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On the Nucleophilic Reactions of 5-Trifluoroacetyl-3,4-dihydro-2*H*-pyran

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Summary. 5-Trifluoroacetyl-3,4-dihydro-2*H*-pyran react readily with many nucleophiles such as amines and *Grignard* reagents to give the rign opened products NuCH=CR^1R^2 (R^1: $(CH_2)_3OH$, R^2: CF_3CO). The compound with $Nu = Et_2N$ is unstable; it rearranges to 1-hydroxyl-1-trifluoromethyl-2-diethylaminomethylene-tetrahydropyran and 2-diethylamino-3-trifluoroacetyl-tetrahydropyran *via* an intramolecular nucleophilic addition reaction. Hydrazine and hydroxylamine attack the carbonyl carbon of the title compound to form $(\overline{CH_2)_3OCH=CC(CF_3)=NZ}$($Z = NH_2$, OH). In the presence of KOH, however, hydroxylamine hydrochloride reacts additionally to 2-hydroxyl-2-trifluoromethyl-3-cyano-tetrahydropyran. Upon heating with triethylphosphite, the title compound reacts as a heterodiene and gives the corresponding cyclophosphorane. X-Ray diffraction analyses of two compound are presented.

Keywords. 5-(Trifluoroacetyl)-3,4-dihydro-2*H*-pyran; Nucleophilic reactions; Tetrahydropyran derivatives; X-Ray.

Zur nucleophilen Reaktion von 5-Trifluoracetyl-3,4-dihydro-2*H*-pyran

Zusammenfassung. 5-Trifluoracetyl-3,4-dihydro-2*H*-pyran reagiert bereitwillig mit vielen Nucleophilen wie Aminen oder *Grignard*-Verbindungen zu ringgeöffneten Produkten des Typs NuCH=CR^1R^2 (R^1: $(CH_2)_3OH$, R^2: CF_3CO). Die Verbindung mit $R = Et_2N$ ist instabil und lagert über eine intramolekuare nukleophile Additionsreaktion zum 1-Hydroxy-1-trifluormethyl-2-tetrahydropyran um. Hydrazin und Hydroxylamin greifen das Carbonylkohlenstoffatom der Titelverbindung an und geben dabei Verbindungen des Typs $(CH_2)_3O\overline{CH=CC(CF_3)=NZ}$ ($Z = NH_2$, OH). In Gegenwart von KOH reagiert Hydroxylamin jedoch zusätzlich zu 2-Hydroxy-2-trifluormethyl-3-cyano-tetrahydropyran. Bei Erhitzen mit Triethylphosphit reagiert die Titelverbindung als Heterodien zum entsprechenden Cyclophosphoran. Die beiden Verbindungen wurden mittels Röntgenstrukturanalyse charakterisiert.

Introduction

α,β-Unsaturated carbonyl compounds are of interest because of their possible applications in the preparation of various heterocycles. β-Ethoxyvinyltrifluoromethyl ketone (EtOCH=CHCOCF$_3$, **1**) is a potential fluorinated 1,3-dicarbonyl compound and was first prepared in 1967 [1]. Its preparation and chemical

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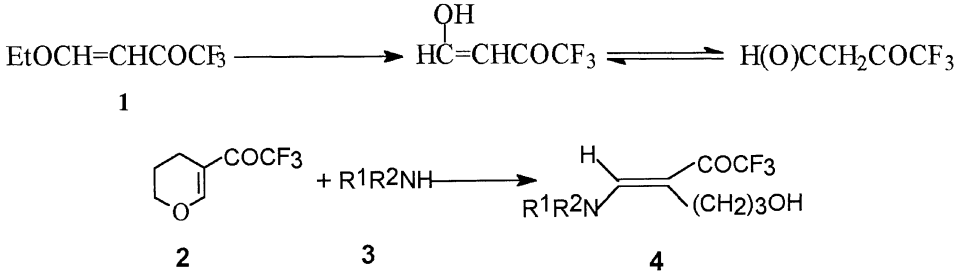
reactions have been extensively investigated [2–5]. However, only a few reactions have been studied with the cycloanalogue ($\overline{(CH_2)_3OCH=CC(O)CF_3}$ (**2**). Thus, it has been found that in the presence of a small amount of KOH and wet benzene **2** hydrolyzed to 3,4-dihydro-2*H*-pyran-5-carboxylic acid [6]. In wet CH_3CN the product has been 2-trifluoromethyl-2-hydroxyl-3-formyl-tetrahydropyran; however, no details for this reaction and no identification of the product have been described [6]. During studies on push-pull ethylenes [7–9], we prepared this compound and studied its nucleophilic reactions in detail.

Results and Discussion

Compound **1** has been shown to hdyrolyze easily in dilute acids to give trifluoroacetyl acetaldehyde and ethanol[5]. However, under the same conditions, 5-trifluoroacetyl-3,4-dihydro-2*H*-pyran (**2**) did not react even when heated at 70°C with concentrated HCl for 8 hours. Amines such as aniline, morpholine, or diethyl amine reacted readily with **2** at room temperature to give the corresponding enamines.



