases the regioselectivity of reactions with particular C-nucleophiles dramatically depends on the conditions,[5] as well as the substrate and reagent structures.[6]

Reactions with glycine derivatives as C-nucleophiles are of particular interest because the introduction of the α-aminoester moiety becomes possible. This can be useful for the construction of new amino acids and/or the formation of heterocyclic systems. Earlier we described the reaction of alkoxyenones **1** with *N*-benzoyl glycine that led to the formation of pyrones **2** *via* the corresponding 2-phenyloxazolinone intermediates (Scheme 1, the reactions of trifluoromethyl enone **1a** are given as examples).[7] Recently, the reaction of enone **1a** with (benzylideneamino) acetates to form trifluoroacetyl pyrroles **3** was reported.[8] It should be noted that the initial attack of nucleophiles occurred in the β-position of enone **1a** in both cases. However, the heterocyclizations took place in different ways. While the keto group of **1** and the carbonyl function of glycine are involved in the cyclization leading to pyrones **2**, a reaction of the imino group at the α-position of the glycine moiety is required for the formation of pyrroles **3**.

[a]*Institute of Bioorganic Chemistry and Petrochemistry, National Ukrainian Academy of Sciences, Murmanska 1, Kiev-94, 02660, Ukraine*
[b]*Organisch-Chemisches Institut, Universität Münster, Corrensstraße 40, D-48149 Münster, Germany. E-mail: haufe@uni-muenster.de; Fax: +49-251-83-39772; Tel: +49-251-83-33-33281*

†Dedicated to Academician Professor Dr Valery P. Kukhar on the occasion of his 70th birthday.

‡Electronic supplementary information (ESI) available: Spectroscopic and mass spectrometric data, elemental analyses, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra of all new compounds **1**, **4**, **5**, **7**, **8**, **10**, **11**, **12**, **13**, **14**, **15** and **16** together with X-ray data of compound **8d**. CCDC 887922. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26176f



Scheme 1 Reaction of β-ethoxyvinyl trifluoromethyl ketone **1a** with glycine derivatives as C-nucleophiles.

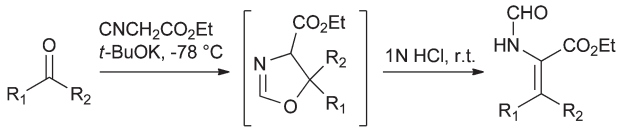
Reactions of enones **1** with other glycine derivatives such as alkyl isocyanoacetates have not been described in the literature although isocyanoacetates are versatile polyfunctional reagents with useful chemical properties. They were found to be especially important in multicomponent reactions and in the synthesis of amino acid derivatives.[9] Also reactions of isocyanoacetates with several fluorinated carbonyl compounds have been investigated[10] and applied to the stereoselective synthesis of fluorinated amino acid derivatives.[10a,11]

Continuing our investigations on the synthesis of new fluorinated amino acids,[12] in this paper we present our results of the reactions of enones **1** with ethyl isocyanoacetate and its application to the synthesis of new fluorinated pyrroles.

Results and discussion

Reaction of α,β-unsubstituted enones 1a–e

The reaction of enones **1** with ethyl isocyanoacetate was investigated under Schöllkopf's conditions (*t*-BuOK, THF, −78 °C),



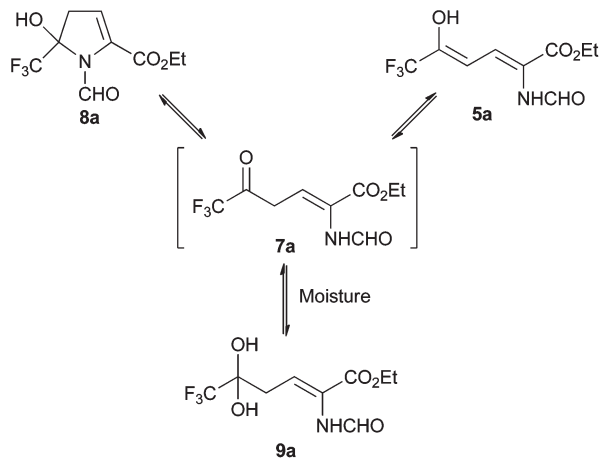
Scheme 2 Reactions of trifluoromethyl ketones with ethyl isocyanoacetate to give ethyl *N*-formyl-α-amino-β-trifluoromethyl-α,β-unsaturated esters.[10b]

which were previously used for the preparation of *N*-formyl-α-amino-α,β-unsaturated esters[13] including the stereoselective synthesis of some α-formylamino-β-trifluoromethyl-α,β-unsaturated esters starting from trifluoromethyl ketones[10b] (Scheme 2).

