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SPECIAL ISSUE

Fluorinated Synthons

Synthesis and Properties of Polyfunctional Cyclic β-Alkoxy-α,β-Unsaturated Ketones Based on 4-Methylene-1,3-dioxolanes

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Abstract: New CCl_3- and CF_3-substituted enones, bearing additional hidden hydroxymethyl functions, were prepared by acylation of 4-methylene 1,3-dioxolanes. The synthesized enones are interesting building blocks for agrochemical and medicinal chemistry research. The reactivity of synthesized enones with various amines was studied, and enaminones **13** and **14** were obtained under NH_3 interaction; the reaction with aliphatic primary amines afforded enaminones **17** in high yields as equilibrium mixtures of *E* and *Z* isomers. The reaction of fluorinated enone **9c** with anilines afforded a mixture of products, including non-aromatic heterocyclic compounds **25** and **26** bearing the CF_3 group as well as furan **27** with CF_3 and amino functions at positions 5 and 3, respectively. The hydrolysis of enone **9c** afforded cyclic compound **11**.

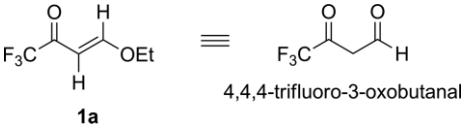
Introduction

Organofluorine compounds have a profound impact on the modern Drug Discovery. For example in the years 2001–2011, 40 new fluorine containing substances were approved as drugs and in general fluorine is present in about 25 % of drug molecules on the market.[1] Remarkable application of organofluorine compounds are resulting from unique properties of fluorine/fluoroalkyl groups the introduction of which into the active molecule often leads to enhanced binding interactions, metabolic stability, changes in physical and chemical properties of fluorinated compounds.[2]

CF_3-group is one of the most popular fluoroalkyl groups which present in numerous drugs and drug-candidates, agrochemicals and substances used in Material Science. Therefore numerous synthetic methods to introduce CF_3-group were developed.

Among them the approaches based on CF_3-containing building blocks are of particular interest because often lead to a selective formation of target molecules with certain arrangement of trifluoromethyl substituent and other groups.[3]

For instance, CF_3-containing β-dicarbonyl compounds (e.g. β-diketones) are widely used for the synthesis of heterocycles, bearing CF_3-group in required position. The one of the simplest CF_3-containing β-dicarbonyl compound – 4,4,4-trifluoro-3-oxobutanal – is not stable however often enone **1a** can be used as its synthetic equivalent where aldehyde group is "hidden" as ethoxyvinyl group (Figure 1).

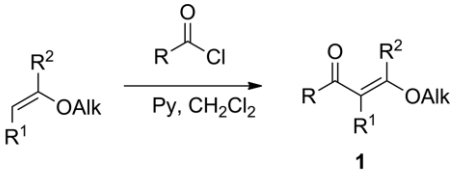


1a

Figure 1. Enone **1a** as a synthetic equivalent of 4,4,4-trifluoro-3-oxobutanal.

While the first examples of enone **1a** application were published 30 years ago it is still extensively used in the synthesis of diverse organofluorine compounds.[4]

Also there is a huge interest to other similar compounds of general structure **1** bearing various polyfluoroalkyl groups as well as other substitutions in α- and/or β-position.[5] These compounds can be easily obtained by acylation of the corresponding enol ethers (Scheme 1).[6] Also the method can be used to synthesize compounds bearing CCl_3-group instead of polyfluoroalkyl group (R = CCl_3). Such enones are also valuable for further synthesis of functionalized heterocyclic compounds since trichloromethyl moiety is a widespread precursor for the synthesis of carboxylic function.[7]



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R^1, R^2 = H, Alk, Ar
R = CF_3, C_2F_5, C_3F_7, CF_2Cl, CF_2Br, CF_2H, CCl_3

Scheme 1. Classical synthesis of β-alkoxyvinyl polyhaloalkyl ketones **1**.

Among others compounds **1** bearing an additional functional group in α- or β-position are of particular interest since

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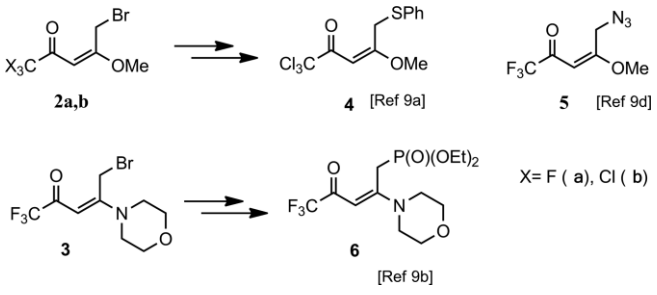
they can be involved in further transformation to produce more complex/functionalized molecules.

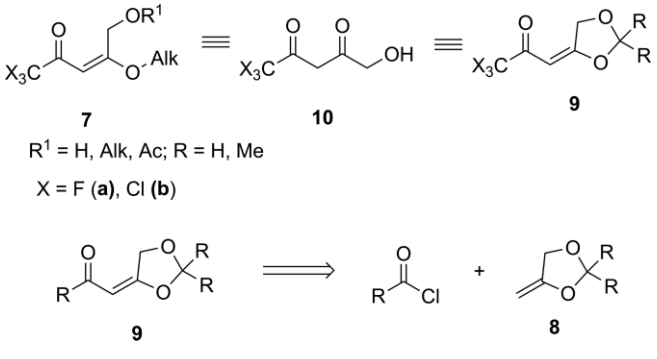
For example, previously we demonstrated synthesis of CF_3- and CCl_3-γ-bromosubstituted enones **2a**,**b**[8] as well as enaminone **3** and demonstrated their application for the preparation of functionalized molecules as **4**–**6**, as a result of selective substitution of bromine by S-, N- and P-nucleophiles (Scheme 2).[9] Obtained compounds **4**–**6** were found to be convenient starting materials for further heterocyclizations.[7a,9]



Scheme 2. Bromination of β-alkoxyvinyl trifluoroalkyl ketones **3**.

At the same time application of the similar methodology to substitute bromine with various *O*-nucleophiles is challenging. Thus, bromine substitution by acetate in CF_3-enone **2a** and the synthesis of *O*-acetylated enone **7a** (R^1 = Ac) was described previously.[7b] At the same time our own attempts to synthesize compounds like **7a** (R^1 = Alk) by substitution of Bromine in enone **2a** using such *O*-nucleophiles as methanol and benzyl alcohol in the presence of a base failed. Different conditions were tried using various bases (e.g. K_2CO_3, Py, MeONa, DBU), solvents (e.g. DMF, MeOH, THF, CH_2Cl_2) and temperature (0–100 °C) but in all the cases complex mixtures were formed.

In order to develop an alternative approach to enone **7** analogues we considered an alternative approach by acylation of available 4-methylene-1,3-dioxolanes **8** to synthesize enones **9a**,**b**. As enones **7** (R^1 = H) compounds **9** are synthetic equivalent of γ-hydroxy-β-diketone **10**. However in enones **9** γ-hydroxy- and β-carbonyl function are "hidden" as part of methylene-1,3-dioxoalne moiety (Scheme 3).



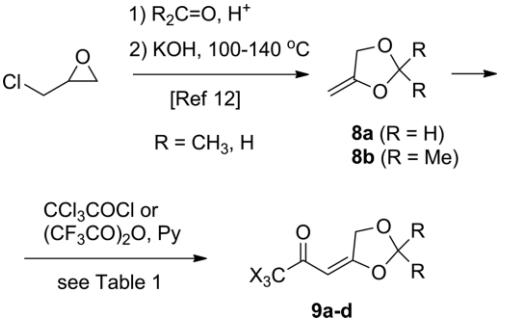
Scheme 3. Enones **7a**,**b**, and **9a**,**b** as synthetic equivalents of diketone **10**. Retrosynthetic approach to compounds **9a**,**b** from methylene dioxolanes **8**.

