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Halogenation of fluorinated cyclic 1,3-dicarbonyl compounds: new aspects of synthetic application☆

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ABSTRACT

In order to elaborate on an approach towards 2-(fluoroacyl)phenols being the superior alternative to the conventional Fries-rearrangement based methodology, the behaviour of cyclic fluorinated 1,3-dicarbonyls in reactions with halogenating agents was examined. The synthetic relevance of the polyhalogenated compounds obtained was demonstrated by the synthesis of several new heterocycles. An aromatization via a halogenation–dehydrohalogenation sequence proved to be a rewarding synthetic route to 2-(fluoroacyl)phenols and previously unknown 3-(fluoroacyl)thiochromones. The structure of one of the synthesized compounds was confirmed by X-ray diffraction analysis.

1. Introduction

Due to the particular nature of the fluorine atom, fluorinated organic compounds have unique physical, chemical and biological properties,[1] which are proven to be especially valuable over a wide range of applications within the pharmaceutical and agrochemical industries, as well as in material science.[2] Structurally simple and suitably functionalized fluorinated compounds, which can be used as building blocks for the synthesis of complex fluorinated molecules are of particular interest. In spite of significant advances achieved in preparative organofluorine chemistry,[3] the convenient, reliable and economically realistic methods to obtain such fluorinated compounds on a multigram scale remains a challenge for chemists. Indeed, the preparation of highly important methyl trifluoropyruvate is complicated by numerous side reactions,[4] by far the simplest fluorinated 1,3,5-triketone (1,1,1,7,7,7-hexafluoroheptane-2,4,6-trione) was synthesized in 2006 only,[5] synthesis of ethyl 4,4,4-trifluoroacetoacetate under classic Claisen condensation conditions in a reasonable yield and purity is troublesome to this day.[6] One such 'small molecule' is 2-(trifluoroacetyl)phenol **1a** (Chart 1). Over the years, we[7] and other[8] could demonstrate synthetic potential of this compound and its derivatives **2** in organic, organoelement and coordination chemistry. Unfortunately, the reported approach[8] towards **1a** has significant drawbacks like vigorous reaction conditions and insufficient yield of the product rendering it only poor suitable for the scale-up purposes. Thus, we directed our efforts to designing more convenient and practical synthetic methods to synthesize phenol **1a** and related compounds. The findings and observations made are reported in this paper.

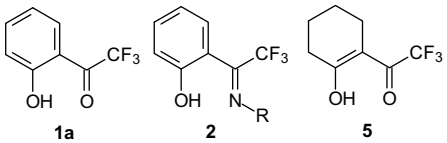

Chart 1.

2. Results and discussion

The published synthetic protocol[8] to obtain phenol **1a** consists of a $AlCl_3$ mediated Fries-rearrangement of phenyl trifluoroacetate

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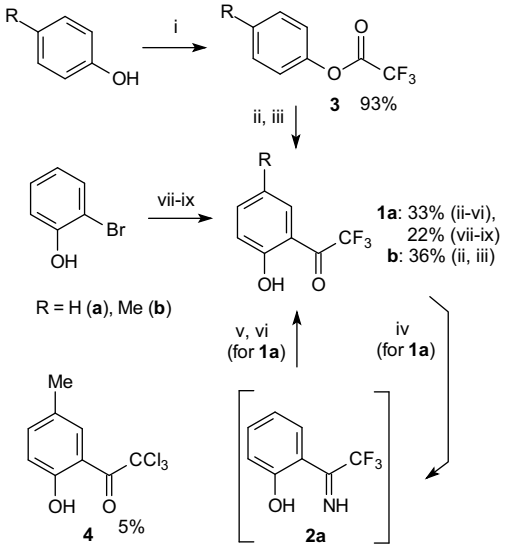
3a conducted at 115 °C, where CS_2 was used as a solvent during the chelation of **3a**. In addition, after very careful decomposition of the aluminium complex of **1a**, a quite tricky purification procedure was necessary which involved a intermediary formation of imine **2a** and its isolation as copper(II) chelate (Scheme 1). We have found that the rearrangement can be performed under solvent-free conditions, however, the yield of target **1a** remained modest (33% vs 42% according[8]). Somewhat unexpectedly, a very similar yield of *o*-rearranged product (36%) was obtained starting from *p*-substituted ester **3b**, although the purification via the copper(II) complex was not necessary. Notwithstanding, an additional problem appeared during the reaction: a certain amount of the target substance **1b** was lost through an $AlCl_3$ mediated halogen exchange, whereupon a trichloroacetyl-containing compound **4** was isolated in 5% yield as a by-product (Scheme 1). The organometallic approach was also tested however with moderate success: dilithiation of *o*-bromophenol[9] followed by trifluoroacetylation yielded only 22% of **1a** after several purification steps (Scheme 1).



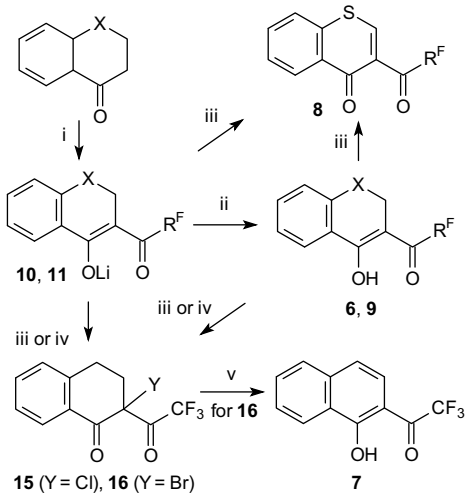
Scheme 1. Synthesis of phenols **1**, **4** by Fries-rearrangement. Reagents and conditions: (i) $(CF_3CO)_2O$ (1 equiv), 100–110 °C; (ii) $AlCl_3$ (1.1 equiv), 100 °C, 2 h, then 55–60 °C, 16 h; (iii) 10% aq HCl; (iv) aq NH_4OH, (v) $Cu(OAc)_2 \cdot H_2O$ (0.55 equiv), EtOH, rt; (vi) concd aq HCl; (vii) BuLi (2.2 equiv), Et_2O–hexane, −25 °C to rt, 2 h; (viii) CF_3CO_2Et (1.1 equiv), −90 °C, 10 min, −90 °C to rt, 1 h; (ix) 10% aq HCl.

All these facts prompted us to search for an alternate synthetic route to the phenols of type **1**. Taking into account our synthesis of bis(polyfluoroacyl)phenols from the corresponding cyclohexanones,[10] we attempted to prepare compounds **1** using a similar methodology.

The direct dehydrogenation[11,12] of easily available 2-(trifluoroacetyl)cyclohexanone **5**[13] was investigated to no avail. According to the ^{19}F NMR spectroscopy no reaction at all was observed upon heating **5** with elemental sulfur (solvent-free, 210 °C) or with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, benzene solution, bp); in the reaction with Pd/C catalyst carried out in a decaline solution at 190 °C a complex mixture was formed (^{19}F NMR yield of **1a** less than 10%).