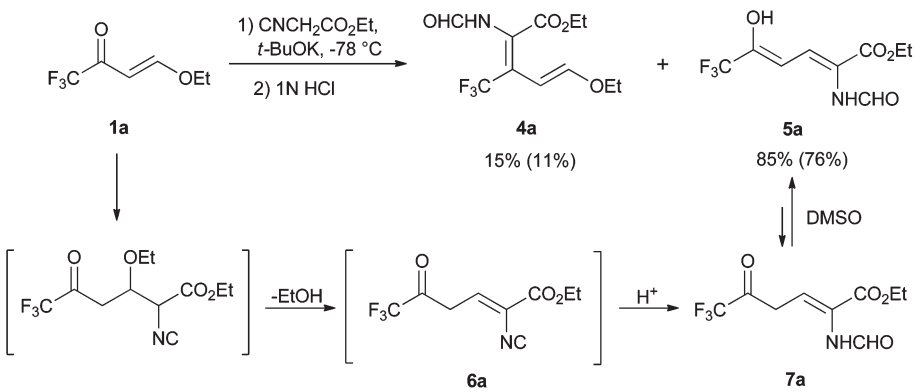
We found that treatment of trifluoromethyl enone **1a** with ethyl isocyanoacetate led to the expected compound **4a** only as a minor product (15%) formed by reaction of the carbonyl group (Scheme 3). The main reaction starts with an attack at the β-position of the alkoxyenone **1a** leading to the formation of product **5a** (main tautomer by NMR spectra in DMSO-d_6). The regioselectivity of this reaction was not temperature dependent. Thus at −40 and −90 °C the ratios of **4a** were 14 and 12%, respectively. Since the reaction products of CF_3-ketones with isocyanoacetate possessed the *Z*-configuration of the formed C═C double bond,[10b] this configuration is also anticipated for the C═C double bond of compound **4a**.

As shown in Scheme 3, the initial attack at the β-position and subsequent EtOH elimination gave intermediate **6a**. Hydrolysis of the isocyano group under acidic conditions led to the formation of **7a**, which in DMSO-d_6 solution tautomerizes to the more stable enol tautomer **5a**.

After isolation of **5a** the equilibrium of several tautomeric forms in DMSO-d_6-solution was investigated (Scheme 4). The most distinctive signals of the ^{1}H NMR spectrum of **5a** in



Scheme 4 Equilibrium between compounds **5a**, **7a**–**9a** which were identified in DMSO-d_6 (**5a**, **8a**) and $CDCl_3$ (**5a**, **7a**–**9a**) solutions.



Scheme 3 Reaction of trifluoromethyl enone **1a** with ethyl isocyanoacetate (isolated yields are presented in parentheses, see Table 1).

DMSO-d_6 are two doublets at δ = 5.85 and 7.28 ppm (J = 12.6 Hz), which correspond to protons of the *Z*,*Z*-1,3-diene system. Two other doublets ($\delta \sim$ 5.95 and 7.33 ppm, J = 12.5 Hz, 10% by integral intensity) were also observed in the spectrum, which presumably correspond to another stereoisomer (*E*,*Z*-, *Z*,*E*- or *E*,*E*-) of compound **5a**. The cyclic tautomer **8a**, formed as a result of intramolecular cyclization by nucleophilic attack of the formamide nitrogen on the carbonyl group of tautomer **7a**, was also observed by NMR in a small amount (~14% in DMSO-d_6). The tautomer **7a** itself was not observed in the mixture.

In contrast the product of β-attack, the cyclic tautomer **8a**, was the major component of the equilibrium mixture in $CDCl_3$.

Ketone **7a** and its hydrate, the *gem*-diol **9a** (see Scheme 4), as well as the enol tautomer **5a**, were also identified in $CDCl_3$ solution by ^{1}H and ^{19}F NMR spectra.[14] The minor open-chain forms **5a**, **7a** and **9a** constituted about 15% together.[15] The part of acyclic forms **5a**, **7a** and **9a** increased when a more polar solvent such as THF-d_8 was added to the $CDCl_3$ solution. Thus, ^{19}F NMR spectra in mixtures of $CDCl_3$/THF-d_8 (10 : 1, 2 : 1, 1 : 1) indicated ratios of **8a**/(**5a** + **7a** + **9a**) of 77 : 23, 58 : 42, 51 : 49, respectively.[16] In solutions with >50% THF-d_8 or pure THF-d_8 or CD_3CN the ^{19}F NMR spectra became more complex and several new peaks appeared between −72 and −83 ppm. This reflects the presence of other stable tautomeric forms in average share up to 27%.

Surprisingly, the reaction of ethyl isocyanoacetate with alkoxyenones **1b–e** bearing other polyfluoroalkyl groups proceeded with high regioselectivity under the same conditions (*t*-BuOK, THF, −78 °C, Scheme 5). The products of initial attack on the β-position were formed exclusively. In DMSO-d_6 the tautomer **8b** predominates (for the CHF_2-product, Table 1, entry 2), while the tautomers **5c–e** were mainly observed for CF_2Cl-, C_2F_5-, C_3F_7-compounds (Table 1, entries 3–5). In addition, the DMSO-d_6 solutions of CHF_2- and CF_2Cl-products contained both cyclic tautomers **8b,c** and enols **5b,c**, while for the C_2F_5- and C_3F_7-products only the corresponding enols **5d,e** were found in DMSO-d_6 solution (see Table 1).