In this report we present simple synthetic approach to enones **9a**–**d** and particularities of their reactivity with various amines.

Results and Discussion

1.1. Synthesis of Enones 9a–d

In order to synthesize enones **9**, the starting compounds 4-methylene-1,3-dioxolanes **8a**,**b** were prepared by literature procedure in 71–81 % common yields by a convenient two-step protocol from epichlorohydrin (Scheme 4).[10] Next, compounds **8a**,**b** were acylated by trifluoroacetic anhydride or trichloroacetyl chloride in the presence of pyridine affording the corresponding enones **9a**–**d** in moderate to high yields (Scheme 4, Table 1). While fluorinated enones **9a**,**c** are relatively stable and can be stored at +4 °C for months without changes chloro-containing enones **9b**,**d** demonstrate spontaneous decomposition within several weeks at +4 °C which accompanied with their darkening. Enone **9d** was shown to be the most unstable.

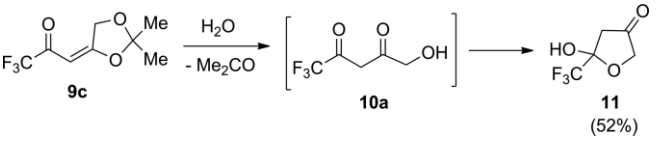


Scheme 4. Synthesis of enones **9a**–**d**.

Table 1. Synthesis of enones **9a**–**d**: starting materials and yields.

Entry	Starting material	Product	X	R^1	Yield [%]
1	**8a**	**9a**	F	H	73
2	**8a**	**9b**	Cl	H	71
3	**8b**	**9c**	F	CH_3	71
4	**8b**	**9d**	Cl	CH_3	60

We also investigated the hydrolysis of obtained enones **9c**,**d**. The reaction was performed by stirring it with water without any alkali or acid catalyst at room temp. for 2–3 days. In the cases of compound **9c** instead of expected diketone **10a**, the product **11** was obtained in moderate yield (Scheme 5). In contrast to fluorinated enone **9c**, the hydrolysis of trichloromethyl-containing enone **9d** afforded complex mixture of unidentified products as dark tarry material.



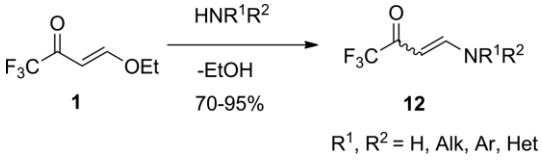
Scheme 5. Hydrolysis of enone **9c**.

1.2. Reactions of Compounds 9a–d with Ammonia. Reactions of 9c with Primary Aliphatic Amines

Our next step was to investigate the reaction of enones **9a**,**d** with ammonia and amines and compare the outcome of the

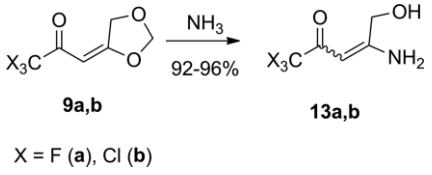
reaction with previously described reaction of enones **1** with N-nucleophiles.

Earlier the same reaction was investigated in details with enone **1a** which readily reacts with amines to provide the corresponding enaminones **12** in high yields (Scheme 6).[6a,11]



Scheme 6. Reaction of enone **1** with amines.

First, enones **9a**,**b** were treated with ammonia in several solvents (water, CH_2Cl_2, CH_3CN, etc.). In all the cases the corresponding enaminones **13a**,**b** were formed in high yields (Scheme 7).

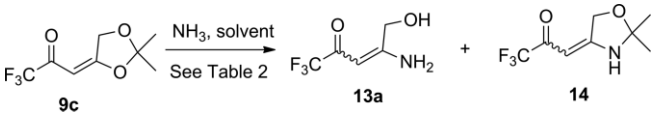


Scheme 7. Reaction of enone **9a**,**b** with ammonia.

It should be noted that non-halogenated analogs of the enaminones **13** were insufficiently described in literature and were previously used for the synthesis of some monoamino oxidase inhibitors like geiparvarin.[12]

Reaction of enone **1a** with amines led to non-reactive ethanol elimination. At the same time reaction of enones **9a**,**b** led to liberation of reactive formaldehyde. As a result the amination of enones **9a**,**b** led to rather complex product mixture which is difficult to purify. At the same time amination of the corresponding acetonides **9c**,**d** leads to liberation of less-reactive acetone which can be easily removed under work-up. Therefore for further investigation we mainly used enones **9c**,**d**.

As expected enone **9c** reacted with ammonia (as enone **9a**) giving enaminone **13a** only in water solution. At the same time when reaction was carried out with bubbling ammonia gas in different solvents formation of additional unexpected product **14** was observed (Scheme 8, Table 2). The ratio of both products depended on the solvent nature and obviously, both high polarity and water presence decrease the percentage of **14**. The latter was easily separated by hexane extraction from more polar enaminone **13a**.



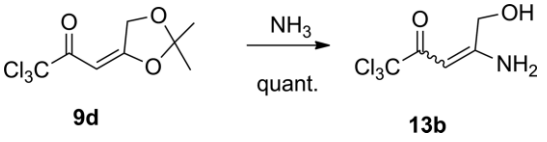
Scheme 8. Reaction of enone **9c** with NH_3.

At the same time enaminone **13b** was the only product in the case of CCl_3-containing enone **9d** reaction with ammonia. We did not observe formation of cyclic enaminone analogous to **14** under different conditions (Scheme 9).

Table 2. Reaction of enone **9c** with NH_3: ratio of products depending on the solvent.

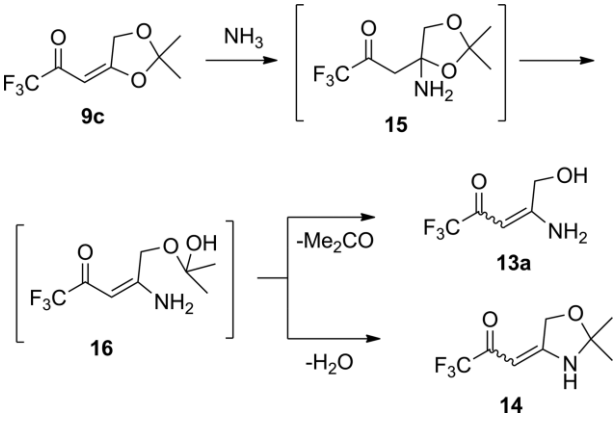
Entry	Solvent	Product ratio[a] [%]	
		13a	**14**
1	Hexane	60	40
2	CH_2Cl_2	80	20
3	MeCN	90	10
4	MeCN/H_2O (9:1)	99	< 1
5	H_2O	100	0

[a] Determined based on ^{19}F NMR spectra of reaction mixtures.



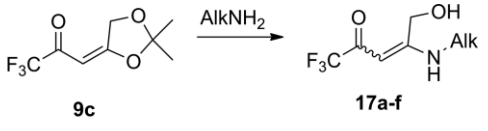
Scheme 9. Reaction of enone **9d** with NH_3.

The proposed mechanism of compound **14** formation is presented on Scheme 10 and includes the addition of ammonia to double bond of enone **9a**, followed by transformation of intermediate **15** into enaminone **16** bearing semiketal fragment.[14] The elimination of either acetone or water from intermediate **16** afforded enaminones **13a** or **14**, respectively.



Scheme 10. Proposed mechanism of compound **13a** and **14** formation.

Also similar to interaction with ammonia the reaction of **9c** with several aliphatic primary amines afforded the corresponding enaminones **17** in high yields, as expected (Scheme 11).