On the other hand, the halogenation–dehydrohalogenation sequence appeared to be very efficient for the 'aromatization' purposes.[10,14] Indeed, starting from 2-(trifluoroacetyl)-1-tetralone **6** the α-naphthol **7** was obtained in two steps in 35% overall yield (Table 1, entry 1). This methodology could be applied for the synthesis of heterocyclic analogs: thiochromones **8a–d** were obtained with 67–94% yields treating 2-acylthiochromanones **9** with sulfuryl chloride (Table 1, entries 5, 7–9). Compounds **8a–c** represent

Table 1
Synthesis of α-naphthol **7** and thiochromones **8** from the corresponding 1,3-dicarbonyl derivatives **6**, **9**, **10**, **11**[a]

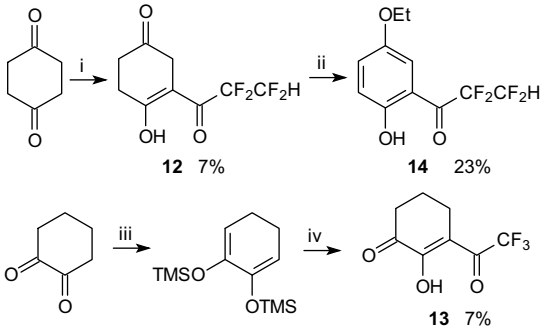


Entry	R^F	X	Intermediates **10**, **11** [yield (%)]	Intermediates **6**, **9**, **15**, **16** [yield (%)]	Products **7**, **8** [yield (%)]
1	CF_3	CH_2	**10** [94]	**6** [75] then **16** [52]	**7** [67]
2	CF_3	CH_2	**10**	**6** then **15** [71]	—
3	CF_3	CH_2	**10**	**15** [59]	—
4	CF_3	CH_2	**10**	**16** [37]	**7**
5	CF_3	S	**11a** [74]	**9a** [93]	**8a** [94]
6	CF_3	S	**11a**	—	**8a** [21]
7	CF_2CF_2H	S	**11b**	**9b** [77[b]]	**8b** [74]
8	C_2F_5	S	**11c**	**9c** [74[b]]	**8c** [85]
9	H	S	**11d**	**9d** [85[b]]	**8d** [67]

[a] Reagents and conditions: (i) LiH (1.1–1.2 equiv), RCO_2R' (1.2 equiv), benzene, bp, 4–20 h; (ii) 10% aq H_2SO_4; (iii) SO_2Cl_2 (1.1–1.2 equiv), $CHCl_3$; (iv) Br_2 (1.1 equiv), $CHCl_3$, (v) *o*-dichlorobenzene, bp, 5 h.
[b] The yield refers to starting thiochromanone.

a previously unknown class of 3-(fluoroacyl)thiochromones and are promising substrates for the heterocyclic transformations. Particularly, using the Li-enolate **11a** as a starting compound, **8a** was isolated in significantly lower yield (entry 6, 21% vs 94% from **9a**).

In order to synthesize hydroquinones bearing *one* fluoroacyl moiety using previous observations[10] we have prepared triketones **12** and **13** starting from the corresponding cyclohexanediones (Scheme 2). Surprisingly, the aromatization of **12** via bromination–dehydrobromination succeeded only when carried out in chloroform with an admixture of ethanol. 4-Ethoxyphenol **14** was formed in this case in 23% yield as a product of aromatization followed by a HBr mediated alkylation with EtOH. As for the aromatization of **13**, only complex mixtures were produced by brominations. The



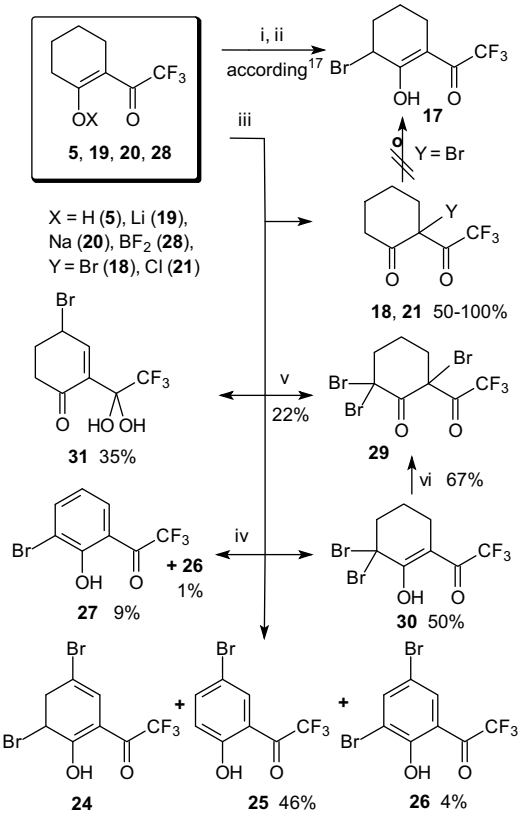
Scheme 2. Synthesis of phenols triketones **12**, **13** and phenol **14**. Reagents and conditions: (i) LDA (1 equiv), $HCF_2CF_2CO_2Me$ (1 equiv), THF, −78 °C, then rt, 12 h; (ii) Br_2 (1.3 equiv), $CHCl_3$, rt, 14 h; (iii) TMSOTf (2.4 equiv), NEt_3 (3 equiv), 0 °C to rt, 2 h; (iv) TMSOTf (0.3 equiv), $(CF_3CO)_2O$ (2.4 equiv), CH_2Cl_2, 0 °C to rt, 20 h.

required 3-(trifluoroacetyl)-1,2-hydroquinone was detected by the NMR (δ_F=−70.4 s), however, our attempts to isolate it failed.

After the question about removal of two hydrogen atoms from 6-membered cycle (compounds **6**, **9**, **12**) was answered, we have returned to the more complicated substrate **5** where *four* hydrogen atoms are 'excessive'. Since the test reaction using 2 equiv of bromine [conditions for the synthesis of 2,6-bis(trifluoroacetyl)phenols[10]] did not give a satisfactory result, we have investigated the halogenations of **5** and related compounds in more detail.

An introduction of *one* halogen atom in a fluorinated β-dicarbonyl framework (mostly in α-position) can be easily achieved, and the corresponding reactions are well documented.[6a,13,15–17] The formed compounds are very valuable and versatile synthons.[16–18] Indeed, the direct halogenations of 1,3-diketone **6** as well as its lithium enolate **10** proceeded smoothly affording α-chloro- and α-bromodicarbonyls **15**, **16** in 37–75% yields (Table 1, entries 1–4). In the case of non-fused analogs, the situation is not so unequivocal. Recently, Flores et al. have reported that the successive treatment of 2-(trihaloacetyl)cycloalkanones with 1 equiv Br_2 and pyridine provides products of ω-substitution (e.g. **17**, Table 2, entry 1) in good yields.[19,20] In our hands, several experiments with **5** under described conditions delivered complex mixtures only, where the starting 1,3-diketone and only very small amounts of declared[19] 6-bromo-2-(trifluoroacetyl)cyclohexanone **17** could be identified by NMR spectroscopy [δ_H=4.74 (t, J=3.5 Hz, 1H), 14.2 (br s, 1H, OH); δ_F=−74.3 (s, CF_3) in $CDCl_3$ solution]. On the other hand, subjecting **5** to bromination (1 equiv Br_2 in $CHCl_3$ solution) we have obtained α-bromo-β-diketone **18** as a major product (Table 2, entry 2). The use of lithium salt **19** instead of **5** or *N*-bromosuccinimide (NBS) instead of elemental bromine in this reaction appeared to be more efficient, giving rise to **18** as a sole product in a higher yield (Table 2, entries 3–7 vs 2). A similar situation was observed in the course of chlorinations. Diketone **5** and its salts **19**, **20** could be converted with sulfuryl chloride or elemental chlorine into α-chloro-β-diketone **21** in 74–92% yields (Table 2, entries 8–10). The product of ω-substitution **22** could be isolated in low yield from the mixture formed in the bromination of copper(II) complex of 2-(trifluoroacetyl)cyclopentanone **23** (Table 3). The α- or ω-halogen structure of compounds **18**, **21**, **22** could be easily established based on the ^{1}H and ^{13}C NMR spectroscopy data. In **18**, the chemical shift value of tertiary 2-C nucleus verifies the position of bromine atom (δ_C=65.2) supported by DEPT135 experiment. The absence of enolic OH signal in ^{1}H NMR spectra of **18**, **21** is in accordance with the

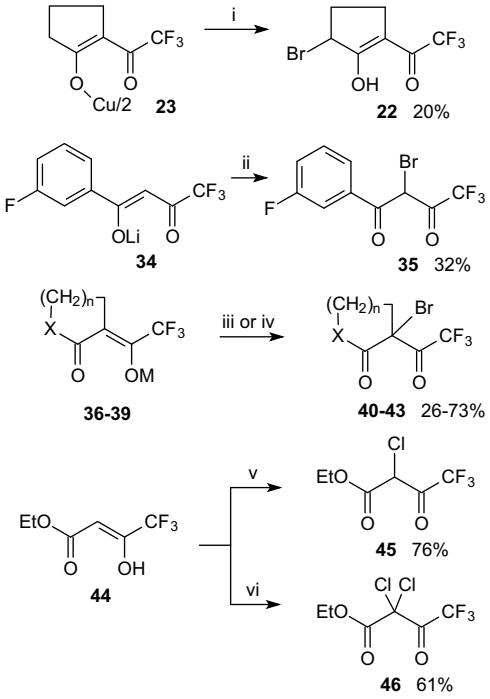
Table 2
Halogenations of 2-(trifluoroacetyl)cyclohexanone **5** and its derivatives **19**, **20**, **28**