X-ray analysis of the C_2F_5 product shows that only tautomer **5d** is present in the lattice (Fig. 2), which possesses the *Z*,*Z*-configuration of the C=C double bonds.[17] This configuration is presumed to be the most stable for all compounds **5a–e** in DMSO-d_6 solution.

The CHF_2-product exists as the single cyclic tautomer **8b** in $CDCl_3$ solution, while equilibria of the keto-forms **7c–e** and

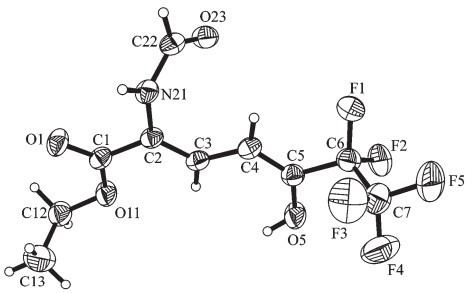
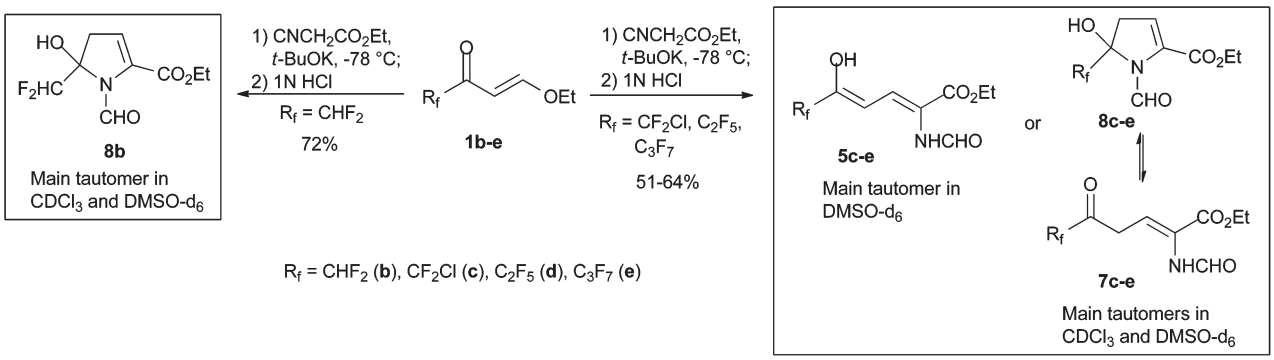


Fig. 2 Molecular structure of compound **5d** obtained by X-ray diffraction. Thermal ellipsoids are shown with 50% probability.



Scheme 5 Reactions of enones **1b–e** with ethyl isocyanoacetate (structure of products in DMSO-d_6 and $CDCl_3$ solutions, see Table 1 for ratio of tautomers).

Table 1 Reaction of enones **1a–e** with ethyl isocyanoacetate: products and their tautomers in DMSO-d_6 and $CDCl_3$ solutions

Entry	Starting compounds	R_f	Product(s), ratio[a] (isolated yield, %)	Major tautomer in DMSO-d_6 [a] (%)	Minor tautomer in DMSO-d_6 [a] (%)	Major tautomer(s) in $CDCl_3$ (%)	Minor tautomer(s) in $CDCl_3$ (%)
1	**1a**	CF_3	**4a**/**5a**,[b] 15/85 (11/76)	**5a** (85)[c]	**8a** (15)	**8a** (85)	**5a**, **7a**, **9a** (15)
2	**1b**	CHF_2	**8b**[b] 100 (72)	**8b** (82)	**5b** (18)	**8b** (100)	—
3	**1c**	CF_2Cl	**5c**[b] 100 (64)	**5c** (77)[c]	**8c** (23)	**8c** (85)	**7c**, **9c** (15)[d]
4	**1d**	C_2F_5	**5d** 100 (68)	**5d** (100)[c]	—	**8d** (58)	**7d**, **9d** (48)[d]
5	**1e**	C_3F_7	**5e** 100 (51)	**5e** (100)[c]	—	**7e**, **9e** (54)[d]	**8e** (46)

[a] Product ratios of components were determined by ^{1}H and ^{19}F NMR spectroscopy. [b] Major tautomer in DMSO-d_6. [c] Along with signals of protons corresponding to the *Z*,*Z*-1,3-diene, there were also peaks, which presumably correspond to another stereoisomer (*E*,*Z*-, *Z*,*E*- or *E*,*E*-) of compounds **5a, 5c–e**. [d] The ratio **7** : **9** is in the range between 30 : 1 and 6 : 1 depending on concentration of the sample and moisture.

cyclic forms **8c–e** were observed in the other cases. Low amounts (3–7%) of hydrate forms **9c–e** were also observed.

The data shown in Table 1 indicate that within this series the tautomeric ratio **8**/(**7** + **9**) strongly depends on the size of the polyfluoroalkyl group. Increasing the volume of the polyfluoroalkyl group (from CHF_2 to C_3F_7) resulted in a decreasing share of cyclic tautomer **8** (from 100% to 46%). That fact can be explained by an increase of intramolecular repulsion between the polyfluoroalkyl group and the neighboring CHO and CO_2Et groups.