Alk = Me (**17a**), Et (**17b**), *i*-Pr (**17c**), *t*-Bu (**17d**), *c*-Pr (**17e**), *c*-Pen (**17f**).

Scheme 11. Reaction **9c** with primary amines.

1.3. *E*/*Z*-Isomers of Enaminones 13a,b, 14, 17a–f

Previously *E*/*Z*-isomerization behavior of compounds **12** was investigated in details.[13] They were found to exist as a mixture of *E*- and *Z*-isomers (when R^1 = H), and the observed isomer

ratio (by NMR and IR spectroscopy) mainly depends on solvent polarity: in low polar solvents (e.g. hexane, CCl_4) mainly (95 %) *Z*-form is detected, stabilized by intramolecular hydrogen bond, whereas in high polar solvents (DMF, DMSO, *etc.*) – as equilibrium mixture of mainly (75 %) two *E*-forms as a result of restricted rotation around the C–N bond. When $R^1 = R^2 = Alk$, compounds **12** exist in *E*-form only (Figure 2).[11]

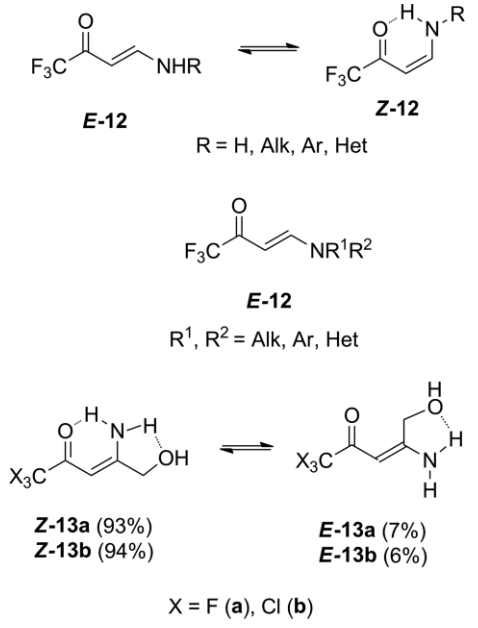
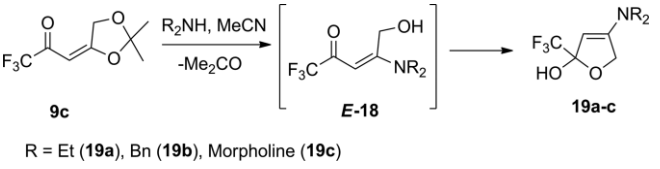


Figure 2. *E,Z*-isomers of compounds **12** and **13a,b**.

The observed *E*-/*Z*-isomer ratio of compounds **13a,b**, **14**, **17a**–**f** was estimated based on ^1H and/or ^{19}F NMR spectra and also depended on the polarity of used solvent. In case of enaminones **13a,b** we observed about 10 % of *E*-isomer in [D_6]DMSO. Again such a stability of *Z*-form is resulting from intramolecular hydrogen bond formation between NH_2- and CO-groups. Such interaction is easily observed in ^1H NMR spectra as signal of NH at ≥ 10 ppm instead of unbound NH-proton peak, typically observed at 7–8 ppm in analogous compounds. In both *E*-**13a,b** and *Z*-**13a,b** it can be assumed also an additional H-bond formation between neighboring OH- and NH_2-groups (Figure 2).

Compounds **17** also exist as an equilibrium mixture of *Z*- and *E*-isomers (Scheme 12, Table 2, entries 1–6). Remarkably, in this case the isomer ratio depended only slightly on the solvent polarity in contrast to the corresponding α-/β-unsubstituted enaminones **12** (Figure 2, above). Also for the most of compounds **17** *E*-isomer dominates in both solvents: $CDCl_3$ and DMSO (see Table 2). We suggest such behavior of enaminone **17** resulted from hydroxymethyl group presence in β-position which can form an additional intramolecular hydrogen bond with both nitrogen and oxygen atoms in *E*-**17** competing with hydrogen bond in *Z*-**17** (Figure 3). This intramolecular interaction diminishes influence of the solvent on the isomer ratio (Table 3).

We also studied the behavior of enaminone **14** in various solvents and found out that the E-/Z-isomer ratios in $CDCl_3$ and DMSO are very similar to enaminone **12a** bearing Me-group at the Nitrogen (see Figure 3, Table 2, entries 7,8). Such a significant difference in behavior of structurally similar enaminones **17** and **14** or **12a** is also in accordance with the assumption. Thus, in compounds **17** intramolecular hydrogen bond formation (with participation of CH_2OH-unit) is the main factor determining *E*/*Z*-isomer ratio and the solvent has minor influence in contrast to cases of compounds **14** or **12a** where *E*/*Z*-isomer ratio is very sensitive to solvent nature.



Scheme 12. Reaction of enone **9c** with secondary amines.

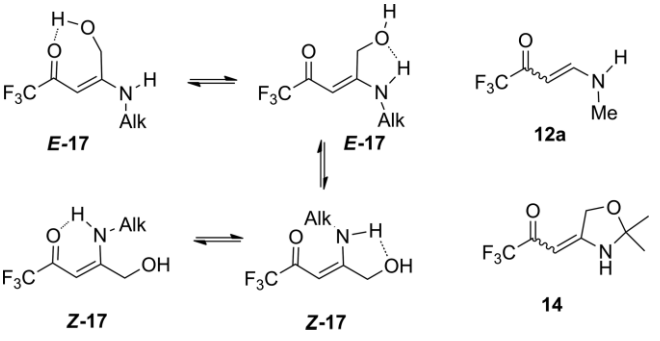


Figure 3. Intramolecular hydrogen bond formation in *Z*/*E*-isomers of enaminones **17** and structures of enaminones **12a** and **14** (see Table 3).

Table 3. The ratio of *E*-/*Z*-isomers of enaminones **17**, **14 and 12a** in various solvents (see Figure 3).

Entry	Alk	Enaminone	Ratio of *Z*-/*E*-isomers,[a] [%]			
			[D_6]DMSO		$CDCl_3$	
			Z	*E*	*Z*	*E*
1	Me	**17a**	29	71	42	58
2	Et	**17b**	39	61	41	59
3	*i*Pr	**17c**	48	52	37	63
4	*t*Bu	**17d**	36	64	18	82
5	*c*Pr	**17e**	38	62	52	48
6	*c*Pen	**17f**	52	48	45	55
7	–	**14**	37	63	96	4
8	–	**12a**[b]	25	75	95	5

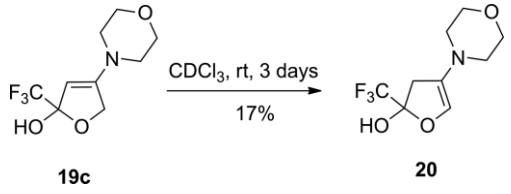
[a] Determined by ^1H and ^{19}F NMR spectroscopy. [b] From the published data.[11,13]

1.4. Reaction of Enones 9c,d with Other Amines

Reaction of enone **9c** with different secondary dialkylamines (e.g. diethylamine, dibenzylamine, and morpholine) resulted solely in formation of 4-dialkylamino-2-trifluoromethyl-2,5-dihydrofuran-2-ol **19a**–**c**, which were isolated in moderate yields (Scheme 12). Presumably the reaction takes place through the corresponding intermediate enaminones **18** were detected in the reaction mixture by NMR spectra but not isolated. In case of di-isopropylamine, no conversion was observed under different conditions (room temperature for 1–7 days or at 80 °C for 1 h). Easiness of cyclic product **19a**–**c** formation can be explained by

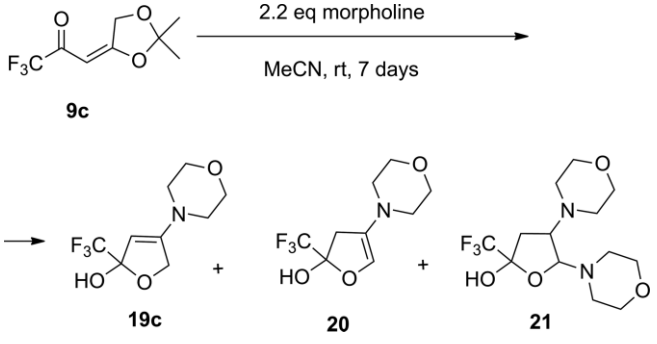
a rapid intramolecular cyclization of the intermediate enaminones **18** (which exists as *E*-isomer only), due to close spatial arrangement of CO and CH_2OH functional groups in ***E*-18**.