Entry	Starting compound	Reagents and conditions (i–vi)	Product(s)	Yield (%)
1[19]	**5**	(i) Br_2, anhyd $CHCl_3$, rt, (ii) Py, rt	**17**	95[19]
2	**5**	(iii) Br_2, $CHCl_3$, rt	**18**	50[a]
3	**5**	(iii) NBS, $CHCl_3$, rt	**18**	87
4	**5**	(iii) 2 NBS, $CHCl_3$, rt, bp	**18**	ca. 100[a]
5	**5**	(iii) 3 NBS, $CHCl_3$, rt, bp	**18**	ca. 100[a]
6	**5**	(iii) 5 NBS, $CHCl_3$, rt, bp	**18**	ca. 100[a]
7	**19**	(iii) Br_2, $CHCl_3$, rt	**18**	92
8	**20**	(iii) 2 Cl_2, CH_2Cl_2, −196 °C to rt.	**21**	76
9	**20**	(iii) SO_2Cl_2, $CHCl_3$, rt	**21**	92[a]
10	**5**	(iii) 2 SO_2Cl_2, $CHCl_3$, rt	**21**	74[a]
11	**19**	(iii) 3 Br_2, $CHCl_3$, rt, bp, then silica gel	**24**, **25**, **26**	46 (**25**), 4 (**26**)
12	**19**	(iii) 3 Br_2, $CHCl_3$, rt; (iv) 1/2 K_2CO_3, CH_2Cl_2, rt	**26**, **27**	1 (**26**), 9 (**27**)
13	**28**	(iii) 2 Br_2, $CHCl_3$, rt; (v) 2 Br_2, $CHCl_3$, rt	**29**	22
14	**28**	(iii) 2 Br_2, $CHCl_3$, 0 °C to rt	**30**	50
15	**28**	(iii) 2 Br_2, $CHCl_3$, 0 °C to rt, then bp	**31**	35
16	**30**	(vi) 2 Br_2, $CHCl_3$, rt	**29**	67

[a] Virtual yield determined by ^{19}F NMR.

Table 3
Halogenations of 1,3-dicarbonyl derivatives **23**, **34**, **36**–**39**, **44**[a]



n	X	Starting compound	M	Product	Yield (%)
1	O	**36**	Na	**40**	60
2	O	**37**	Na	**41**	50
1	NH	**38**	K	**42**	26
2	NH	**39**	K	**43**	73

[a] Reagents and conditions: (i) Br_2 (2 equiv), $CHCl_3$, rt, 48 h; (ii) Br_2 (1 equiv), $CHCl_3$, rt, 20 h; (iii) Br_2 (1.1 equiv), $CHCl_3$, rt, 24 h; (iv) Br_2 (1 equiv), CH_2Cl_2, 0 °C to rt, 30 min; (v) SO_2Cl_2 (4 equiv), $Bz_2O_{2cat.}$, HCl/Et_2O, rt, 20 h; (vi) SO_2Cl_2 (7.4 equiv), $Bz_2O_{2cat.}$, HCl/Et_2O, rt, 48 h, bp, 40 h, rt, 7 days.

proposed structure. The NMR data of **22** are consistent with the parameters reported by Flores et al.[19] Only one set of signals was obvious in all NMR spectra measured, where the resonance of OH proton (δ_H=11.0) and chemical shift value of 5-C nuclei (δ_C=108.2) suggest strongly the enol structure of diketone **22** in the solution. Besides, the signal of CHBr moiety carbon (confirmed by DEPT135) appeared at 47.6 ppm, thus, the conclusion about the ω-Br-structure of **22** can be reached.

α-Halogen compounds **18**, **21** were found to be absolutely stable. In a substance or in a $CDCl_3$ solution they can be stored in a sealed flask at ambient temperature without any change for several weeks. Even after heating to reflux in $CHCl_3$ solution for 21 h (**18**) or to 220 °C in a substance (**21**) no dehydrohalogenation or rearrangement[21] into ω-halogen isomer of type **17** could be detected by NMR technique.

Upon treatment of the salt **19** with triple excess on elemental bromine an aromatization of the cyclohexanone ring occurred. However, the outcome of this reaction depended strongly on the reaction conditions. Bromination carried out at ambient temperature followed by the prolonged heating delivered compounds **24**–**26**, where bromophenols **25**, **26** could be isolated (Table 2, entry 11). When the product of the initial bromination was treated with K_2CO_3, phenols **26**, **27** were obtained (Table 2, entry 12).

The multiple halogenation of cyclohexanone framework could not be achieved applying NBS, Br_2 or SO_2Cl_2 [whether by the reaction of **5**, **19**, **20** with excess of halogenating agent (Table 2, entries 4–6, 8, 10–12) nor by the further halogenation of **18**, **21**]. Nevertheless, we managed to accomplish this task using boron chelate **28**[22] as a starting compound. Through a triple bromination with excess of bromine the 1,3-diketone **29** was formed (Table 2, entry 13). Use of two equiv of Br_2 allowed us to obtain dibromo-derivative **30** in 50% yield (Table 2, entry 14). Notewrthy, the reaction pathway in this case depends strongly on the reaction conditions: carried out under larger dilution this reaction afforded 4-bromo-2-(trifluoroacetyl)cyclohex-2-enone. It was isolated as *gem*-diol **31** (Table 2, entry 15), whose structure was confirmed by X-ray single-crystal investigation (Fig. 1). Diketone **29** could be obtained from **30**, too (Table 2, entry 16).

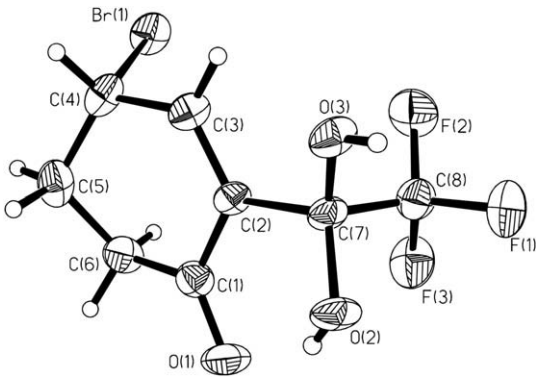
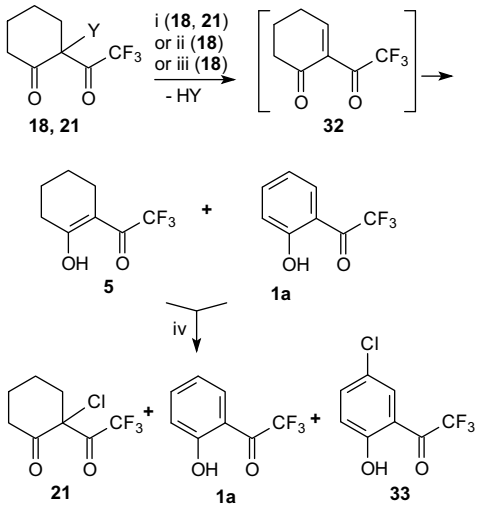


Figure 1. Molecular structure of compound **31** (thermal ellipsoids with 50% probability).