Reaction of α- and β-substituted enones 1f–o

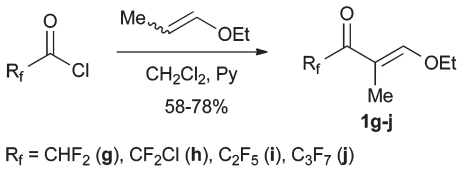
Next we investigated the reaction of a series of α-substituted enones **1f–l** with ethyl isocyanoacetate in order to explore the influence of an α-substituent on the reactivity. Hitherto unknown enones **1g–j** were obtained by acylation of 1-ethoxypropene according to the standard procedure (Scheme 6).[18]

In the case of the reaction of CF_3- and CHF_2-enones **1f,g** with ethyl isocyanoacetate under typical conditions (*t*-BuOK, THF, −78 °C) a mixture of the alternative products **4f,g** incorporating the carbonyl group and products **8f,g** formed by attack at the β-position were obtained (Scheme 7, Table 2, entries 1,2).

In contrast the reaction of enones **1h–j** was regioselective giving the corresponding compounds **8h–j** as single tautomers. Other tautomers such as **5** or **7** were not observed by NMR spectroscopy in $CDCl_3$ solutions. According to the NMR spectrum of compound **8f** in DMSO-d_6 solution, less than 5% of the tautomer **5f** was present.

Compounds **8f–j** were obtained as single diastereomers. The relative configuration of the CHF_2-compound **8g** was confirmed by NOE experiments, which indicated a *trans*-orientation of the 4-methyl and 5-CHF_2-groups. Due to the similarity of the spectral data, the same relative configuration is anticipated for the products **8f,h–j**.

In the case of the α-halogen-substituted CF_3-enones **1k,l** as well as in the case of the cyclic alkoxyenones **1m,n** (Scheme 8)

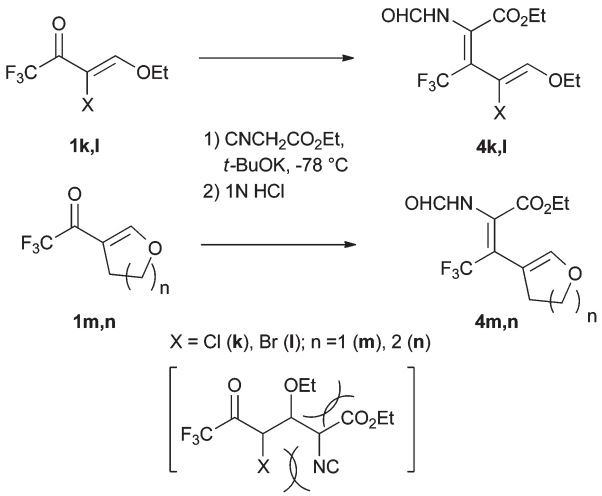


Scheme 6 Synthesis of enones **1g–j**.

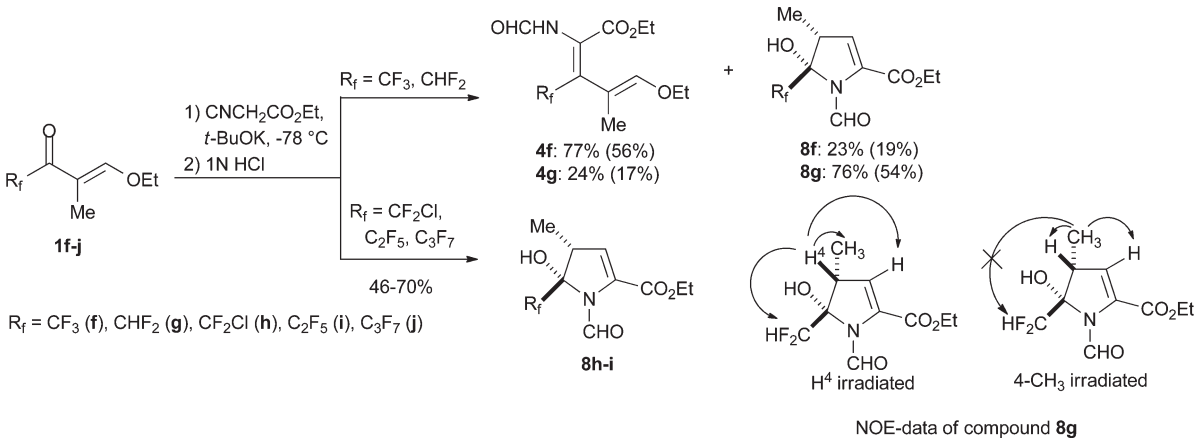
Table 2 Reaction of enones **1f–j** with ethyl isocyanoacetate: products, ratios, yields

Entry	Starting compound	R_f	Products, ratio[a] (isolated yield), %
1	**1f**	CF_3	**4f/8f**, 77/23 (56/19)
2	**1g**	CHF_2	**4g/8g**, 24/76 (17/54)
3	**1h**	CF_2Cl	**8h**, 100 (46)
4	**1i**	C_2F_5	**8i**, 100 (66)
5	**1j**	C_3F_7	**8j**, 100 (70)

[a] Determined by ^1H and ^{19}F NMR spectroscopy.