Products **19a**–**c** were shown to be stable in [D_6]DMSO solution on prolonged standing (by ^1H and ^{19}F NMR spectra). Product **19c** was stable in pure form whereas **19a**,**b** afforded to complex mixtures of unidentified products. Remarkably when compound **19c** was dissolved in $CDCl_3$, its slow conversion into isomer **20** as a result of an intramolecular double C=C bond migration (Scheme 13). The isomerization can be easily observed by ^{19}F NMR spectrum showed initially a singlet at –85.03 ppm, which corresponded **19c**, while on standing a new singlet at –85.53 ppm appeared due to compound **20** formation. The detected signal ratio reached 0.83:0.17 after 3 days (17 % conversion of **19c** to **20** in $CDCl_3$).



Scheme 13. Isomerization of dihydrofuran **19c** into **20**.

When an excess of morpholine (2.2 equiv.) was used in the reaction with enone **9c** on prolonged reaction time (7 days) at room temperature, an unexpected tetrahydrofuran **21** formation was observed, along with previously detected products **19c** and **20** (Scheme 14). Unfortunately, our attempts to obtain products as **20** and **21** starting from enone **9c** and diethylamine or benzylamine under different conditions failed.



Scheme 14. Reaction of enone **9c** with excess of morpholine.

Compound **21** was isolated and purified by crystallization from benzene in moderate yield. It was shown by NMR that in [D_6]DMSO solution compound **21** existed as a mixture of diastereomers with ratio 1:2 and broadened signals in ^1H, ^{19}F and ^{13}C NMR spectra can be explained by its dynamic isomerization. At the same time in solid compound **21** exists as *trans*-isomer only that was unambiguously proved by X-ray analysis (Figure 4).

We suggest compound **21** is formed from **20** which probably exists in the solution in equilibrium with ketoaldehyde form **22**. The latter can react with one more morpholine molecule giving semiaminal **23** which undergoes further cyclization to its more stable tetrahydrofuran tautomer **21** (Scheme 15). Equilibrium of

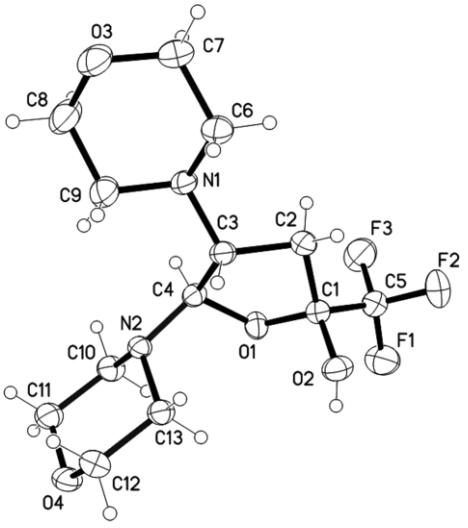
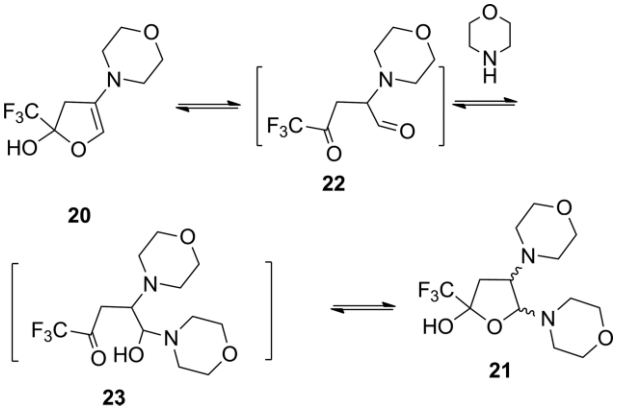


Figure 4. X-ray structure of compound **21**.

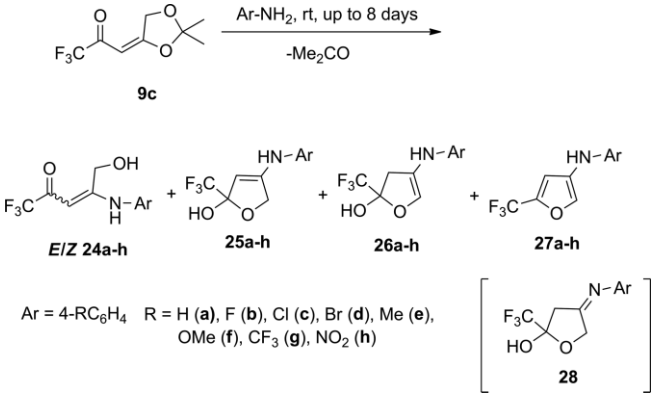
21 and opened form **23** also explains dynamic isomerization of *cis*-/*trans*-**21**. At the same time we did not observed any characteristic signals of aldehyde **22** in the reaction mixture.



Scheme 15. Proposed mechanism of compound **21** formation.

The reaction of fluorinated enone **9c** with anilines resulted in a complex mixture of products. Based on ^{19}F and ^1H NMR spectroscopic data analysis, the following forms were identified: enaminones **24** (as mixture of *E* and *Z*-isomers, the characteristic signals of enaminone fragment are very similar to *N*-alkyl-containing analogs **17**), two isomeric dihydrofurans compounds **25** and **26** (their spectroscopic characteristics are similar to products **19a**–**c** and **20**, see above), and furan **27** with CF_3- and amino groups at 5th and 3^{d} positions, correspondingly (Scheme 16).

Compounds **25** and **26** formed in similar way as **19a**–**c** and **20**, respectively, while furan **27** is a result of compound **26** dehydroxylation. This compound can be easily detected in the reaction mixture because of characteristic chemical shift of CF_3 group (–63 ppm), typical for 2-CF_3-substituted furans.[14] as well as two singlets of furan ring protons at ^1H NMR spectra in the field 8.6–8.7 and 7.1–7.2 ppm. Isomers **25** and **26** can be also easily distinguished by NMR spectroscopy. For instance, vinyl C=CH-proton of dihydrofuran **25g** had the typical chemical shift



Scheme 16. Reaction of enone **9c** with Ar-amines.

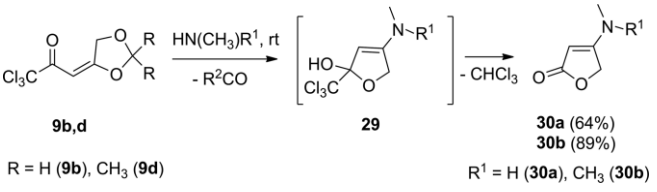
at δ = 5.19 ppm in ^{1}H NMR, whereas the vinyl C=CH-proton of compound **26g** has upfield shift to 4.87 ppm by the influence of adjacent oxygen. In the ^{19}F NMR spectrum of the reaction mixtures corresponding signals of the CF_3-groups were found at: –82.51 ppm for **25g**, –82.91 ppm for **26g**. Presumably compounds **26** are formed from **25** through the formation of imines **28**. At the same time we did not observed the presence of compounds **28** in NMR spectra of the reaction mixtures.