The equimolar mixtures of **1a** and **5** arose from the attempts of an oxidative aromatization of **18**, **21** regardless of the amount of the oxidizing agent employed (Scheme 3). Apparently, the intermediary formed endione **32** undergoes disproportionation rather than further oxidation by sulphur or DDQ occurs.[11] A thermolysis of **18** without any oxidizing agent gave similar results: maintaining at 240 °C for 20 min caused mixture of **1a** and **5**. As expected, compounds **1a** and **5** could not be separated by distillation, therefore a chlorination of the mixture was undertaken in order to recycle compound **5**. Unfortunately, phenol **1a** turned to be also reactive, and



Scheme 3. Oxidative aromatizations of 2-halogenated 1,3-diketones **18**, **21**. Reagents and conditions: (i) S_8 (0.125/0.5 equiv), 200–240 °C, 1–4 h, (ii) DDQ (2.5 equiv), benzene, bp, 4 h; (iii) 240 °C, 20 min; (iv) SO_2Cl_2 (3 equiv), CH_2Cl_2, rt, 60 h.

a mixture of **1a**, **21** and **33** was obtained (Scheme 3). Similarly, a thermolysis attempt with **29** yielded both brominated phenols **26** and **27**.

To pursue the topic of halogenation of fluorinated 1,3-dicarbonyls a little further, we involved several other compounds in our investigation. Upon treatment of lithium enolate of 3-benzoyl-1,1,1-trifluoroacetone with bromine the phenyl moiety bromination occurred as reported by Filyakova et al.[23] Introduction of a fluorine atom in a phenyl group allowed us to redirect this reaction: converting Li salt **34** the 2-bromo-1,3-diketone **35** was obtained (Table 3). Similarly, the bromination of alkali salts of 2-(trifluoroacetyl)lactones **36**, **37** and -lactams **38**, **39** proceeded smoothly to yield the corresponding 2-brominated compounds **40**–**43** (Table 3). Hahn et al. have pointed out that 2-chloro-1,1,1-trifluoroacetoacetic acid ethyl ester **45** cannot be obtained via chlorination of **44** with sulfuryl chloride,[16] and elemental chlorine is an indispensable reagent for this purpose.[6a,16,17a] In our hands, **45** could be synthesized readily with SO_2Cl_2. Moreover, we were able to control the chemoselectivity: using excess of SO_2Cl_2 the dichloro-derivative **46** was prepared in 61% yield (Table 3).

Only one set of signals was evident in the ^1H and ^{19}F NMR spectra of the 1,3-diketonates **10**, **11a**, **34**, verifying the presence of only one of two possible geometrical isomers at ambient temperature. Analogously to starting 1,3-dicarbonyls,[6,13] the enol was the predominant tautomeric form for 1,3-dicarbonyl products which possess a proton in the 2-position, as verified by NMR spectroscopy. The only exception was the 1,3-ketoester **45**, where the diketo form was detected solely. For the deuterated chloroform solutions of other enolizable 1,3-dicarbonyl compounds, only one set of signals was observed within the limits of detection, with resonance of the enol OH proton as the most characteristic feature. The deshielding degree of these protons (δ_H>11.0) corresponds to the presence of the hydrogen bond. An especially valuable information is provided by the $^5J_{F,H}$ splittings observed in the spectra of cyclic 1,3-dicarbonyl compounds and their Li salts. This coupling results probably from the through-space interaction of the nuclei, and confirms the U-type structure[24] of enolone moiety. As for fast 'enol–enol' tautomersim,[25,26] the $^3J_{H,F}$ coupling constant of CF_2H moiety in **9b**, **12** is 5.1–5.3 Hz; this suggests that the *endo*-enol is a preferred tautomeric form under measurement conditions.[28] The same conclusion can be reached for 3-formylthiochromanone **9d** considering the magnitude of $^3J_{H,H}$ coupling in the =CH–OH moiety.[29] These facts

are in accordance with the concept dealing with the *exo-endo*-enolization of 6-membered systems.[30]

Similarly to the parent phenol **1a**[31] and related compounds,[10] the synthesized phenols **1b**, **4**, **7**, **14**, **25**–**27**, **33** feature an intramolecular O–H···O hydrogen bond which manifests itself through the downfield shift of the OH protons (δ_H range 10.9/12.9). The observed $^5J_{F,H}$ splitting is in accordance with the U-structure of the compounds under discussion.

Beside the already mentioned compound **31**, several synthesized 2-halogenated 1,3-dicarbonyl compounds (**15**, **16**, **35**, **40**–**43**)[32] as well as of 3-(polyfluoroacyl)thiochromones **8a**–**c**[34] revealed the enhanced tendency to the hydrate formation. These hydrates are *gem*-diols across polyfluoroacyl moiety, as confirmed by NMR spectroscopy whereas two OH signals in the ^{1}H NMR spectra and δ_F values of $C(OH)_2CF_2R$ groups are particularly characteristic. Within the **8a–c** array the affinity to the hydrate formation changes as follows: **8a** (R_F=CF_3)>>**8c** (C_2F_5)>**8b** (C_2F_4H).[34]

The reactivity of some prepared 2-halogenated 1,3-dicarbonyls (or their hydrates, respectively) towards the simplest binucleophiles has been studied. The pyrazole **47** was isolated in 42% yield reacting **22** with hydrazine hydrate. In the case of monohydrate of **35** as substrate the 4-Br-pyrazole **48** was obtained with the 4-H (**49**) and 4-MeO (**50**) analogs as by-products (Chart 2). Probably, the methoxy derivatives **47** and **50** arose from the substitution of bromine atom with the reaction solvent molecule. Reaction of **35**·H_2O with thiourea provided 2-aminothiazole **51** in 27% yield.

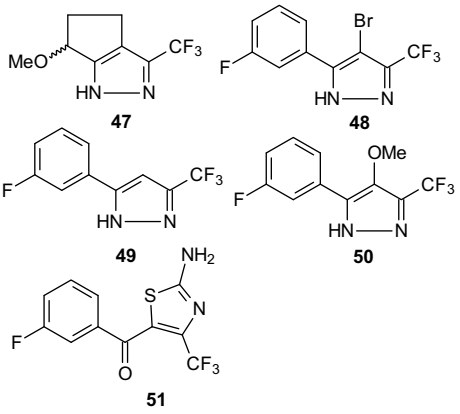
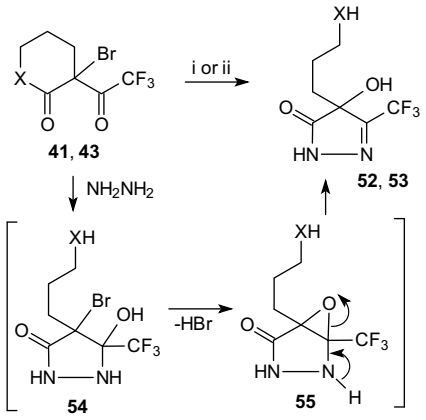


Chart 2.

Table 4
Reaction of 2-bromo compounds **41**, **43**[a] with hydrazine[b]



X	Starting compound	Product	Yield (%)
O	**41**	**52**	94
NH	**43**	**53**[c]	75

[a] As monohydrates.
[b] Reagents and conditions: (i) $NH_2NH_2·H_2O$ (2.5 equiv), MeOH, bp, 20 h; (ii) $NH_2NH_2·H_2O$ (1 equiv), MeOH, bp, 12 h, then concd aq HBr.
[c] Isolated as an HBr salt.

Somewhat unexpected results were obtained from the reaction of hydrates of 2-bromolactone **41** and -lactam **43** with hydrazine. In this case, 4-hydroxy-2*H*-pyrazol-3-ones **52** and **53** were obtained in 94 and 75% yields, respectively (Table 4). In our opinion, the mechanism of reaction consists of intermediary formation of 5-hydroxypyrazol-3-one **54**,[18d,36] followed by an epoxide ring closure. The 'aromatization' of the derived bicycle **55** furnished the final 4-hydroxypyrazoles **52**, **53**. The plausibility of such mechanism with an intermediary epoxide formation is supported by the absence of 2-methoxy analogs of **52**, **53** in the reaction mixture, although methanol was used as a reaction medium (compare to the formation of **50**). The pyrrolidine or furan intermediates (due to ring closure participating XH moiety) have not been detected.