4a: R^1 = Ph, R^2 =H **4b:** R^1, R^2 = -$(CH_2)_2O(CH_2)_2$- **4c:** $R^1 = R^2$= Et

All amines attacked the double bond crbon atom C(6) to give the ring opened products, *i.e.* 1,1,2-trisubstituted ethylenes **4**. It was obvious that the fluorine substitution caused C(6) to become more sensitive towards nucleophilic attack. All ethylenes **4** have (*E*) configuration. They are solids and could be easily separated from the reaction mixture. Recrystallization from $CH_3CN/CHCl_3$ (1:1) gave suitable crystals for analysis. Their structures were fully characterized by spectroscopic methods and X-ray diffraction analysis (for **4b**). Figure 1 shows the molecular structure of **4b**. Selected bond lengths and bond angles are listed in Table 1. Remarkably, the bond distances N(1)–C(4) (1.35 Å) and C(3)–C(2) (1.46 Å) are shorter than the corresponding single bonds (C–N, 1.47 Å; C–C, 1.54 Å), whereas the double bonds (C(3)=C(4) (1.37 Å) and C(2)=O(1) (1.23 Å) are elongated (C=C, 1.34 Å; C=O, 1.22 Å). These data clearly indicate the occurrence of conjugation.

Compound **4c** is unstable. Upon standing at room temperature for a week it rearranged to two products **5a** and **5b** in a ratio of 5:4. A possible reaction pathway is described in as Scheme 1.

The hydroxyl group in **4c** attacks either the carbonyl carbon atom (path a) affording **5a** or the double bond carbon atom (path b), followed by proton transfer to yield **5b**. These two products could be separated. Their structures were

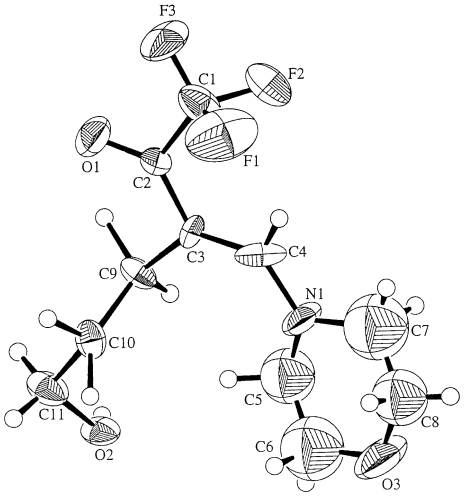
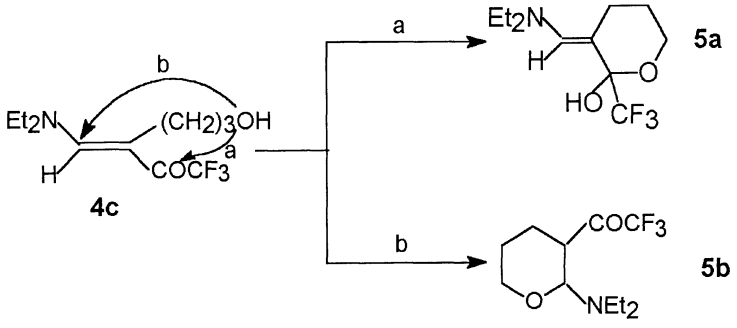


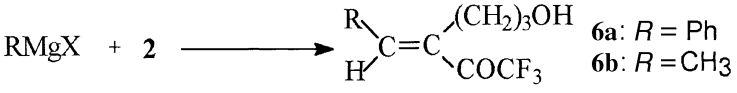
Fig. 1. Molecular structure of **4b**



Scheme 1

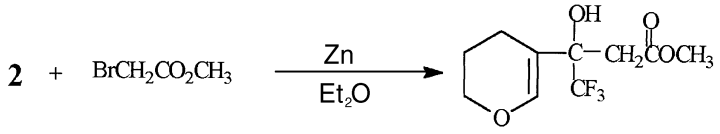
established *via* their spectroscopic data. The rearrangement of compound **4** is accelerated upon heating. For example, when **4** was heated at 80°C (without solvent), it nearly quantitatively rearranged to **5a** and **5b** within 12 h.

Grignard reagents such as PhMgBr or MeMgI reacted with **2** to formd the α,β-unsaturated trifluoromethyl ketones which also arise as a result of the nucleophile attack on the double bond carbon atom. These reactions were carried out in Et_2O at 0°C. Compounds **6a** or **6b** were obtained as the sole product after quenching with diluted HCl. It has been reported that the enone **1** react with PhMgBr to give two products [5]. However, in the case of **2**, no reduced product could be detected.



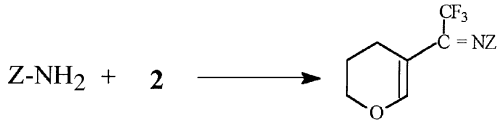
In contrast to *Grignard* reagents, organozinc compounds (formed *in situ*) added to the carbonyl group of **2**. For example, **7** was formed in 72% yield from a one pot reaction of **2** with methyl bromoacetate and zinc powder in ether. The different

results obtained from the reactions of **2** with *Grignard* reagents and the organozinc compound could be attributed to a stronger coordination of the carbonyl oxygen atom to the zinc reagent.