Scheme 8 Reaction of enones **1k–m** with ethyl isocyanoacetate and the presumably unstable intermediate of initial attack at the β-position.



Scheme 7 Reactions of α-methyl enones **1f–j** with ethyl isocyanoacetate and relative configuration of compound **8g** established by NOE (isolated yields are given in parentheses, see Table 2).

the reaction led unexpectedly to products **4k–n** incorporating the carbonyl group exclusively. No trace of other products was observed in the reaction mixtures.

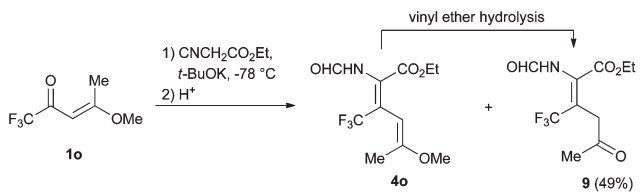
Obviously, the formation of products of attack at the β-position is disfavored because of increased steric interaction (in comparison to unsubstituted **1a** or α-Me-substituted enones **1f**) of the bulky α-substituent and the ethyl cyanoacetate anion in the anticipated transition state (Scheme 8).

In the case of the β-methyl substituted enone **1o** the reaction also proceeded regioselectively on the carbonyl group. However, along with product **4o** the corresponding ketone **10** was formed (Scheme 9, ratio **4o**/**10**, 59 : 41) as a result of partial hydrolysis of the methoxyvinyl group under the acidic work-up conditions. Also by using a weaker acid (15% citric acid) we failed to prevent formation of compound **10** (ratio **4o**/**10**, 50 : 50). Compound **4o** was found to be unstable under the conditions of column chromatography (silica gel). Only the product **10** was isolated in 49% yield.

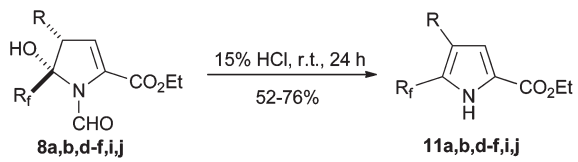
Synthesis of pyrroles 11–14

The tautomers **8a–i** have to be considered as hydroxy dihydropyrroles and we expected that formal elimination of formic acid would lead to the corresponding polyfluoroalkyl pyrroles **11**. This assumption was supported by the fact that traces of the corresponding pyrroles **11** were observed in the reaction mixtures after work-up by 1 N HCl in the synthesis of compounds **8** (or their tautomers **5** and **7**).

Fluoroalkylated pyrroles are increasingly interesting for medicinal chemistry and agrochemistry.[19] Therefore we investigated formic acid elimination from **8a**[20] under acidic conditions (Scheme 10). Vigorous stirring of **8a** in 15% HCl at r.t. for 24 h was found to be most convenient. White crystals of pyrrole **11a** were isolated in 63% yield by filtration and purification by column chromatography. Isolation by extraction and evaporation of the solvent was found to be less effective due to the high volatility of **11a**. The same reaction conditions were successfully applied for the transformation of 4-unsubstituted dihydropyrroles

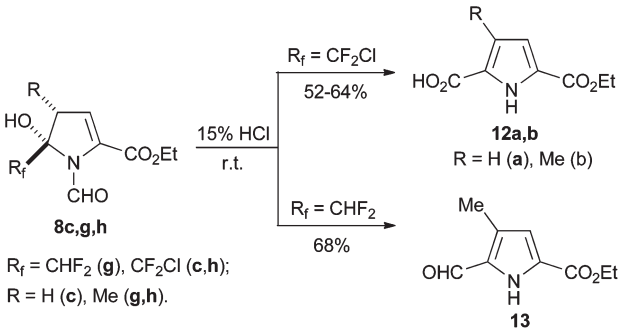


Scheme 9 Reaction of enone **1o** with ethyl isocyanoacetate.



R_f = CF_3 (**a**,**f**), CHF_2 (**b**), C_2F_5 (**d**,**i**), C_3F_7 (**e**,**j**).
R = H (**a**,**b**,**d**,**e**), Me (**f**,**i**,**j**).

Scheme 10 Synthesis of pyrroles **11**.[20]



Scheme 11 Synthesis of pyrroles **12a,b** and **13**.[20]

8b,d,e and 4-methyl dihydropyrroles **8f,i,j** to the corresponding pyrroles **11**, which were isolated in 52–76% yield (Scheme 10).