3. Conclusion

We have carried out a detailed study of the behaviour of cyclic and linear fluorinated 1,3-dicarbonyls and their boron and metal derivatives towards common halogenating agents. The optimal reaction conditions for the straightforward synthesis of mono-, di-, and trihalogenated products were established. The synthetic value of the polyfunctional compounds obtained was demonstrated by the synthesis of several new heterocyclic derivatives. An aromatization via the halogenation–dehydrohalogenation sequence was shown to be a rewarding synthetic route to 2-(fluoroacyl)phenols and previously unknown 3-(fluoroacyl)thiochromones. The synthesis of the parent 2-(trifluoroacetyl)phenol **1a** could not be achieved using this method, however, we succeeded to solve this problem in other ways. This chemistry will be reported in a forthcoming work.[37]

4. Experimental

4.1. General

Melting and boiling points are uncorrected. ^{1}H (200 MHz), $^{13}C\{^1H\}$ (50 or 100 MHz), and ^{19}F (188 MHz) NMR spectra were recorded at 22 °C on a Bruker DPX-200, Bruker DRX-400 and Jeol JNM-LA 400 spectrometers scaled to TMS (^{1}H and ^{13}C) and CCl_3F (^{19}F). NMR chemical shifts are referenced with respect to the residual solvent signals (^{1}H: δ=7.25, 2.05, 2.50 and 3.31 for $CDCl_3$, acetone-d_6, DMSO-d_6, and MeOH-d_4, respectively; ^{13}C: δ=77.0, 29.9 and 49.2 for $CDCl_3$, acetone-d_6, and MeOH-d_4, respectively). IR spectra were recorded on Perkin–Elmer Spectrum BX-II instrument. Reaction progress was monitored by ^{19}F NMR spectroscopy for samples from the reaction mixtures dissolved in $CHCl_3$ containing hexafluorobenzene as an internal reference (without lock). Signals in the ^{13}C NMR spectra of compounds **18**, **22**, **29** were assigned on the basis of DEPT135 experiments. MS was carried out by EI (70 eV) on a Finnigan MAT-8200 and MAT-95 spectrometers, by CI (NH_3 as reactant gas) on a MAT-8200 spectrometer, and by ESI on a Esquire instrument. HRMS was carried out by the peak matching method on a Finnigan MAT-95 spectrometer. 1,3-Diketone **5**,[13] 2,3-bis-(trimethylsiloxy)cyclohexa-1,3-diene,[38] salts **19**, **20**, **36**, **37** as well as chelates **23**, **28**[22] were prepared according to the published procedures. 2-(Trifluoroacetyl)lactams **38**, **39** were prepared by Claisen condensations of *N*-vinyl-2-pyrrolidone or *N*-diethoxymethyl-2-piperidone, respectively, with CF_3CO_2Et in THF using NaH as a base, following by removal of the protecting group. The target lactams were isolated as monohydrates (i.e., as *gem*-diols across the trifluoroacetyl moiety), prior to use, the water was removed with boiling toluene azeotropically.[39] 85% α-Tetralone by

Acros Organics was distilled prior to use. Other chemicals are commercially available and were used as purchased unless otherwise specified. Reactions in anhyd solvents ($CHCl_3$ and CH_2Cl_2 from P_2O_5; benzene, toluene, Et_2O and THF from sodium/benzophenone ketyl) were performed in oven-dried glassware under a static N_2 atmosphere. Silicagel grade 60, 320–630 mesh (MP Biomedicals Germany GmbH) was used for column chromatography.

4.2. X-ray crystallography of 31

Crystallographic measurement was performed at −100(2) °C on an Siemens-P4 diffractometer with a graphite monochromated Mo Kα radiation (λ 71.073 pm) and the low-temperature device LT2. The structure was solved by direct methods and refined by full-matrix least-squares technique on F^2 using SHELX[40,41] program package. All non-H-atoms were refined anisotropically, the positions of the other hydrogen atoms were calculated as a 'riding' model. An absorption correction was carried out using empirical (DIFABS) method.

The diffraction-quality single crystals of **31** were obtained via crystallization from toluene. X-ray crystal data for **31**: Colorless prisms; Formula: $C_8H_8BrF_3O_3$; Molecular weight: 289.05; Crystal size: 0.60×0.40×0.20 mm^3; Crystal system: monoclinic; Space group: $P2_1/n$; Unit cell dimensions: a=615.0(2), b=1043.8(2), c=1555.9(4) pm, β=96.161(2)°; V=0.9930(5) nm^3; Z=4; D=1.933 g cm^{-3}; Difference electron density 0.828 and −0.854 e Å^{-3}; Index range $-1\le h\le 7$, $-13\le k\le 13$, $-20\le l\le 20$; 2θ range 2.63 to 27.53°; 5701 reflections collected, 2278 [R(int)=0.0502]; Completeness to θ_{max}=27.53°: 99.9%; Data/restraints/parameter 2278/0/143; Goodness-of-fit at F^2 1.030; Final R indices [$I>2\sigma(I)$]: R_1=0.0448, wR_2=0.1171; R indices (all data): R_1=0.0555, wR_2=0.1231.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication no CCDC730655 and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].

4.3. Phenyl trifluoroacetate (3a)

Phenol (94.0 g, 1.0 mol) was placed into a 500 mL two necked round bottom flask equipped with a magnetic stirring bar, reflux condenser, dropping funnel and drying tube ($CaCl_2$). Trifluoroacetic anhydride (220.0 g, 1.05 mol) was added, where approx 4/5 were added quickly at rt, after that the well stirred mixture was heated gradually. At ca. 60 °C (oil bath temperature) a vigorous reaction started, the phenol was dissolved and the resulted soln become blue. The residual trifluoroacetic anhydride was added dropwise, and the mixture was heated to reflux for 1 h (oil bath temperature 110 °C). Trifluoroacetic acid formed was distilled off using Vigreux-column, and the distillation of the residue afforded **3a**. Yield: 177.3 g (93%); colorless liquid; bp 147–149 °C/760 Torr, lit.[42] bp 148–149 °C/760 Torr; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.19–7.29 (m, 2H), 7.33–7.49 (m, 3H); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−75.3 (s, CF_3).

4.4. *p*-Tolyl trifluoroacetate (3b)

p-Cresol (27.0 g, 0.25 mol) was placed into a 250 mL two necked round bottom flask equipped with a magnetic stirring bar, reflux condenser, dropping funnel and drying tube ($CaCl_2$) and ice cooled. Trifluoroacetic anhydride (52.5 g, 0.25 mol) was added dropwise at this temperature, the well stirred mixture was allowed to reach rt, and then heated gradually. After heating to reflux for 30 min (oil bath temperature 100 °C), the mixture was stirred overnight at room temperature. Trifluoroacetic acid formed was distilled off using Vigreux-column, and the residue was distilled in vacuo to furnish **3b**.

Yield: 47.7 g (93%); pale yellow liquid; bp 69–70 °C/15 Torr, lit.[43] bp 68 °C/18 Torr; the physical properties as well as the ^{1}H, ^{19}F NMR data matched with those described in the literature.[43]