7

As mentioned above, N-nucleophiles such as $PhNH_2$ or Et_2NH attacked the double bond carbon atom (C-6) affording the ring opened products. It was interesting to find that in the reaction of **2** with hydrazine hydrate or hydroxylamine hydrochloride, the product is 5-(1-(2,2,2-trifluoroethylidene-hydrazono))-3,4-dihydro-2*H*-pyran (**9a**) or 5-(1-(2,2,2-trifluoroethylidenehydroximino)-3,4-dihydro-2*H*-pyran (**9b**). In these reactions, the nucleophile added to the carbonyl group followed by elimination of water to give **9a** or **9b**.

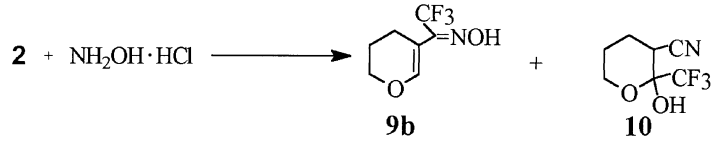


8a: $Z = NH_2$ **9a**: $Z = NH_2$

8b: $Z = OH$ **9b**: $Z = OH$

Compound **9a** has been obtained as a by-product (in 4% yield) from the reaction of $CF_3CCl{=}NN{=}CClCF_3$ with 3,4-dihydro-2*H*-pyran [10]. The NMR and IR spectra of **9a** are identical with the reported values. Compound **9b** is new; its spectra and elemental analysis comply fully with the proposed structure.

However, when **2** reacted with hydroxylamine hydrochloride in the presence of KOH, apart from **9b** 2-hydroxyl-2-trifluoromethyl-3-cyanotetrahydro-pyran (**10**) was isolated in 34% yield. It was identified by its spectroscopic data and by X-ray structure analysis (Fig. 2).



9b **10**

The formation of **10** might be explained by two possible reaction pathways (Scheme 2). In path a, the reagent NH_2OH attacks the double bond carbon atom followed by an intramolecular nucleophilic addition to form the intermediate product **A** which undergoes proton migration and water elimination to give **10** [11]. Another possible way is that the hydroxyl group attacks C(6) of **2** to give **11** which then reacts with NH_2OH followed by proton migration and water elimination to afford **10**. When **2** reacted with KOH in a mixed solvent (H_2O/CH_3CN), **11** was obtained in 61% yield.

Intermolecular hydrogen bonding between the N atom and the hydrogen atom of the hydroxyl group was observed; the distance is 2.10 Å. Selected bond lengths,

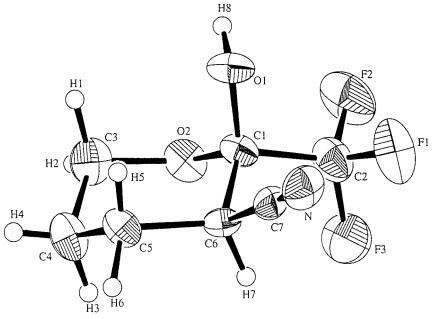
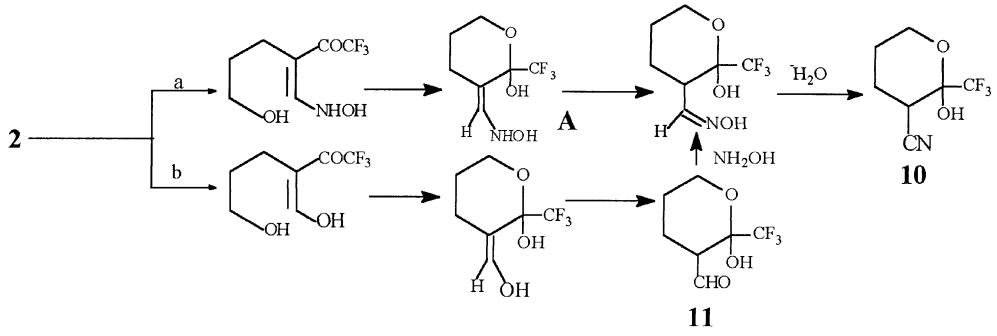