The reaction outcome was found to be sensitive to *para*-substituent in aniline structure (see Supporting Information, Table S1). It can be concluded that in the case of electron-withdrawing substituents the percentage of dihydrofurans **25** and **26** is higher than in the case of electron-donor groups. Such observation can be explained by destabilization of hydrogen bond between NH- and OH-groups in enaminones **24** due to electron-poor character of aromatic ring. This makes favorable unbound OH-group attack on carbonyl group with formation of **25** and its further isomerization to **26**. On the other hand, anilines bearing electron-withdrawing groups react much slowly because of law NH_2-group nucleophilicity. For instance, in the case of *para*-nitroaniline, the starting enone was the component in the reaction mixture even after 8 days at room temp.

In the case of the reaction with anilines bearing electron-donor substituents the corresponding enaminones **24** were isolated and shown to be stable compounds in solid state. For instance, compound **24f** was characterized as a mixture of *E*- and *Z*-isomers by ^{1}H and ^{19}F NMR spectra after dissolving in [D_6]DMSO and immediate spectral analysis, while ^{13}C NMR spectrum was too complex for unambiguous signal assignment. In other cases the ratio of components **24**–**27** in the reaction mixture was determined based on ^{19}F NMR results. Unfortunately, all our attempts to isolate and characterize individual heterocyclic compounds **25**–**27** were not successful.

The influence of solvent nature on reaction behavior was studied using *p*-CF_3-aniline which is easy to observe by NMR spectra (see Supporting Information, Table S2). It was found that the decrease of solvent polarity (DMSO > MeCN > THF > CCl_4) is favorable for the dihydrofuran **25g** formation and subsequent C=C-double bond migration to **26g** and further dehydroxylation to furan **27g**.

Finally the interaction of trichloromethyl-containing enones **9b**,**d** with some primary or secondary amines was studied and was shown to proceeds in other way then in case of fluorinated enone **9c**. For instance, in the case of the reaction with methylamine and dimethylamine the only products, isolated from the reaction mixture in high yields, were derivatives of tetronic acid **30a**,**b** (Scheme 17). Compounds **30a**,**b** formation can be explained by intramolecular addition of hydroxymethyl function to carbonyl group with the formation of intermediate cyclic semiketals **29** and following haloform reaction under basic conditions with $CHCl_3$ liberation.[15]



Scheme 17. Reaction of enone **9b**,**d** with amines.

Structural assignment of **30** was based on the identity of their ^{1}H and ^{13}C NMR spectroscopic data and melting points with the literature data for **30a**.[16]

Conclusions

New polyfunctional cyclic β-alkoxy-α,β-unsaturated ketones **9a**–**d**, bearing trifluoromethyl- and trichloromethyl- groups, were synthesized by acylation of readily available 4-methylene-1,3-dioxolanes **8a**,**b** in high yield. Enones **9a**–**d** are interesting building blocks for agrochemical and medicinal chemistry research. Amination and hydrolysis of the enones **9** led to different products depending on both enone **9a**–**d** and starting amine structure. In cases of ammonia and aliphatic primary amines, the expected enaminones (e.g. compounds **13** and **17**) while in the case of secondary amines and anilines with unexpected dihydrofurans (compounds **19**, **20**, **25**, **26**) and furan derivatives (**27**) as a result of initial intramolecular attack of CH_2OH-unit on carbonyl group. In case of enaminones **17** *E*-/*Z*-isomerization behavior is significantly different from previously studied enaminones **12** due to participation of CH_2OH-unit in additional intramolecular hydrogen bond formation. Also CCl_3-enones **9b**,**d** were shown to be less stable and produced more complex reaction mixtures (including formation of products without CCl_3-group). Further application of enones **9a**–**d** as a precursor to new CF_3- and CCl_3-containing heterocycles by their reaction with different binucleophiles is now underway.

Experimental Section

General Methods: All reagents were commercially available and used as received. Solvents were purified according to standard procedures. Starting materials were purchased from Acros, Merck, Fluka, and Enamine. Melting points are uncorrected. Characterization of intermediates and final compounds was done using ^{1}H, ^{13}C, ^{19}F NMR and IR spectroscopy. ^{1}H NMR spectra were recorded on Varian Unity Plus at 400 MHz and Bruker DRX-500 at 25 °C. Chemical shifts are reported downfield from TMS (for ^{1}H and ^{13}C NMR) and

CCl_3F (for ^{19}F NMR), coupling constants are given in Hz. Multiplicity is given as (s) for singlet, (br.s) for broad singlet, (d) for doublet, (t) for triplet, (q) for quartet, (dd) for doublet of doublets, and (m) for multiplet. ^{13}C NMR spectra were recorded at 125 MHz with the central peak of $CDCl_3$, triplet (δ C = 77.23 ppm) as the internal reference. ^{19}F NMR spectra were recorded at 376.3 MHz using $CFCl_3$ as internal signal. IR absorptions were recorded at Bruker Vertex 70 in CH_2Cl_2 and KBr, the absorptions are given in wave numbers (cm^{-1}). The progress of reactions was monitored by using TLC (silica gel 60 F254, Merck). Column chromatography was carried out on silica gel 60 (Merck, particle size 0.040–0.063 mm). Compounds **8a**,**b** were obtained according to the literature procedures.[10]

General Procedure for the Preparation of Enones 9a–d: To a solution of 4-methylene-1,3-dioxolane (17.0 g, 0.197 mol) or 2,2-dimethyl-4-methylene-1,3-dioxolane (22.8 g, 0.197 mol) in 100 mL of DCM was added 17.1 mL (17.1 g, 0.217 mol) of pyridine. To the stirred reaction mixture cooled to 10–15 °C and was then added a solution of trifluoroacetic anhydride (41.4 g, 0.197 mol) or trichloroacetyl chloride (35.8 g, 0.197 mol) in 50 mL DCM. The reaction mixture was left to stand over 12 h at room temp. then diluted with 70 mL of hexane and washed twice with acidified water. The combined organic phases were dried with $MgSO_4$, filtered, and the solvents were evaporated. The residue was purified by vacuum distillation.

(*E*)-3-(1,3-Dioxolan-4-ylidene)-1,1,1-trifluoropropan-2-one (9a): Yield: 71 % (30.2 g) as yellow liquid, b.p. = 66–68 °C (12 mm/Hg). ^1H NMR (500 MHz, [D_6]DMSO): δ = 5.04 (s, 2 H, CH_2), 5.59 (s, 2 H, CH_2), 6.28 (s, 1 H, =CH) ppm. ^{19}F NMR (376.3 MHz, [D_6]DMSO): δ = –76.86 (s, CF_3) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 70.8, 89.6, 99.6, 116.1 (q, $^1J_{C\text{-}F}$ = 291.7 Hz), 177.9, 178.6 (q, $^2J_{C\text{-}F}$ = 33.9 Hz) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2896, 1701, 1610, 1313, 1204, 1150, 1093, 939 cm^{-1}. $C_6H_5F_3O_3$ (182.10): calcd. C 39.58, H 2.77; found C 39.77, H 2.52.

(*E*)-1,1,1-Trichloro-3-(1,3-dioxolan-4-ylidene)propan-2-one (9b): Yield: 60 % (27.4 g), as yellow needles, m.p. 64–65 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.99 (s, 2 H, CH_2), 5.43 (s, 2 H, CH_2), 6.36 (s, 1 H, =CH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 70.5, 89.9, 96.5, 98.9, 174.7, 181.4 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2894, 1700, 1619, 1367, 1256, 1146, 977, 905, 834 cm^{-1}. $C_6H_5Cl_3O_3$ (231.46): calcd. C 31.14, H 2.18; found C 31.33, H 2.01.