4.5. Fries-rearrangement of 3a

Powdered $AlCl_3$ (138.0 g, 1.04 mol) was placed into a 2 L round bottom flask equipped with a magnetic stirring bar, dropping funnel and effective reflux condenser with an outlet pipe (to remove the HCl formed). **3a** (177.3 g, 0.93 mol) was added dropwise under stirring at rt. The mixture was heated gradually to 100 °C (oil bath temperature). After maintaining at this temperature for 1 h the reaction mixture become black and foamed up (caution: in the case of vigorous reaction the oil bath should be removed immediately, and the flask has to be cooled down with ice–water mixture). The mixture was stirred at 100 °C (oil bath temperature) for additional 1 h and then left at 55–60 °C overnight. After cooling down to room temperature, 10% aq HCl was added very carefully until the black crust was crushed, and the HCl gas evolution was discontinued. CH_2Cl_2 (300 mL) was added, the mixture was filtered, and the organic layer was separated. After additional extraction with CH_2Cl_2 (4×70 mL) the combined organic phases were dried (Na_2SO_4) and concentrated. The oily residue was distilled in vacuo to afford a yellow liquid (88.0 g, boiling interval 71–77 °C/20 Torr, 1:4 mixture of phenol and **1a** by NMR). This mixture was added dropwise to an ice cooled mixture of $Cu(OAc)_2\cdot H_2O$ (92 g), concd aq NH_4OH (200 mL) and ethanol (200 mL) under stirring. The mixture was stirred for 48 h at rt, the brownish precipitate of **2a**·Cu/2 complex was filtered off and air-dried. It was treated with concd aq HCl until solid phase disappeared. After extraction with CH_2Cl_2 (4×150 mL) the combined organic phases were dried (Na_2SO_4) and concentrated. The oily residue was purified via vacuum distillation using Vigreux-column to furnish **1a**. Yield: 58.0 g (33%); volatile yellow liquid (solidified in a refrigerator); bp 80–85 °C/35 Torr, lit.[8] bp 92 °C/55 Torr; ^{1}H NMR (200 MHz, $CDCl_3$): δ=6.99 (ddd, $^3J_{H,H}$=8.3 Hz, $^3J_{H,H}$=7.2 Hz, $^4J_{H,H}$=1.2 Hz, 1H, 4-H), 7.07 (dd, $^3J_{H,H}$=8.5 Hz, 1H, 6-H), 7.61 (ddd, $^4J_{H,H}$=1.5 Hz, 1H, 5-H), 7.81 (dm, 1H, 3-H), 11.05 (s, 1H, OH); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−70.78 (d, $^5J_{F,H}$=2.2 Hz, CF_3).

4.6. Fries-rearrangement of 3b

Powdered $AlCl_3$ (36.0 g, 0.27 mol) was placed into a 1 L round bottom flask equipped with a magnetic stirring bar, dropping funnel and effective reflux condenser with an outlet pipe (to remove the HCl formed). **3b** (47.0 g, 0.23 mol) was added dropwise under stirring at rt. The mixture was heated gradually to 100 °C (oil bath temperature). After maintaining at this temperature for 1 h the reaction mixture become black and foamed up (caution: in the case of vigorous reaction the oil bath should be removed immediately, and the flask has to be cooled down with ice–water mixture). The mixture was stirred at 100 °C (oil bath temperature) for 14 h. After cooling down to room temperature, 10% aq HCl was added very carefully until the black crust was crushed, and the HCl gas evolution was discontinued. After extraction with diethyl ether (3×70 mL) the combined organic phases were dried (Na_2SO_4) and concentrated. The oily residue was distilled in vacuo to afford a yellow liquid (25.7 g, bp 94–95 °C/20 Torr, 1:3 mixture of *p*-cresol and **1b** by NMR) which solidified in a refrigerator. The twofold recrystallization from hexane at −30 °C afforded **1b**. The oily residue from the first distillation was distilled in a deeper vacuum to provide a yellow liquid (bp 82–84 °C/6 Torr), which solidified immediately and was recrystallized from hexane at −30 °C to afford compound **4**.

*4.6.1. 4-Methyl-2-(trifluoroacetyl)phenol (**1b**)*

Yield: 17.0 g (36%); yellow needles; mp 42–44 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.33 (s, 3H, CH_3), 6.98 (d, $^3J_{H,H}$=8.3 Hz, 1H, 6-H), 7.43 (dd, $^4J_{H,H}$=2.0 Hz, 1H, 5-H), 7.6 (br s, 1H, 3-H), 10.92 (s, 1H, OH); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−70.64 (d, $^5J_{F,H}$=2.3 Hz, CF_3); MS (EI, 70 eV): *m*/*z* (%)=204 (88) [M^+], 135 (100) [$M-CF_3$]$^+$, 107 (22) [$M-CF_3CO$]$^+$; HRMS: *m*/*z* [M^+] calcd for $C_9H_7F_3O_2$: 204.0398; found: 204.0400; −0.8 ppm, −0.2 mu, $R\approx$9000.

*4.6.2. 4-Methyl-2-(trichloroacetyl)phenol (**4**)*

Yield: 2.7 g (5%); yellow needles; bp 82–84 °C/6 Torr, mp 84–85 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.32 (s, 3H, CH_3), 6.99 (d, $^3J_{H,H}$=8.7 Hz, 1H, 6-H), 7.37 (dd, $^4J_{H,H}$=1.8 Hz, 1H, 5-H), 8.1 (br s, 1H, 3-H), 11.00 (s, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ=20.7 (CH_3), 95.0 (CCl_3), 111.3 (2-C), 119.2, 131.5, 139.3 (3-C, 5-C, 6-C), 127.7 (4-C), 163.1 (1-C), 185.3 (7-C); MS (EI, 70 eV): *m*/*z* (%)=252 (7) [M^+], 135 (100) [$M-CCl_3$]$^+$, 107 (11) [$M-COCCl_3$]$^+$; HRMS: *m*/*z* [M^+] calcd for $C_9H_7{}^{35}Cl_3O_2$: 251.9512; found: 251.9506; 2.2 ppm, 0.6 mu, $R\approx$10,000.

4.7. Trifluoroacetylation of dilithiated *o*-bromophenol

Anhyd diethyl ether (150 mL) was placed into a 1 L round bottom flask equipped with magnetic stirring bar, thermometer, dropping funnel and N_2 inlet. A soln of butyllithium in hexane (64 mL, 0.16 mol) was added dropwise while maintaining the mixture at −40 °C. After stirring at this temperature for 10 min the mixture was allowed to reach −25 °C, and *o*-bromophenol (12.5 g, 72.3 mmol) was added dropwise at this temperature. The reaction mixture was allowed to reach rt and stirred for 2 h at this temperature. The pale yellow soln formed was cooled to −90 °C, and CF_3CO_2Et (11.3 g, 80 mmol) was added carefully at this temperature. After stirring at −90 °C for 10 min the temperature was allowed to increase to rt within 1 h, stirred at rt for 5 min, cooled to −5 °C and then quenched by the dropwise addition of 10% aq HCl (200 mL) and brine (100 mL). The phases were separated, the aqueous phase was extracted with diethyl ether (3×70 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated. The liquid left was distilled in vacuo twice to provide mixture of **1a** and butylbromide (by NMR) as a yellow liquid, 4.2 g, bp 70 °C/15 Torr. This liquid was dissolved in diethyl ether (10 mL) and treated with 5% aq NaOH to pH=14. The phases were separated, and diethyl ether (10 mL) was added to a aqueous phase. After treatment of this mixture with 10% aq HCl to pH=1 the organic phase was separated, the aqueous phase was extracted with diethyl ether (2×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was distilled in vacuo to afford **1a**, yield: 3.0 g (22%).

4.8. Lithium 1,3-diketonates 10, 11a, 34. General procedure

A soln of the appropriate ketone (46 mmol) and CF_3CO_2Et (53 mmol) in dried benzene (20 mL) was added carefully to a magnetically stirred suspension of finely powdered LiH (0.40 g, 50 mmol) in benzene (150 mL). After complete addition, few drops of anhyd EtOH were added, and the mixture was heated at reflux (**10**: for 4 h, **11a**, **34**: for 20 h). The mixture was cooled to rt, and (for **10**—after stirring at rt for additional 16 h) precipitate was filtered off, washed with pentane (2×20 mL) and dried in vacuo.

*4.8.1. Lithium 2-(trifluoroacetyl)-1-tetralonate (**10**)*

Yield: 94%; white powder; mp >230 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ=2.50–2.82 (m, 4H, 3,4-H), 7.10–7.41 (m, 3H, 5,6,7-H), 8.03 (d, $^3J_{H,H}$=7.0 Hz, 1H, 8-H); ^{19}F NMR (188 MHz, acetone-d_6): δ=−69.0 (s, CF_3).