Fig. 2. Molecular structure of **10**



Scheme 2

Table 1. Selected bond lengths (Å) and bond angles (°) of **4b** and **10**

4b		**10**	
C(5)–N(1)	1.39(3)	C(7)–N	1.136(5)
C(7)–N(1)	1.47(4)	O(1)–H(8)	0.83(4)
C(4)–N(1)	1.35(2)	C(1)–C(1)	1.383(5)
C(4)–C(3)	1.37(2)	O(2)–C(1)	1.384(4)
C(3)–C(2)	1.46(2)	O(2)–C(3)	1.440(5)
C(3)–C(9)	1.53(2)	C(6)–C(7)	1.446(5)
C(2)–O(1)	1.23(2)	C(1)–C(6)	1.533(5)
C(4)–H(1)	0.95	C(1)–C(2)	1.536(5)
C(7)–N(1)–C(5)	113(1)	N–C(7)–C(6)	176.2(5)
C(1)–C(4)–C(3)	129(1)	H(8)–O(1)–C(1)	112.0(3)
H(1)–C(4)–C(3)	111.5	O(1)–C(1)–C(2)	109.5(3)
H(1)–C(4)–N(1)	118.9	O(1)–C(1)–C(6)	106.6(3)
C(4)–C(3)–C(9)	130(1)	O(1)–C(1)–O(2)	114.1(3)
C(2)–C(3)–C(4)	118(1)	C(1)–C(6)–C(7)	111.6(3)
C(9)–C(3)–C(2)	110(1)	C(1)–C(6)–H(7)	107.0(2)
O(1)–C(2)–C(3)	125(1)	C(7)–C(6)–C(5)	109.1(3)

Table 2. Crystallographic data of **4c** and **10**

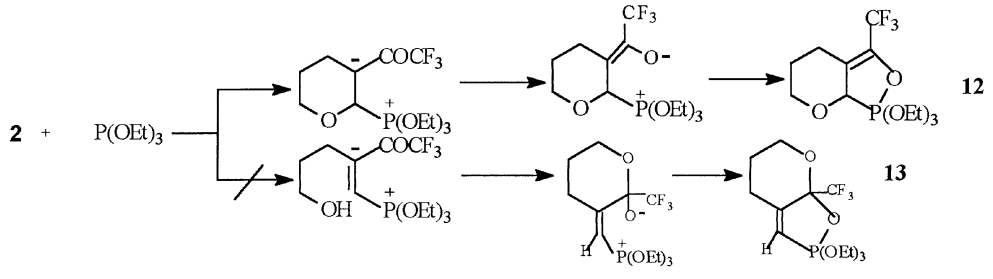
	4c	**10**
Formula	$C_{11}H_{16}O_3F_3N$	$C_7H_9F_3O_2N$
Fw	267.25	196.15
Z	4	4
D (calcd.) (g/cm^3)	1.397	1.494
Cryst. system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a (Å)	12.401(3)	11.754(2)
b (Å)	20.555(3)	13.433(3)
c (Å)	4.984(3)	5.5227(8)
V (Å^3)	1270.3	872.0(3)
λ(MoK_α, Å)	0.71069	0.71069
F(000)	560.00	404.00
Temp. (°C)	20.0	20.0
R	0.072	0.039
R_w	0.080	0.053
μ(MoK_α, cm^{-1})	1.28	1.49

$R = F_0 - F_c/F_0; R_w = ((F_0 - F_c)^2/wF_0^2)^{1/2}$

bond angles, and the crystallographic data of compounds **4b** and **10** are summarized in Tables 1 and 2.

As mentioned above, many reagents attack C(6) of **2** to form the ring opened products. Triethylphosphite reacted with **2** affording the cyclophosphorane **12**. Another possible reaction product, **13**, was ruled out by the ^{1}H NMR and ^{19}F NMR spectra. In this reaction **2** acted as a heterodiene and reacted with triethylphosphite.

In conclusion, the fluorinated α,β-unsaturated ketone **2** is very reactive in nucleophilic reactions. Both the carbonyl and the double bond carbon atoms are sensitive toward nucleophilic attack. In many cases, the products formed by attack at C(6) undergo subsequent intramolecular nucleophilic additions to give tetrahydropyran derivatives.



Scheme 3

Experimental

Melting and boiling points are uncorrected. M.p.s were measured on a Mel-Temp apparatus. Solvents were purified and dried before use. ^{1}H NMR (60 MHz), ^{13}C NMR (75.3 MHz), and ^{19}F NMR (54.6 MHz) spectra were recorded on a Varian-360 L instrument of a Bruker AM-300 spectrometer with *TMS* and *TFA* ($\delta_{CFCl_3} = \delta_{TFA} + 76.8$ ppm) as internal and external standard. X-Ray structure analysis was performed with a Rigaku AFC 7R Diffractometer. IR spectra were obtained with an IR-440 Shimadzu spectrophotometer. Low and high resolution mass pectra (HRMS) were obtained on a Finningan GC-MS 4021 and a Finnigan MAT-8430 instrument. Elemental analyses were performed by this Institute and found to be in satisfactory agreement with the caculated values. Compound **2** was prepared according to Ref. [2].

Rection of **2** *with N-nucleophiles; general procedure*

Amine (0.9 g, 10 mmol) was added into a 25 ml flask containing a solution 1.8 g **2** (10 mmol) and 10 ml CH_2Cl_2. This reaction mixture was stirred at room temperature and the reaction progress was monitored by TLC. After stirring for 2 h, the solvent was evaporated. The crude product was crystallized from $CH_3CN/CHCl_3$ to give the pure product.