(*E*)-3-(2,2-Dimethyl-1,3-dioxolan-4-ylidene)-1,1,1-trifluoropropan-2-one (9c): Yield: 73 % (30.2 g) as yellow liquid, b.p. = 69–71 °C (15 mm/Hg). ^1H NMR (500 MHz, [D_6]DMSO): δ = 1.56 (s, 6 H, $2CH_3$), 5.16 (s, 2 H, CH_2), 6.15 (s, 1 H, =CH) ppm. ^{19}F NMR (376.3 MHz, [D_6]DMSO): δ = –76.75 (s, CF_3) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 24.4, 70.8, 89.0, 116.2 (q, $^1J_{C\text{-}F}$ = 292.0 Hz), 117.5, 178.0, 178.5 (q, $^2J_{C\text{-}F}$ = 34.0 Hz) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2998, 1699, 1560, 1339, 1203, 1149, 1077, 904 cm^{-1}. $C_8H_9F_3O_3$ (210.15): calcd. C 45.72, H 4.32; found C 45.82, H 4.21.

(*E*)-1,1,1-Trichloro-3-(2,2-dimethyl-1,3-dioxolan-4-ylidene)-propan-2-one (9d): Yield: 71 % (36.3 g), as yellow needles, b.p. = 140 °C (0.5 mm/Hg). Enone **9d** can be crystallized from hexane, m.p. 40–42 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.57 (s, 6 H, $2CH_3$), 5.12 (d, ^4J = 1.5 Hz, 2 H, CH_2), 6.30 (t, ^4J = 1.5 Hz, 1 H, =CH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.05, 70.60, 88.97, 96.16, 116.15, 175.24, 181.25 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2998, 1696, 1608, 1389, 1219, 1096, 843 cm^{-1}. $C_8H_9Cl_3O_3$ (259.52): calcd. C 37.03, H 3.50; found C 37.28, H 3.27.

5-Hydroxy-5-(trifluoromethyl)dihydrofuran-3(2*H*)-one (11): Enone **9c** (3.0 g, 14.28 mmol) was mixed with 15 mL of water. The mixture was stirred in 2–3 d giving the homogeneous solution. The aqueous solution was evaporated in vacuo. The pure product was obtained using the extraction with ethyl acetate from the residue. As white needles, yield: 51.9 % (1.26 g), m.p. 40–41 °C. ^1H NMR (500 MHz, [D_6]DMSO): δ = 2.63 (d, ^2J = 18.6 Hz, 1 H, H_a of CH_2), 3.04 (d, ^2J = 18.6 Hz, 1 H, H_b of CH_2), 4.24 (d, ^2J = 17.1 Hz, 1 H, H_a of CH_2), 4.28 (d, ^2J = 17.1 Hz, 1 H, H_b of CH_2), 8.06 (s, 1 H, OH) ppm. ^{19}F NMR (376.3 MHz, [D_6]DMSO): δ = –82.93 (s, CF_3) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 43.1, 70.7, 100.0 (q, $^2J_{C\text{-}F}$ = 33.4 Hz), 122.5 (q, $^1J_{C\text{-}F}$ = 285.0 Hz), 209.5 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3546, 1775, 1192, 1102, 1060 cm^{-1}. IR (KBr): $\tilde{\nu}$ = 3420, 1772, 1181, 1116, 1063, 990, 808, 733, 630, 587 cm^{-1}. $C_5H_5F3O_3$ (170.09): calcd. C 35.31, H 2.96; found C 35.51, H 2.79.

General Procedure for the Preparation of Enaminones 13a,b from Enones 9a–d: 5.1 mL (67.1 mmol) of 25 % aq. solution of NH_3 was added to the solution of the corresponding enone **9a** (8.1 g, 44.7 mmol), **9b** (10.3 g, 44.7 mmol), **9c** (9.4 g, 44.7 mmol) or **9d** (11.6 g, 44.7 mmol) of in 50 mL of acetonitrile under vigorous stirring. The reaction mixture was stirred for 1 h at room temp. Then the solvent was evaporated to obtain almost pure target enaminone which was purified by crystallization from water.

4-Amino-1,1,1-trifluoro-5-hydroxypent-3-en-2-one (13a): Yield from **9a**: 96.0 % (7.26 g), as yellow crystals, m.p. 110–111 °C; spectra in [D_6]DMSO: *Z*-isomer: (92.6 %): ^1H NMR (500 MHz, [D_6]DMSO): δ = 4.19 (d, ^3J = 5.8 Hz, 2 H, CH_2OH), 5.38 (s, 1 H, OH), 5.71 (t, ^3J = 5.8 Hz, 1 H, =CH), 8.68 (br.s, 1 H, NH), 9.81 (br.s, 1 H, NH) ppm. ^{19}F NMR (376.3 MHz, [D_6]DMSO): δ = –75.32 (s, CF_3) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 60.5, 82.7, 117.4 (q, $^1J_{C\text{-}F}$ = 291.0 Hz), 174.1, 174.2 (q, $^2J_{C\text{-}F}$ = 32.0 Hz) ppm. *E*-isomer (7.4 %): ^1H NMR (500 MHz, [D_6]DMSO): δ = 4.61 (d, ^3J = 5.8 Hz, 2 H, CH_2OH), 5.42 (s, 1 H, OH), 5.73 (t, ^3J = 5.8 Hz, =CH), 8.03 (br.s, 1 H, NH), 8.77 (br.s, 1 H, NH) ppm. ^{19}F NMR (376.3 MHz, [D_6]DMSO): δ = –74.88 (s, CF_3) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = too low intensity of the signals. NMR spectra in $CDCl_3$: *Z*-isomer (97.7 %): ^1H NMR (500 MHz, $CDCl_3$): δ = 2.4–2.6 (br.s, 1 H, OH), 4.44 (s, 2 H, CH_2OH), 5.32 (s, 1 H, =CH), 6.9–7.1 (br.s, 1 H, NH), 10.0–10.2 (br.s, 1 H, NH) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ = –77.62 (s, CF_3) ppm. *E*-isomer (2.3 %): ^1H NMR (500 MHz, $CDCl_3$): δ = 4.82 (s, 2 H, CH_2), 5.39 (s, 1 H, =CH) ppm, the signals of OH and NH_2 groups in *E*- and *Z*-isomers are overlapped. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ = –77.47 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3213, 2923, 1651, 1558, 1441, 1318, 1244, 1133, 770, 731 cm^{-1}. $C_5H_6F_3NO_2$ (169.10): calcd. C 35.51, H 3.58, N 8.28; found C 35.35, H 3.43, N 8.32.

4-Amino-1,1,1-trichloro-5-hydroxypent-3-en-2-one (13b): Was obtained using standard procedure above starting from **9b** or **9d**. Yield from **9b**: 93 % (9.1 g), from **9d**: 99 % (9.7 g), as yellow crystals, m.p. 96–100 °C (with decomposition); in NMR spectra in $CDCl_3$ only *Z*-isomer was observed. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.37 (br.s, 1 H, OH), 4.45 (s, 2 H, CH_2), 5.65 (s, 1 H, =CH), 6.76 (br.s, 1 H, NH), 9.59 (br.s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 61.8, 81.7, 97.0, 169.6, 181.6 ppm. ^{13}C NMR spectra in [D_6]DMSO: *Z* (93.9 %): ^1H NMR (500 MHz, [D_6]DMSO): δ = 4.19 (d, ^3J = 5.4 Hz, 2 H, CH_2), 5.68 (t, ^3J = 5.4 Hz, 1 H, =CH), 5.69 (s, 1 H, OH), 8.36 (br.s, 1 H, NH), 9.36 (br.s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 60.9, 79.9, 97.5, 173.2, 179.0 ppm. *E* (6.1 %): ^1H NMR (500 MHz, [D_6]DMSO): δ = 4.60 (d, ^3J = 4.9 Hz, 2 H, CH_2), 5.68 (br.s, 1 H, OH), 5.79 (s, 1 H, =CH), 7.76 (br.s, 1 H, NH), 8.59 (br.s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = too low intensity of the signals. IR (CH_2Cl_2): $\tilde{\nu}$ = 3608, 3457, 1637, 1600, 1537, 830 cm^{-1}. IR (KBr): $\tilde{\nu}$ = 3373, 3286, 2899, 2829, 1646, 1532, 1407, 1323, 1096, 1050, 810, 742, 664 cm^{-1}. $C_5H_6Cl_3NO_2$ (218.47): calcd. C 27.49, H 2.77, N 6.41; found C 27.29, H 2.63, N 6.56.