*4.8.2. Lithium 3-(trifluoroacetyl)thiochromanonate (**11a**)*

Yield: 74%; yellow solid; mp 270–272 °C; ^{1}H NMR (200 MHz, acetone-d_6): δ=3.83 (q, $^5J_{H,F}$=1.1 Hz, 2H, 2-H), 7.19 [ddd, $^3J_{H,H}$=7.8 Hz, $^3J_{H,H}$=5.6 Hz, $^4J_{H,H}$=3.0 Hz, 1H, 6(7)-H], 7.26–7.36 [m, 2H, 7(6)-H, 8-H], 8.03 (ddd, $^3J_{H,H}$=7.7 Hz, $^4J_{H,H}$=1.4 Hz, $^4J_{H,H}$=0.9 Hz, 1H, 5-H); ^{19}F NMR (188 MHz, acetone-d_6): δ=−70.47 (t, $^5J_{F,H}$=1.0 Hz, CF_3); MS [ESI, acetone–CH_3CN (1:10), positive]: *m*/*z* (%)=539 (50) [2A+3Li]$^+$; MS [ESI, acetone-CH_3CN (1:10), negative]: *m*/*z* (%)=525 (32) [2A+Li]$^-$, 259 (100) [A^-].

*4.8.3. Lithium 4,4,4-trifluoro-1-(3-fluorophenyl)butane-1,3-dionate (**34**)*

Yield: 77%; white powder; mp >285 °C (dec); ^{1}H NMR (200 MHz, acetone-d_6): δ=6.23 (s, 1H, 2-H), 7.24 (dddd, $^3J_{H,F}$=8.4 Hz, $^3J_{H,H}$=8.4 Hz, $^4J_{H,H}$=2.7 Hz, $^4J_{H,H}$=0.9 Hz, 1H, *p*-H), 7.47 (ddd, $^3J_{H,H}$=8.0 Hz, $^4J_{H,F}$=5.7 Hz, 1H, *m*-H), 7.64 (ddd, $^3J_{H,F}$=10.2 Hz, $^4J_{H,H}$=1.5 Hz, 1H, *o*-H), 7.75 (ddd, 1H, *o*′-H); ^{19}F NMR (188 MHz, acetone-d_6): δ=−115.09 (ddd, $^3J_{F,H}$=10.3 Hz, $^3J_{F,H}$=8.6 Hz, $^4J_{F,H}$=5.8 Hz, 1F, C_6H_4F), −76.84 (s, 3F, CF_3); MS [ESI, acetone–CH_3CN (1:10), positive]: *m*/*z* (%)=487 (12) [2A+3 Li]$^+$, 123 (100) [FC_6H_4CO]$^+$; MS [ESI, acetone–CH_3CN (1:10), negative]: *m*/*z* (%)=473 (92) [2A+Li]$^-$, 233 (100) [A^-].

4.9. 1,3-Diketones 6, 9a. General procedure

A suspension of salt **10** or **11a** (32 mmol) in CH_2Cl_2 (100 mL) was treated with 10% aq H_2SO_4 (50 mL), the organic layer was separated. After additional extraction with CH_2Cl_2 (3×50 mL) the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and evaporated to give product of sufficient quality, which was converted without further purification.

*4.9.1. 2-(Trifluoroacetyl)-1-tetralone (**6**)*

Yield: 75%; yellow crystals; mp 50 °C, lit.[13] mp 51–52 °C; the physical properties as well as the ^{1}H, ^{13}C and ^{19}F NMR data matched with those described in the literature.[27a]

*4.9.2. 3-(Trifluoroacetyl)thiochromanone (**9a**)*

Yield: 93%; yellow crystals; mp 77–80 °C; (Found: C, 50.92; H, 2.55. $C_{11}H_7F_3O_2S$ requires: C, 50.77; H, 2.71%.) ^{1}H NMR (200 MHz, $CDCl_3$): δ=3.79 (q, $^5J_{H,F}$=0.8 Hz, 2H, 2-H), 7.22–7.47 (m, 3H, 6,7,8-H), 7.99 (dd, $^3J_{H,H}$=7.8 Hz, $^4J_{H,H}$=1.0 Hz, 1H, 5-H), 15.62 (s, 1H, OH); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−71.99 (t, $^5J_{F,H}$=0.7 Hz, CF_3); MS (EI, 70 eV): *m*/*z* (%)=260 (100) [M^+], 240 (30) [$M-HF$]$^+$, 191 (20) [$M-CF_3$]$^+$, 163 (32) [$M-CF_3CO$]$^+$. Yield 66%, mp 228–229 °C.

4.10. 1,3-Diketones 9b–d. General procedure

A soln of thiochromanone (2.0 g, 12 mmol) and appropriate ester (**9b**: $HCF_2CF_2CO_2Me$, **9c**: $C_2F_5CO_2Me$, **9d**: HCO_2Et, 15 mmol) in dried benzene (25 mL) was added carefully to a well stirred suspension of finely powdered lithium hydride (0.12 g, 15 mmol) in benzene (40 mL). After complete addition, the mixture was heated at reflux (**9b**,**d**: for 12 h, **9c**: 16 h). The mixture was cooled to rt, and concentrated in vacuo to about one-half. Hexane (25 mL) was added, and the precipitated lithium salt (yellow solid) was filtered off, washed with hexane (2×15 mL) and dried in vacuo. A suspension of the solid in CH_2Cl_2 (30 mL) was treated with 10% H_2SO_4 (25 mL), the organic layer was separated. After additional extraction with CH_2Cl_2 (2×20 mL), the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and evaporated to leave a product (in the case of **9c**,**d** the quality of the product was satisfactory and these compounds were converted without further purification).

*4.10.1. 3-(2,2,3,3-Tetrafluoropropanoyl)thiochromanone (**9b**)*

Yield: 77%; red oil [after purification of the crude product by column chromatography ($CHCl_3$)]; (Found: C, 49.75; H, 2.37.

$C_{12}H_8F_4O_2S$ requires: C, 49.32; H, 2.76%.) ^{1}H NMR (200 MHz, $CDCl_3$): δ=3.89 (t, $^5J_{H,F}$=0.8 Hz, 2H, 2-H), 6.22 (tt, $^2J_{H,F}$=52.7 Hz, $^3J_{H,F}$=5.3 Hz, 1H, CF_2H), 7.20–7.44 (m, 3H, 6,7,8-H), 7.99 (ddd, $^3J_{H,H}$=7.9 Hz, $^4J_{H,H}$=1.5 Hz, $^5J_{H,H}\approx$0.6 Hz, 1H, 5-H), 16.01 (s, 1H, OH); ^{19}F NMR (188.3 MHz, $CDCl_3$): δ=−139.21 (dm, $^2J_{F,H}$=52.6 Hz, 2F, CF_2H), −119.82 (m, 2F, $COCF_2$); MS (EI, 70 eV): *m*/*z* (%)=292 (100) [M^+], 272 (31) [M−HF]$^+$, 241(21) [M−CF_2H]$^+$, 191 (52) [M−CF_2CF_2H]$^+$, 189 (28) [M−HCF_2CF_2H−2H]$^+$, 163 (64) [M−$COCF_2CF_2H$]$^+$.

*4.10.2. 3-(Pentafluoropropanoyl)thiochromanone (**9c**)*

Yield 74%; yellow solid; mp 55–56 °C; (Found: C, 46.55; H 2.35. $C_{12}H_7F_5O_2S$ requires: C, 46.46; H, 2.27%.) ^{1}H NMR (200 MHz, $CDCl_3$): δ=3.84 (t, $^5J_{H,F}$=0.8 Hz, 2H, 2-H), 7.22–7.47 (m, 3H, 6,7,8-H), 8.02 (ddd, $^3J_{H,H}$=7.9 Hz, $^4J_{H,H}$=1.5 Hz, $^5J_{H,H}\approx$0.6 Hz, 1H, 5-H), 16.07 (s, 1H, OH); ^{19}F NMR (188.3 MHz, $CDCl_3$): δ=−117.36 (m, 2F, CF_2), −82.56 (t, $^3J_{F,F}$=1.5 Hz, 3F, CF_3); MS (EI, 70 eV): *m*/*z* (%)=310 (100) [M^+], 241 (24) [M−CF_3]$^+$, 191 (60) [M−C_2F_5]$^+$, 189 (26) [M−C_2F_5−2H]$^+$, 163 (60) [M−COC_2F_5]$^+$, 69 (14) [CF_3^+].