3-(Hydroxypropyl)-4-(phenylamino)-1,1,1-trifluorobut-3-en-2-one (**4a**; $C_{11}H_{14}F_3NO_2$)

Yield: 87% m.p.: 65–67°C; ^{1}H NMR (60 MHz, $CDCl_3$, δ): 7.62 (s, =CH), 6.73 (s, C_6H_5), 3.62–3.45 (broad, OH, NH), 3.30 (t, OCH_2, $J_{HH} = 4$ Hz), 2.17 (t, CH_2–C=, $J_{HH} = 4$ Hz), 1.54–1.63 (m, CH_2) ppm; ^{19}F NMR (54.6 MHz, $CDCl_3$, δ): −69 (s, CF_3) ppm; IR (KBr): $\nu = 3359$ (m, OH), 2938 (w), 1782 (s, C=O), 1672 (s, C=C), 1234, 1141 (s, C–F) cm^{-1}; MS: *m*/*z* (%) = 273 (M^+, 60.54), 228 (M^+–$OHCH_2CH_3$, 100.00), 130 ($C_6H_5NHC_3H_2$, 79.57), 97 (CF_3CO^+, 2.75), 77 ($C_6H_5^+$, 26.04); HRMS: calcd.: 273.0988, found: 273.0993.

3-(3-Hydroxypropyl)-4-(morpholino)-1,1,1-trifluorobut-3-en-2-one (**4b**; $C_{11}H_{16}NF_3O_3$)

Yield: 89%; m.p.: 70–72°C; ^{1}H NMR (60 MHz, $CDCl_3$, δ): 7.26 (s, =CH), 4.03–3.36 (m, 7H, OH, $3OCH_2$), 3.43 (t, 4H, $2NCH_2$), 2.53 (t, 2H, CH_2–C=, $J_{HH} = 4$ Hz), 1.63 (m, 2H, CH_2) ppm; ^{19}F NMR (54.6 MHz, $CDCl_3$, δ): −73.4 (s, CF_3) ppm; IR (KBr): $\nu = 3283$ (m, OH, NH), 2963, 2857 (w), 1674 (s, C=O), 1581 (s, C=C), 1243, 1206, 1182, 1154 (s, C–F) cm^{-1}; MS: *m*/*z* (%) = 268 (M^+H, 100.00), 222 (M^+-CH_2CH_2OH, 74.29), 170 (M^+-CF_3CO, 12.63), 97 (CF_3CO^+, 2.14), 69 (CF_3^+, 10.27)

3-(3-Hydroxypropyl)-4-(diethylamino)-1,1,1-trifluorobut-3-ene-2-one (**4c**; $C_{11}H_{18}NF_3O_2$)

Yield: 85%; m.p.: 64–65°C; ^{1}H NMR (60 MHz, $CDCl_3$, δ): 7.30 (s =CH), 3.63–3.48 (m, 7H, OH, OCH_2, $2NCH_2$), 2.53 (t, 2H, CH_2–C=, $J_{HH} = 4$ Hz), 1.72–1.65 (m, CH_2), 1.30 (t, 6H, $2CH_3$, $J_{HH} = 4$ Hz) ppm; ^{19}F NMR (54.6 MHz, $CDCl_3$, δ): −65.4 (s, CF_3) ppm; IR (KBr): $\nu = 3324$ (m, OH), 2978, 2934 (w), 1708 (s, (C=O), 1577 (s, C=C), 1239, 1221, 1176 (s, C–F) cm^{-1}; ^{13}C NMR (75.3 MHz, $CDCl_3$, δ): 177.9 ($^{2}J_{CF} = 30$ Hz, CF_3CO), 153.1 (=CH), 118.4 ($^{1}J_{CF} = 292$ Hz, CF_3), 104.1 (=$CCOCF_3$), 67.7 (NCH_2), 67.3 (NCH_2), 60.6 (OCH_2), 43.1 (CH_2), 33.0 (CH_2), 14.2 (CH_3) ppm; MS: *m*/*z*, (%) = 254 (M^+H, 77.71), 253 (M^+, 35.23), 184 (M^+-CF_3, 32.95), 156 (M^+-CF_3CO, 28.13), 97 (CF_3CO^+, 3.05), 69 (CF_3^+, 7.60).

Rearrangement of **4c**

A 10 mL round bottom flask containing 2 g **4c** (8 mmol) equipped with a reflux condenser, drying tube and a magnetic stirring bar was heated to 80°C and stired for 10 h. TLC analysis showed that all

4c had disappeared and two new compounds were formed. The reaction mixture was separated and purified by column chromatography on silca gel (petroleum ether/EtOAc, 4:1).