Reaction of Enone 9c with NH_3 (Gas): NH_3 was bubbled through the solution of enone **9c** (1.87 g, 8.9 mmol) in 10 mL of hexane for 5 min. The reaction mixture was stirred for 1 h and then the solvent was evaporated. The crude mixture was washed with hot hexane for 2 times giving a crude mixture of compounds **14** and **13a**. The product **14** was crystallized from hexane. The yield is 28 % (0.52 g). The rest is containing almost pure enaminone **13a**, which can be additionally purified by crystallization from water. The yield is 69.8 % (1.05 g). The reaction in other solvents was carried out using the same approach (for the ratio of products see Table 2, main text).

3-(2,2-Dimethyloxazolidin-4-ylidene)-1,1,1-trifluoropropan-2-one (14): As yellow crystals, m.p. 40–42 °C.; in NMR spectra in $CDCl_3$ only *Z*-isomer was observed. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.55 (s, 6 H, $2CH_3$), 4.80 (s, 2 H, CH_2), 5.36 (s, 1 H, =CH), 10.3 (br.s, 1 H, NH) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ = –77.23 (s, CF_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.2, 71.3, 80.2, 98.7, 117.5 (q, $^1J_{C\text{-}F}$ = 288.2 Hz), 164.9, 177.4 (q, $^2J_{C\text{-}F}$ = 33.4 Hz) ppm; spectra in [D_6]DMSO: *Z*-isomer (62.5 %): ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 1.46 (s, 6 H, $2CH_3$), 4.81 (s, 2 H, CH_2), 5.29 (s, 1 H, =CH), 10.75 (br.s, 1 H, NH) ppm. ^{19}F NMR (376.3 MHz, [D_6]DMSO): δ = –75.27 (s, CF_3) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 26.4, 71.1, 78.3, 98.8, 117.4 (q, $^1J_{C\text{-}F}$ = 290.4 Hz), 164.1, 173.7 (br. q) ppm. *E*-isomer (38.5 %): ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 1.41 (s, 6 H, $2CH_3$), 5.06 (s, 2 H, CH_2), 5.40 (s, 1 H, =CH), 10.35 (br.s, 1 H, NH) ppm. ^{19}F NMR (376.3 MHz, [D_6]DMSO): δ = –75.28 (s, CF_3) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 26.8, 72.1, 79.8, 95.9, 117.6 (q, $^1J_{C\text{-}F}$ = 293.1 Hz), 167.2, 173.7 (br. q) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2992, 1645, 1564, 1324, 1108, 853 cm^{-1}. $C_8H_{10}F_3NO_2$ (209.17): calcd. C 45.94, H 4.82, N 6.70; found C 45.82, H 4.67, N 6.83.

General Procedure for the Preparation of Enaminones 17a–f: To the solution of enone **9c** (1 g, 4.76 mmol) in 10 mL acetonitrile was added the corresponding amine (5.71 mmol). The reaction mixture was stirred for 1 h, and then the solvent was evaporated to obtain pure enaminone **21** which did not require further purification. All the spectroscopic data and other physical chemical properties are presented in Tables S3–S5.

General Procedure for the Synthesis of Compounds 19a–c: The corresponding secondary amine was added to the solution containing 3 g (14.28 mmol) of enone **9c** in 10 mL of acetonitrile. The reaction mixture was stirred for 12 h, then the solvent was removed in vacuo. The residue was then purified by column chromatography on silica gel (ethyl acetate: hexane = 1:4).

4-(Diethylamino)-2-(trifluoromethyl)-2,5-dihydrofuran-2-ol (19a): As brown oil, 36.6 %. ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 1.04 [t, ^3J = 7.1 Hz, 6 H, 2(CH_2CH_3)], 3.01 [q, ^3J = 7.1 Hz, 4 H, 2(CH_2CH_3)], 4.07 (s, 1 H, =CH), 4.52 (d, ^2J = 12.0 Hz, 1 H, H_a of CH_2), 4.66 (d, ^2J = 12.0 Hz, 1 H, H_b of CH_2), 6.3–8.0 (br.s, 1 H, H) ppm. ^{19}F NMR (376.3 MHz, [D_6]DMSO): δ = –82.78 (s, CF_3) ppm. $C_{10}H_{16}F_3NO_2$ (239.24): calcd. C 50.21, H 6.74, N 5.85; found C 50.43, H 6.50, N 6.02.

4-(Dibenzylamino)-2-(trifluoromethyl)-2,5-dihydrofuran-2-ol (19b): As brown oil, 41.3 %, ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 4.25 [s, 4 H, 2(CH_2Ph)], 4.30 (s, 1 H, =CH), 4.65 (d, ^2J = 12.5 Hz, H_a of CH_2), 4.78 (d, ^2J = 12.5 Hz, 1 H, H_b of CH_2), 7.22 (d, ^3J = 7.1 Hz, 4 H, Ph), 7.27 (t, ^3J = 7.1 Hz, 2 H, Ph), 7.35 (dd, ^3J = 7.1 Hz, 4 H, Ph), 7.0 (br.s, 1 H, OH) ppm. ^{19}F NMR (376.3 MHz), [D_6]DMSO): δ = –82.85 (s, CF_3) ppm. $C_{18}H_{17}F_3NO_2$ (336.33): calcd. C 64.28, H 5.09, N 4.16; found C 64.39, H 5.07, N 4.32.

4-Morpholino-2-(trifluoromethyl)-2,5-dihydrofuran-2-ol (19c): As light yellow crystals, 53.1 %, m.p. 103–105 °C. ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 2.93 (m, 4 H, NCH_2CH_2), 3.61 (m, 4 H, OCH_2CH_2), 4.43 (s, 1 H, =CH), 4.52 (d, ^2J = 12.7 Hz, 1 H, H_a of CH_2), 4.67 (d, ^2J = 12.7 Hz, 1 H, H_b of CH_2), 7.26 (s, 1 H, OH) ppm. ^{19}F NMR (376.3 MHz, [D_6]DMSO): δ = –82.64 (s, CF_3) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 47.2, 65.4, 70.9, 87.8, 106.9 (q, $^2J_{C\text{-}F}$ = 32.9 Hz), 123.3 (q, $^1J_{C\text{-}F}$ = 286.7 Hz), 153.2 ppm. IR (KBr): $\tilde{\nu}$ = 3337, 3132, 2963, 2881, 1645, 1406, 1319, 1269, 1165, 1086, 955, 866, 765 cm^{-1}. IR (CH_2Cl_2): $\tilde{\nu}$ = 3574, 2972, 2864, 1641, 1451, 1270, 1181, 1121, 1089 cm^{-1}. In NMR spectra in $CDCl_3$ the step-by-step isomerization of compound **19c** to **20** was observed. After 3 d the percentage of **20** was ca. 17 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.66 (br.d, ^2J = 17.7 Hz, 1 H, H_a of CH_2), 2.84 (br.d, ^2J = 17.7 Hz, 1 H, H_b of CH_2), 2.95 (m, 4 H, NCH_2CH_2), 3.74 (m, 4 H, OCH_2CH_2), 3.93–4.02 (br.s, 1 H, OH), 4.27 (m, 1 H, =CH) ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ = –85.00 (s, CF_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 47.7, 66.2, 72.1, 87.8, 107.7 (q, $^2J_{C\text{-}F}$ = 34.4 Hz), 123.0 (q, $^1J_{C\text{-}F}$ = 287.2 Hz), 154.3 ppm. $C_9H_{12}F_3NO_3$ (239.19): calcd. C 45.19, H 5.06, N 5.86; found C 45.32, H 4.97, N 6.07.