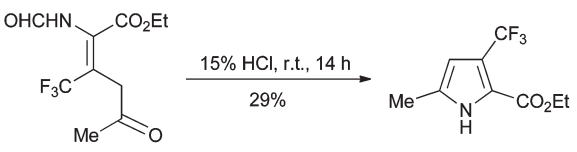
5-Polyfluoroalkyl-2-ethoxycarbonyl pyrroles **11** have not been described in the literature yet. Thus, the presented two-step pathway starting from enones **1** through compounds **8** is a convenient method to synthesize 1-unsubstituted 5-polyfluoroalkyl pyrrole carboxylates **11**. The method demonstrates application of ethyl isocyanoacetate for the preparation of α-polyfluoroalkyl substituted pyrroles, while earlier only β-polyfluoroalkyl substituted pyrroles were synthesized using this reagent.[21] By contrast under acidic conditions compounds **8c,h** containing a CF_2Cl group and **8g** containing a CHF_2 group were transformed to the acids **12a,b** and aldehyde **13**, respectively, as a result of acidic hydrolysis of the polyfluoroalkyl groups (Scheme 11).

Similar lability of CHF_2 and CF_2Cl groups was recently described for the corresponding 3-polyfluoroalkyl pyrroles.[22] We failed to find a milder set of conditions in order to prevent hydrolysis of the polyfluoroalkyl groups and for the synthesis of pyrroles **11c,g,h**.

Under the acidic conditions used for the synthesis of compounds **11**, the ketone **10** gave pyrrole **14** (Scheme 12).

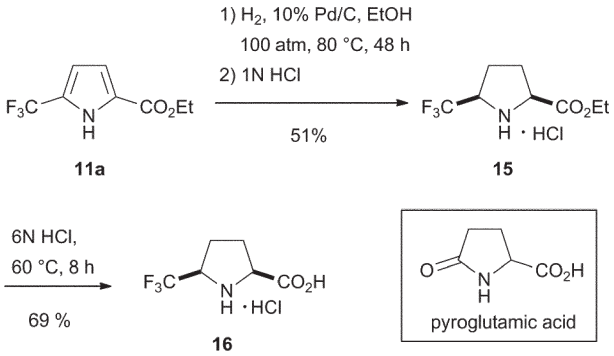
The transformation took place as a result of intramolecular heterocyclization between the carbonyl group and the formylamino group with elimination of formic acid. However, pyrrole **14** was isolated in low yield (29%), because the heterocyclization is accompanied by side processes.

One application of pyrroles **11** is the synthesis of 5-polyfluoroalkyl derivatives of proline by reduction of the pyrrole ring. Earlier we have shown that catalytic hydrogenation of polyfluoroalkyl heterocyclic compounds was effectively used in the synthesis of fluorinated amino acids.[12] On the other hand, catalytic hydrogenation of pyrroles is a well established method for the synthesis of substituted pyrrolidines.[23]



Scheme 12 Synthesis of pyrrole **14**.

Most efficiently, 10% Pd/C in ethanol, 100 atm, 80 °C, 48 h was used. In that case conversion was 100% and the product **15** was isolated as its hydrochloride in 51% yield (Scheme 13).



Scheme 13 Synthesis of 5-CF_3-proline **16**, a mimetic of pyroglutamic acid.[24]

Hydrolysis of the ester function with 6 N HCl led to diastereopure 5-trifluoromethyl proline hydrochloride **16** in 69% yield.[24]

While some CF_3-containing analogues of proline and their derivatives were described in the literature[25] 5-CF_3-proline **16** or its derivatives have not been described in the literature earlier.[26,27] As another 5-substituted proline derivative, this compound is of considerable interest for instance in peptidomimetics design.[26,28] On the other hand, according to Zanda's principle,[29] which considers the CF_3–CHNH fragment as a bioisostere of the CO–NH-function, amino acid **16** can be presented as an analog of the important bioregulator, pyroglutamic acid.

Attempts to apply these conditions for the catalytic hydrogenation of the CHF_2-pyrrole **11b** failed, probably due to lability of the CHF_2 group under these conditions. The search for appropriate hydrogenation conditions for pyrrole **11b** as well as similar polyfluoroalkyl pyrroles **11** is in progress.

Conclusions

The outcome of the reaction of β-alkoxyvinyl polyfluoroalkyl ketones **1** with ethyl isocyanoacetate and potassium *tert*-butoxide is strongly dependent on the structure of the starting enones. The tautomers **5** or **8** resulting from initial attack at the β-position of α-nonsubstituted **1a–e** and α-methylsubstituted ketones **1g–j** were generally isolated as major products, while the reactions of α- or β-substituted enones **1f,k–o** led mainly to the products of nucleophilic attack at the carbonyl carbon. Depending on the solvent, different tautomeric forms were observed for these compounds: enols **5**, ketones **7** and cyclic hemiaminals **8**. The latter compounds are key intermediates for the synthesis of new 5-polyfluoroalkyl-2-pyrrole carboxylates **11**, which are interesting building blocks for agrochemical and medicinal chemistry research. Catalytic hydrogenation of pyrroles **11** is a convenient method for the preparation of 5-polyfluoroalkyl analogs, which was demonstrated by the example of synthesis of earlier unknown 5-CF_3-proline **16**. Further investigations in the field of pyrroles **11** hydrogenation are in progress.