1-Hydroxy-1-trifluoromethyl-2-diethylaminomethylene-tetrahydropyran (**5a**; $C_{11}H_{18}NF_3O_2$)

Yield: 45%; m.p.: 75–77°C; ^{1}H NMR (60 MHz, $CDCl_3$, δ): 7.03 (s, CH=), 3.83–3.30 (m, 7H, OH, OCH_2, $2NCH_2$), 2.40–1.66 (m, 4H, $2CH_2$), 1.33 (t, 6H, $2\times CH_3$) ppm; ^{19}F NMR (54.6 MHz, $CDCl_3$, δ): −85.0 (s, CF_3) ppm; ^{13}C NMR (75.3 MHz, $CDCl_3$, δ): 168.9 (C=C), 116.5 ($^1J_{CF} = 280$ Hz, CF_3), 98.6 ($^2J_{CF} = 34$ Hz, CF_3–C–OH), 98.0 (C=C), 67.9 (NCH_2), 67.3 (NCH_2), 61.6 (OCH_2), 24.9 (CH_2), 22.9 (CH_2), 10.8 ($2CH_3$) ppm ; IR (KBr): $\nu = 3533$ (m, OH), 2988–2860 (m, CH_2CH_3), 1622 (m, C=C), 1200, 1180 (s, C–F) cm^{-1}.

2-Diethylamino-3-trifluoroacetyl-tetrahydropyran (**5b**; $C_{11}H_{18}NF_3O_2$)

Yield: 36%; oil; ^{1}H NMR (60 MHz, $CDCl_3$, δ): 5.33 (d, 1H, $CHNEt_2$), 3.60–3.00 (m, 6H, OCH_2 $2\times NCH_2$), 2.97–2.67 (m, 1H, CHCO), 2.60–1.68 (m, 4H, $2CH_2$), 1.33 (t, 6H, $2CH_3$) ppm; ^{19}F NMR (54.6 MHz, $CDCl_3$, δ): −72.8 (s, CF_3) ppm; ^{13}C NMR (75.3 MHz, $CDCl_3$, δ): 161.7 ($^2J_{CF} = 32$ Hz, C=O), 118.5 ($^1J_{CF} = 280$ Hz, CF_3), 94.01 ($OCHNEt_2$), 64.3 (OCH_2), 45.8 (CHCO), 42.8 (NCH_2), 42.4 (NCH_2), 25.3 (CH_2), 23.7 (CH_2), 10.6 ($2CH_3$) ppm; IR (KBr): $\nu = 2990$–2840 (m, CH_2CH_3), 1745 (m, C=O), 1220, 1183 (s, C–F) cm^{-1}.

Reaction of **2** *with Grignard reagents; general procedure*

A solution of 1.8 g **2** (10 mmol) in 5 ml absolute Et_2O was added at 0°C into a 50 ml flask containing 20 ml of PhMgBr/Et_2O which was prepared by treatment of 1.6 g PhBr (10 mmol) with 0.3 g Mg (12 mmol) in 20 ml Et_2O. After addition, the reaction mixture was stirred for 2 h at 0°C. 5 ml 1 *N* HCl were added, the ether layer was separated, and the aqueous layer was extracted with Et_2O. The ether layers were combined and dried over Na_2SO_4. Et_2O was evaporated, and the residue was purified by column chromatography on silca gel (petroleum ether/EtOAc, 1:1) to give the product.

3-(3-Hydroxypropyl)-4-(phenyl)-1,1,1-trifluorobut-3-en-2-one (**6a**; $C_{13}H_{13}F_3O_2$)

Yield: 62% oil; ^{1}H NMR (60 MHz, $CDCl_3$, δ): 6.96 (s, C_6H_5), 7.40 (s, =CH), 4.30 (s, OH), 3.70 (t, OCH_2, $J_{HH} = 4$ Hz), 2.02 (t, CH_2–C=, $J_{HH} = 4$ Hz), 1.68–1.75 (m, CH_2) ppm; ^{19}F NMR (54.6 MHz, $CDCl_3$, δ): −72.87 (s, CF_3) ppm; IR (KBr): $\nu = 3420$ (m, OH), 3033, 2981, 2939 (w), 1734 (s, C=O), 1681 (s, C=C), 1241, 1236, 1151 (s, C–F) cm^{-1}; MS: *m/z* (%) = 258 (M^+, 27.24), 152 ($CF_3COC_4H_7^+$, 83.65), 107 ($C_7H_7O^+$, 100.00), 77 ($C_6H_5^+$, 38.63), 55 ($C_5H_5^+$), 33.29; MRMS: calcd 258.0869, found: 258.0870.

3-(3-hydroxypropyl)-4-(methyl)-1,1,1-trifluorobut-3-en-2-one (**6b**; $C_8H_{11}F_3O_2$)

Yield: 65%; oil; ^{1}H NMR (60 MHz, $CDCl_3$, δ): 6.63 (s, =CH), 3.96–3.76 (m, 3H, OH, OCH_2), 1.93 (t, CH_2–C=, $J_{HH} = 4$ Hz), 1.82–1.70 (m, CH_2) ppm; ^{19}F NMR (54.6 MHz, $CDCl_3$, δ); −70.7 (s, CF_3) ppm; IR (KBr): $\nu = 3436$ (m, OH), 2954 (w), 1700 (s, C=O), 1657 (s, C=C), 1254, 1159 (s, C–F) cm^{-1}; MS: *m/z* (%) = 197 (M^+H, 57.41), 179 (M^+-OH, 100.00), 127 (M^+CF_3, 4.41), 111 (M^+-OCF_3, 5.33); HRMS: calcd.: 196.0705, found: 196.0699.