4-Morpholino-2-(trifluoromethyl)-2,3-dihydrofuran-2-ol (20): The compound was observed in solutions, but wasn't isolated as individual compound because of low stability. It was observed 17 % after 3 d standing in $CDCl_3$. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ = –85.54 (s, CF_3) ppm.

4,5-Dimorpholino-2-(trifluoromethyl)tetrahydrofuran-2-ol (21): To the solution of 3 g (14.28 mmol) enone **9c** in 10 mL of acetonitrile was added morpholine 3.72 g (42.83 mmol). The reaction mixture was stirred for 1 h and then stand for 3 d, the solvent was evaporated and purification by crystallization from benzene gave **21** as white crystals. Yield: 50 % (2.23 g), m.p. 151–153 °C (with decomp). ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 1.98 (m, 1 H, NCH_2CH_2), 2.13 (m, 0.67 H, NCH_2CH_2), 2.38 (m, 2.33 H, NCH_2CH_2), 2.63 (m, 4 H, NCH_2CH_2), 2.76 (m, 2 H, CH_2), 3.00 (m, 0.33 H, CH), 3.14 (m, 0.67 H, CH), 3.55 (m, 8 H, OCH_2CH_2), 4.69 (d, ^3J = 7.6 Hz, 0.67 H, CH), 4.78 (d, ^3J = 7.3 Hz, 0.33 H, CH), 7.18 (br.s, 0.67 H, OH), 7.25 (br.s, 0.33 H, OH) ppm. ^{19}F NMR (376.3 MHz, [D_6]DMSO): δ = –82.86 (s, 0.33, CF_3), –82.73 (s, 0.67, CF_3) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 36.4, 36.5, 47.6, 47.9, 51.4, 51.7, 60.3, 61.9, 66.1, 66.2, 66.3, 66.4, 97.87 (q, $^2J_{C\text{-}F}$ = 32.4 Hz), 98.09 (q, $^2J_{C\text{-}F}$ = 32.0 Hz), 123.25 (q, $^1J_{C\text{-}F}$ ca. 286.6 Hz), 123.20 (q, $^1J_{C\text{-}F}$ ca. 286.6 Hz) ppm. IR (KBr): $\tilde{\nu}$ = 3239, 2959, 2862, 1458, 1305, 1268, 1169, 1114, 1015, 900, 871, 689 cm^{-1}. $C_{13}H_{21}F_3N_2O_4$ (326.31): calcd. C 47.85, H 6.49, N 8.58; found C 48.06, H 6.32, N 8.72.

General Procedure for the Monitoring the Influence of the Substituent at *p*-Position on the Reaction of Enone 9a with Arylamines: To a solution enone **9a** (1 g, 4.76 mmol) in 10 mL acetonitrile was added the corresponding amine (4.76 mmol). The reaction mixture was stirred for 5 min, and then the sample (0.2 mL) was evaporated and the residue was dissolved in [D_6]DMSO. ^{1}H, ^{19}F NMR s were measured in order to monitor the reaction and to study the influence of the substituent at *p*-position of aniline on its progress (see Table S1).

1,1,1-Trifluoro-5-hydroxy-4-(4-methoxyphenylamino)pent-3-en-2-one (24f): Spectra in [D_6]DMSO: *Z*-isomer (32 %): ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 3.78 (s, 3 H, OCH_3), 4.21 (d, ^3J = 6.0 Hz, 2 H, CH_2), 5.67 (t, ^3J = 6.0 Hz, 1 H, =CH), 5.91 (s, 1 H, OH), 6.9 9 (d, ^3J = 8.5 Hz, 2 H, Ar), 7.29 (d, ^3J = 8.5 Hz, 2 H, Ar), 12.12 (s, 1 H, Ar) ppm. ^{19}F NMR (376.3 MHz, [D_6]DMSO): δ = –75.07 (s, CF_3) ppm; *E*-isomer (68 %): ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 3.79 (s, 3 H, OCH_3), 4.81 (d, ^3J = 5.1 Hz, 2 H, CH_2), 5.22 (s, 1 H, OH), 6.03 (t, ^3J = 5.1 Hz, 1 H, =CH), 7.03 (d, ^3J = 8.5 Hz, 2 H, Ar), 7.21 (d, ^3J = 8.5 Hz, 2 H, Ar), 9.93 (s, 1 H, NH) ppm. ^{19}F NMR (376.3 MHz, [D_6]DMSO): δ = –74.95 (s, CF_3) ppm.

General Procedure for the Monitoring the Influence of the Solvent Polarity on the Reaction of Enone 9a with p-CF_3-Aniline:

To a stirred solution of enone **9a** (1 g, 4.76 mmol) in 10 mL of corresponding solvent *p*-CF_3-aniline (0.7 g, 4.76 mmol) was added at room temp. The reaction mixture was stirred and then the sample (0.2 mL) was evaporated and the residue was dissolved in [D_6]DMSO. The reaction mixtures was monitored using ^{1}H, ^{19}F NMR in 12 h, 48 h and 8 d to study the influence of the substituent at *p*-position on the reaction (See Tables S1 and S2).

General Procedure for the Preparation of Compounds 30a,b: To a solution of enone **9b** (0.89 g, 3.85 mmol) or **9d** (0.99 g, 3.85 mmol) in 15 mL of acetonitrile was added the corresponding amine 7.71 mmol. The reaction mixture was stirred for 1 h and then the solvent was removed in vacuo. The residue was purified by crystallization from hexane.

4-(Methylamino)furan-2(5*H*)-one (30a): As pale crystals, yield from **9b**: 63.9 % (0.28 g), m.p. 180 °C. ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 2.71 (d, ^3J = 4.3 Hz, 3 H, CH_3), 4.50 (s, 1 H, =CH), 4.60 (s, 2 H, CH_2), 7.44 (br.s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 30.6, 66.8, 78.14, 169.7, 174.7 ppm. $C_5H_7NO_2$ (113.12): calcd. C 53.09, H 6.24, N 12.38; found C 53.31, H 6.02, N 12.57.

4-(Dimethylamino)furan-2(5*H*)-one (30b): As pale crystals, yield from **9d**: 88.5 % (0.43 g), m.p. 63–65 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.88 (s, 6 H, $2CH_3$), 4.52 (s, 1 H, =CH), 4.65 (s, 2 H, CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.8 (br.s), 40.1 (br.s), 66.9, 81.1, 169.2, 175.5 ppm. $C_6H_9NO_2$ (127.14): calcd. C 56.68, H 7.13, N 11.02; found C 56.81, H 6.98, N 11.26.

X-ray Crystal Structure Analysis for 21

Formula $C_{13}H_{21}F_3N_2O_4$, M 326.32, monoclinic, space group $P2_1/n$, a = 10.1676(4), b = 14.4938(5), c = 10.8422(4) Å, β = 107.367(2), V = 1524.94(10) Å^3, Z = 4, d_c = 1.421 g cm^{-3}, μ = 0.128 mm^{-1}, $F(000)$ = 688, crystal size ca. 0.08 × 0.08 × 0.30 mm. All crystallographic measurements were performed at 173 K on a Bruker Smart Apex II diffractometer operating in the ω and φ scans mode. The intensity data were collected within the range of 2.41 ≤ θ ≤ 28.8° using Mo-K_α radiation (λ = 0.71078 Å). The intensities of 16494 reflections were collected (3916 unique reflections, R_{merg} = 0.0496).

CCDC 1573151 (for **21**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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