Experimental

General

Melting points are uncorrected. NMR spectra were recorded on spectrometers from Bruker at 300 MHz (Avance II and DRX) and 400 MHz (Advance II) and from Agilent at 500 MHz (VNMRS) and 600 MHz (DD2) at 25 °C. TMS (for ^{1}H and ^{13}C NMR) and CCl_3F (for ^{19}F NMR) were used as internal standards. IR spectra were recorded on a Bruker Vertex 70. Mass spectra (ESI-MS) were measured on a MicroTof Bruker Daltonics. The progress of reactions was monitored by TLC-plates (silica gel 60 F_{254}, Merck). Column chromatography was carried out on silica gel 60 (Merck, particle size 0.040–0.063). Elemental analyses are correct within the limits of ±0.3% for C, H, N.

All starting materials were of the highest commercial quality and were used without further purification. Starting enones **1a**,[23a] **1b,d,e**,[1d] **1c**,[30b] **1f**,[30c] **1k,l**,[30d] **1m,n**,[30e] **1o**[30f] were synthesized by known procedures.

Synthesis of α-methyl enones 1g–j (typical procedure)

*(E)-4-Ethoxy-1,1-difluoro-3-methyl-but-3-en-2-one (**1g**).* A solution of difluoroacetyl chloride (22.9 g, 0.2 mol) in anhydrous CH_2Cl_2 (40 mL) was added to a mixture of 1-ethoxy-propene (mixture of *cis*- and *trans*-isomers) (15.5 g, 0.18 mol) and pyridine (14.2 g, 0.18 mol) in CH_2Cl_2 (200 mL) under stirring and cooling to −10 °C. The reaction mixture was stirred at r.t. for 20 h, water (200 mL) was added and the aq. phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was distilled under reduced pressure giving enone **1g** as a light yellow liquid (b.p. 95–97 °C, 20 mm Hg). Yield: 20.6 g (63%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (3H, t, J = 7.2 Hz, CH_3), 1.73 (3H, s, CH_3), 4.17 (2H, q, J = 7.2 Hz, CH_2O), 5.97 (1H, t, J = 54.5 Hz, CHF_2), 7.59 (1H, s, CH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 7.8, 15.3, 71.2, 111.9 (t, J = 254.3 Hz), 113.1, 163.4 (t, J = 6.2 Hz), 187.5 (t, J = 24.4 Hz) ppm. ^{19}F NMR (470.8 Hz, $CDCl_3$): δ = –118.98 (d, J = 54.5 Hz, CHF_2) ppm. ESI-MS (*m*/*z*): calcd for $C_7H_{10}F_2NaO_2$ (187.0541). Found 187.0538.

Reaction of enones 1a–o with ethyl isocyanoacetate. General procedure. Ethyl isocyanoacetate (1.13 g, 10 mmol) in anhydrous THF (10 mL) was added dropwise *via* a syringe to a solution of *t*-BuOK (1.12 g, 10 mmol) in anhydrous THF (10 mL) at −78 °C. After the addition was complete, the solution was stirred at −78 °C for a further 30 min. Then a solution of the corresponding enone **1a–o** (8 mmol) in THF was added dropwise *via* a syringe. The mixture was stirred at −78 °C for 1 h and warmed up to r.t. during 1–2 h. Aqueous HCl (1 N, 10 mL) was added and the mixture was stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The products were separated and purified by column chromatography of the reaction mixture using an appropriate eluent.

*Ethyl (2Z,4E)-5-ethoxy-2-formamido-3-(trifluoromethyl)-penta-2,4-dienoate (**4a**).* was obtained from enone **1a** (1.34 g, 8 mmol) and purified by column chromatography (EtOAc/c-hex, 1 : 2, R_f = 0.36) giving compound **4a** as a light yellow oil. Yield: 0.25 g (11%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (3H, t, J = 7.1 Hz, CH_3), 1.31 (3H, t, J = 7.1 Hz, CH_3), 3.84 (2H, q, J = 7.1 Hz, OCH_2), 4.30 (2H, q, J = 7.1 Hz, OCH_2), 5.46 (1H, d, J = 12.7 Hz, CH), 6.65 (1H, d, J = 12.7 Hz, CH), 7.71 (1H, s, NH), 8.17 (1H, s, CHO). ^{13}C NMR (126 MHz, $CDCl_3$): δ 13.7,

14.5, 62.2, 66.1, 95.7, 117.4 (q, J = 29.9 Hz), 123.4 (q, J = 276.6 Hz), 127.3, 153.0, 158.8, 164.1. ^{19}F NMR (470.8 Hz, $CDCl_3$): δ −60.58 (s, CF_3). ESI-MS (m/z): calcd for $C_{11}H_{14}F_3NNaO_4$ (304.0767). Found 304.0768.