5-((1-Hydroxy-1-trifluoromethyl-2-methoxylcarbonyl)-ethyl)-3,4-dihydro-2H-pyran (**7**; $C_{10}H_{13}F_3O_4$)

1.8 g **2** (10 mmol), 2.14 g $BrCH_2CO_2CH_3$ (14 mmol), 0.9 g Zn powder (14 mmol), and 20 ml absolute Et_2O were combined in a 50 ml flask. This reaction mixture was stirred for 10 h at 40°C. 5 ml 1 *N*

HCl werre added, the ether layer was separated and the aqueous layer was extracted with 2×15 ml Et_2O. The ether layers were combined and dried over Na_2SO_4. The solvent was evaporated, and the crude product was crystallized from $CHCl_3/CH_3CN$ to give 1.8 g **7**.

Yield: 71%; m.p.: 46–48°C; ^{1}H NMR (60 MHz, $CDCl_3$, δ): 6.73 (s, =CH), 4.60 (broad, OH), 3.93 (t, OCH_2, $J_{HH} = 4$ Hz), 3.76 (s, OCH_3), 2.83 (s, OCH_2CO), 2.06 (t, CH_2, $J_{HH} = 4$ Hz), 1.97–1.66 (m, CH_2) ppm; ^{19}F NMR (54.6 MHz, $CDCl_3$, δ): −81.00 (s, CF_3); IR (KBr): $\nu = 3479$ (s, OH) 2960 (w, C–H), 1707 (s, C=O), 1655 (s, C=C), 1165, 1117, 1091, 1029 (s, C–F) cm^{-1}; MS: *m/z* (%) = 254 (M^+, 11.24), 236 (M^+-H_2O, 16.69), 223 (M^+-OMe, 14.69), 185 (M^+-CF_3, 31.45), 178 (M^+-CO_2CH_3–OH, 11.34), 111 (M^+-CF_3–$CH_3CO_2CH_3$, 38.53), 69 (CF_3^+, 5.30).

Reaction of **2** *with hydrazine hydrate*; *general procedure*

A reaction mixture of 1.8 g **2** (10 mmol), 0.5 g $NH_2NH_2 \cdot H_2O$ (10 mmol), and 5 ml CH_3CN:H_2O (1:1) charged in a 25 ml flask was stirred at room temperature for 2 h A yellowish solid formed which was crystallized from CH_3CN to give the product.

5-(1-(2,2,2-Trifluoroethylidenehydrazono))-3,4-dihydro-2H-pyran (**9a**; $C_7H_9F_3N_2O$)

Yield: 80%; m.p.: 80–82°C; ^{1}H NMR (60 MHz, $CDCl_3$, δ): 7.65 (s, =CH), 3.57 (t, OCH_2, $J_{HH} = 6$ Hz), 3.82–3.22 (s, NH_2), 2.62 (t, CH_2–C=, $J_{HH} = 6$ Hz), 1.84–1.67 (m, CH_2) ppm; ^{19}F NMR (54.6 MHz, $CDCl_3$, δ): −62.00 (s, CF_3) ppm; IR (KBr): $\nu = 3482$ (s, OH), 2958 (w, C–H), 1634 (m, C=C), 1490 (s, C=N), 1234 (s, C=C), 1161, 1129 (s, C–F) cm^{-1}; MS: *m/z* (%) = 195 (M^+H, 25.17), 176 (M^+F, 100.00), 149 (M^+-$HOCH_2CH_2$, 80.4), 69 (CF_3^+, 5.71).

5-(1-(2,2,2-Trifluoroethylidenehydroxyimino))-3,4-dihydro-2H-pyran (**9b**; $C_7H_8NF_3O_2$)

Yield: 73%; m.p.: 85–86°C; ^{1}H NMR (60 MHz, $CDCl_3$, δ): 7.76 (s, =CH), 3.73 (t, OCH_2, $J_{HH} = 4$ Hz), 1.91 (t, CH_2, $J_{HH} = 6$ Hz), 1.85–1.79 (m, CH_2) ppm; ^{19}F NMR (54.6 MHz, $CDCl_3$, δ): −83.0 (s, CF_3) ppm; IR (KBr): $\nu = 3410$ (s, OH), 1622 (s, C=C), 1495 (s, C=N), 1187, 1117 (s, C–F) cm^{-1}; MS: *m/z* (%) = 196 (M^+H, 16.73), 181 (M^+-CH_2,87.06), 152 (M^+-CNOH, 93.90), 108 (M^+-H–OH–CF_3, 100.00), 83 ($C_5H_7O^+$, 63.99), 69 CF_3^+, (54.46).

2-Hydroxy-2-trifluoromethyl-3-cyano-tetrahydropyran (**10**; $C_7H_8NF_3O_2$)

A solution of 1.8 g **2** (10 mmol) in 10 ml of CH_3CN was added into a 50 ml flask containing $NH_2OH \cdot HCl$ (0.75 10 mmol), KOH (0.19 9 mmol) and H_2O (10 ml). After stirring for 8 h at 40°C, the mixture was extracted with Et_2O (2×15 ml) and the ether layer was dried over Na_2SO_4 overnight. After evaporation of the ether, the crude product was purified by column chromatography on silca gel (petroleum ether/EtOAc, 5:1) to give 0.66 g **9b** and 0.88 g **10**.

Yield: 34%; m.p.: 77–78°C; ^{1}H NMR (60 MHz, $CDCl_3$, δ): 7.16 (s, =CH), 3.78 (t, OCH_2, $J_{HH} = 4$ Hz), 3.85–3.74 (broad, OH) 2.86 (t, CHCN, $J_{HH} = 4$ Hz), 2.14–2.08 (m, CH_2CH), 1.65–1.58 (m, CH_2) ppm; ^{19}F NMR (54.6 MHz, $CDCl_3$, δ): −85.6 (s, CF_3) ppm; IR (KBr): $\nu = 3342$ (s, OH), 2946 (w, C–H), 2262 (m, CN), 1278, 1184, 1144 (s, C–F) cm^{-1}; MS: *m/z* (%) = 196 (M^+H, 47.06), 178 (M^+-OH, 21.11), 126 (M^+-CF_3, 12.31), 69 (CF_3^+, 34.84), 54 ($C_4H_6^+$, 100.00).

2-Hydroxy-2-trifluoromethyl-3-fomyl-tetrahydropyran (**11**; $C_7H_9F_3O_3$)

2 (1.8 g, 10 mmol) and 0.3 g KOH (5 mmol) were added to a 50 ml flask containing 10 ml CH_3CN and 10 ml H_2O. This reaction mixture was stirred for 10 h at 70°C, extracted with 2×15 ml Et_2O, and

the ether layer was dried over Na_2SO_4. After evaporation of the ether, the crude product was purified by column chromatography on silca gel (petroleum ether/EtOAc, 3:1).

Yield: 61%; m.p.: 85–86°C; ^{1}H NMR (60 MHz, $CDCl_3$, δ): 9.63 (d, CHO, $J_{HH} = 4$ Hz), 4.13 (broad, OH), 3.92 (t, OCH_2, $J_{HH} = 4$ Hz), 2.85–2.74 (m, CH–CHO), 1.98–1.72 (m, 4H) ppm; ^{19}F NMR (54.6 MHz, $CDCl_3$, δ): −86.1 (s, CF_3) ppm; IR (KBr): $\nu = 3170$ (vs, OH), 2962, 2942, (w, C–H), 1709 (s, CO), 1237, 1178, 1107 (s, C–F) cm^{-1}; MS: *m/z* (%) = 199 (M^++H, 4.16), 181 (M^+-OH, 100.00), 152 (M^+-OH–CHO, 58.53), 83 ($C_5H_7^+$, 72.49), 69 (CF_3^+, 22.37), ^{13}C NMR (75.3 MHz, $CDCl_3$, δ): 201.736 (CHO), 122.661 (CF_3, $J_{CF} = 284.9$ Hz), 93.301 (C-6, $^2J_{CF} = 33.0$ Hz), 20.855 (C-4) ppm.

Tetrahydropyran[b]cyclopentene-5-trifluoromethyl-6-oxa-7-triethoxyl phosphorane (**12**; $C_{13}H_{22}F_3O_5P$)

A mixture of 1.8 g **2** (10 mmol) and 5 ml $P(OEt)_3$ in a 10 ml flask equipped with a reflux condenser and a magnetic stirring bar was stirred for 10 h at 140°C. The excess $P(OEt)_3$ was removed under reduced pressure, and the product (2.18, 62%) was obtained by vacuum distillation.

Yield: 62%; b.p.: 105–107°C/2 torr; ^{1}H NMR (60 MHz, $CDCl_3$, δ): 6.50 (m, CH–O), 3.93 (q, OCH_2), 3.52 (t, OCH_2, $J_{HH} = 4$ Hz), 2.75 (t, CH_2, $J_{HH} = 4$ Hz), 2.12–1.93 (m, CH_2), 1.26 (t, CH_3) ppm; ^{19}F NMR (54.6 MHz, $CDCl_3$, δ): −62.4 (s, CF_3) ppm; IR (KBr): $\nu = 2985$ (w, CH), 1658 (s, C=C), 1253 (s, P–O), 1170 (s), 1137 (s, C–F) cm^{-1}; MS: *m/z* (%) = 347 (M^+H, 1.34), 302 (M^+-OC_2H_5, 47.35), 206 (M^+-$P(OC_2H_5)_2$-F, 100.00), 97 (CF_3CO^+, 18.34), 165 ($P(OC_2H_5)_3$-H, 51.03)

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