*Ethyl (2Z,4Z)-6,6,6-trifluoro-2-formamido-5-hydroxyhexa-2,4-dienoate (**5a**).* was obtained from enone **1a** (1.34 g, 8 mmol) and was purified by column chromatography (EtOAc/c-hex, 1 : 2, R_f = 0.36) giving compound **5a** as a light yellow oil. Yield: 1.54 g (76%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.23 (3H, t, J = 6.9 Hz, CH_3), 4.17 (2H, q, J = 6.9 Hz, OCH_2), 5.85 (1H, d, J = 12.6 Hz, CH), 7.28 (1H, d, J = 12.6 Hz, CH), 8.14 (1H, s, CHO), 9.71 (1H, s, NH), 11.55 (1H, br. s, OH). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.5, 61.3, 100.6, 120.9 (q, J = 270.5 Hz), 123.4, 126.0, 144.7 (q, J = 31.7 Hz), 160.5, 164.3. ^{19}F NMR (470.8 Hz, $CDCl_3$), δ −70.74 (s, CF_3). Anal. calcd for: $C_9H_{10}F_3NO_4$ (253.17): C, 42.70; H, 3.98; N, 5.53. Found C, 42.93; H, 3.82; N, 5.55. ESI-MS (m/z): calcd for $C_9H_{10}F_3NNaO_4$ (276.0454). Found 276.0455.

*Ethyl 1-formyl-5-hydroxy-5-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-2-carboxylate (**8a**).* was found to be a tautomer of **5a** which is the major compound in $CDCl_3$ solution (see Table 1). IR ($CHCl_3$), cm^{-1}: ν 1726, 1183, 1242, 1286, 1314, 1334, 1636, 1666, 1727. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (3H, t, J = 7.2 Hz, CH_3), 2.96 (1H, d, J = 20.0 Hz, H_a of CH_2), 3.14 (dd, J_1 = 20.0 Hz, J_2 = 3.4 Hz, H_b of CH_2), 4.31 (2H, q, J = 7.2 Hz, CH_2O), 6.25 (1H, s, CH), 6.46 (1H, br. s, OH), 9.30 (1H, s, CHO). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.0, 38.6, 62.1, 93.3 (q, J = 33.6 Hz), 121.4, 127.2 (q, J = 283.4 Hz), 133.1, 159.2, 164.1. ^{19}F NMR (470.8 Hz, $CDCl_3$): δ −84.48 (s, CF_3). ESI-MS (m/z): calcd for $C_9H_{10}F_3NNaO_4$ (276.0454). Found 276.0455.

Preparation of pyrroles 11–14 (typical procedure). Ethyl 5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (11a). A mixture of compound **8a** (1.27 g, 5.0 mmol)[20] and 15% aqueous HCl (50 mL) were vigorously stirred at r.t. for 24 h. The obtained precipitate was filtered, washed with water, dried and purified by column chromatography (EtOAc/hex, 1 : 2, R_f = 0.64), giving compound **10a** as a white solid. Yield: 0.65 g (63%). M.p. > 80 °C (sublimation). IR ($CHCl_3$), cm^{-1}: ν 1132, 1175, 1279, 1333, 1578, 1709, 3021, 3434. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (3H, t, J = 7.0 Hz, CH_3), 4.38 (2H, q, J = 7.0 Hz, CH_2O), 6.59 (1H, s, CH), 6.88 (1H, s, CH), 10.20 (1H, br. s, NH). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.3, 61.3, 110.8, 114.8, 120.4 (q, J = 267.2 Hz), 124.6 (q, J = 39.2 Hz), 125.4, 160.9. ^{19}F NMR (470.8 Hz, $CDCl_3$): δ −60.86 (s, CF_3). ESI-MS (m/z): calcd for $C_8H_8F_3NNaO_2$ (230.0399). Found 230.0403.

X-ray diffraction. The data set was collected with a Nonius KappaCCD diffractometer. Programs used: data collection, COLLECT (Nonius B.V., 1998); data reduction, Denzo-SMN;[31] absorption correction, Denzo;[32] structure solution, SHELXS-97;[33] structure refinement, SHELXL-97;[34] and graphics, XP (Bruker AXS, 2000). Thermal ellipsoids are shown with 50% probability, R-values are given for observed reflections, and wR^2 values are given for all reflections.

X-ray crystal structure analysis of compound **5d**:[17] $C_{10}H_{10}F_5NO_4$, M = 303.19, colourless crystals, 0.35 × 0.15 × 0.15 mm, a = 6.4262(3), b = 9.9510(3), c = 10.4639(4) Å, α = 73.787(2), β = 86.704(2), γ = 75.894(4)°, V = 623.11(4) Å^3, ρ_{calc} = 1.616 g cm^{-3}, μ = 0.170 mm^{-1}, empirical absorption correction (0.943 ≤ T ≤ 0.975), Z = 2, triclinic, space group $P\bar{1}$ (No. 2), λ = 0.71073 Å, T = 223(2) K, ω and φ scans, 5389 reflections collected (±h, ±k, ±l), [(sin θ)/λ] = 0.62 Å^{-1}, 2442 independent (R_{int} = 0.052) and 2073 observed reflections [I > 2σ(I)], 187 refined parameters, R = 0.065, wR^2 = 0.157, max. (min.) residual electron density 0.37 (−0.22) e Å^{-3}, hydrogen atom for N21 was refined freely, others were calculated and refined as riding atoms.

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