*4.10.3. 3-Formylthiochromanone (**9d**)*

Yield: 85%; yellow oil; the physical and spectral properties data are in accordance with those described in the literature;[44] ^{1}H NMR (200 MHz, $CDCl_3$): δ=3.67 (s, 2H, 2-H), 7.19–7.41 (m, 3H, 6,7,8-H), 7.99 (dd, $^3J_{H,H}$=7.8 Hz, $^4J_{H,H}$=1.0 Hz, 1H, 5-H), 8.39 (d, $^3J_{H,H}$=3.9 Hz, 1H, CHOH), 14.80 (d, $^3J_{H,H}$=5.4 Hz, 1H, OH).

4.11. 3-(Polyfluoroacyl)thiochromones 8a–c. General procedure

Freshly distilled SO_2Cl_2 (1.0 g, 7.7 mmol) was added carefully to a well stirred soln of the appropriate 3-acylthiochromanone **9** (6.5 mmol) in $CHCl_3$ (100 mL). After stirring at rt for 16 h, the formed yellow soln was evaporated under reduced pressure. The resulting yellow solid was purified by recrystallization from heptane.

*4.11.1. 3-(Trifluoroacetyl)thiochromone (**8a**)*

Yield: 94%; pale yellow needles;[34] mp 126–127 °C; (Found: C, 51.10; H, 1.99. $C_{11}H_5F_3O_2S$ requires: C, 51.17; H, 1.95%.) the diketo and monohydrate (*gem*-diol) forms were registered by NMR in $CDCl_3$ (77:23, respectively) and THF (93:7, respectively) solns as well as by IR spectroscopy; IR (KBr) 3243, 3029, 1705, 1633, 1600, 1588, 1557, 1510 cm^{-1}; MS (EI, 70 eV): *m*/*z* (%)=258 (40) [M^+], 189 (100) [M−CF_3]$^+$, 161 (6) [M−CF_3CO]$^+$.

*4.11.1.1. Diketo form of **8a**.* ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.59–7.73 (m, 3H, 6,7,8-H), 8.59 (dm, $^3J_{H,H}$=7.8 Hz, 1H, 5-H), 8.67 (s, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=115.9 (q, $^1J_{C,F}$=289.7 Hz, CF_3), 126.9, 129.2, 129.4, 129.5, 132.7, 132.9, 135.0 (3-C, C_6H_4), 148.4 (2-C), 176.4 (4-C), 181.8 (q, $^2J_{C,F}$=38.5 Hz, $COCF_3$); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−74.50 (s, $COCF_3$); ^{19}F NMR (188 MHz, anhyd THF, without lock): δ=−75.6 (s, $COCF_3$).

*4.11.1.2. Monohydrate form of **8a**.* ^{1}H NMR (200 MHz, $CDCl_3$): δ=6.6 (br s, 2H, 2×OH), 7.59–7.73 (m, 3H, 6,7,8-H), 8.59 (dm, $^3J_{H,H}$=7.8 Hz, 1H, 5-H), 8.64 (s, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=94.4 (q, $^2J_{C,F}$=33.9 Hz, C–CF_3), 122.9 (q, CF_3, $^1J_{C,F}$=289.4 Hz), 126.7, 127.4, 128.7, 129.1, 131.3, 132.4, 137.0 (3-C, C_6H_4), 143.6 (2-C), 180.7 (4-C); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−86.62 [s, $C(OH)_2CF_3$]; ^{19}F NMR (188 MHz, anhyd THF, without lock): δ=−87.0 [s, $C(OH)_2CF_3$].

*4.11.2. 3-(2,2,3,3-Tetrafluoropropanoyl)thiochromone (**8b**)*

Yield: 74%; pale yellow needles;[34] mp 100–102 °C; (Found: C, 49.78; H, 2.06. $C_{12}H_6F_4O_2S$ requires: C, 49.66; H, 2.08%.) ^{1}H NMR (200 MHz, $CDCl_3$): δ=6.82 (tt, $^2J_{H,F}$=53.6 Hz, $^3J_{H,F}$=5.6 Hz, 1H, CF_2H), 7.60–7.76 (m, 3H, 6,7,8-H), 8.53 (d, $^3J_{H,H}$=7.8 Hz, 1H, 5-H), 8.59 (s, 1H, 2-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=109.6 (tt, $^1J_{C,F}$=252.4 Hz, $^2J_{C,F}$=30.6 Hz, CF_2H), 110.8 (tt, $^1J_{C,F}$=261.4 Hz, $^2J_{C,F}$=27.1 Hz, $COCF_2$), 127.0, 128.9, 129.3, 131.0, 132.6, 132.8, 135.5 (3-C, C_6H_4), 147.8 (2-C), 177.3 (4-C), 187.8 (t, $^2J_{C,F}$=29.0 Hz, $COCF_2$); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−137.50 (dt, $^2J_{F,H}$=53.6 Hz, $^3J_{F,F}$=7.2 Hz, 2F, CF_2H), −123.02 (m, 2F, $COCF_2$); MS (EI, 70 eV): *m*/*z* (%)=290 (32) [M^+], 189 (100) [M−CF_2CF_2H]$^+$, 161 (8) [M−$COCF_2CF_2H$]$^+$.

*4.11.3. 3-(Pentafluoropropanoyl)thiochromone (**8c**)*

Yield: 85%; pale yellow crystals;[34] mp 98–100 °C; (Found: C, 46.50; H, 1.55. $C_{12}H_5F_5O_2S$ requires: C, 46.76; H, 1.64%.) the diketo and monohydrate (*gem*-diol) forms were registered by NMR spectroscopy in $CDCl_3$ (94:6, respectively) soln; MS (EI, 70 eV): *m*/*z* (%)=308 (24) [M^+], 189 (100) [M−C_2F_5]$^+$, 161 (7) [M−COC_2F_5]$^+$.

*4.11.3.1. Diketo form of **8c**.* ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.60–7.76 (m, 3H, 6,7,8-H), 8.53–8.64 (m, 1H, 5-H), 8.47 (s, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=107.2 (tq, $^1J_{C,F}$=271.4 Hz, $^2J_{C,F}$=36.3 Hz, CF_2), 118.2 (qt, $^1J_{C,F}$=288.8 Hz, $^2J_{C,F}$=33.6 Hz, CF_3), 126.9, 128.9, 129.2, 130.8, 132.7, 132.5, 135.3 (3-C, C_6H_4), 146.5 (2-C), 176.5 (4-C), 186.0 (t, $^2J_{C,F}$=29.4 Hz, $COCF_2$); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−119.47 (q, $^3J_{F,F}$=1.0 Hz, 2F, CF_2), −81.28 (t, $^3J_{F,F}$=1.0 Hz, 3F, CF_3).

*4.11.3.2. Monohydrate form of **8c**.* ^{1}H NMR (200 MHz, $CDCl_3$): δ=6.5 (br s, 2H, 2×OH), other signals are overlapped by more intensive signals of the most abundant form; ^{19}F NMR (188 MHz, $CDCl_3$): δ=−125.89 (s, 2F, CF_2), −78.89 (s, 3F, CF_3).

*4.11.4. 3-Formylthiochromone (**8d**)*

Freshly distilled SO_2Cl_2 (1.5 g, 11.4 mmol) was added carefully to a well stirred soln of **9d** (2.0 g, 10.4 mmol) in $CHCl_3$ (100 mL). After stirring at rt for 20 h, the formed orange soln was evaporated under reduced pressure. The resulting brown semi-solid was purified by filtration through a pad of silica gel (10 cm) to give a product as a yellow powder. Yield: 1.3 g (67%); mp 157–158 °C, lit.[45] mp 162–163 °C; the ^{1}H NMR data matched with those described in the literature.[45]

4.12. Chlorination of lithium salt 11a

Freshly distilled SO_2Cl_2 (0.20 g, 1.5 mmol) was added carefully to a well stirred suspension of **11a** (0.38 g, 1.4 mmol) in $CHCl_3$ (30 mL). After stirring at rt for 20 h, the formed yellow soln with a white precipitate was evaporated under reduced pressure. After extraction of the organic part with boiling heptane, LiCl was removed by filtration. The filtrate was cooled to cause precipitation of thiochromone **8a** which was filtered off and dried in vacuo. Yield: 0.10 g (21%).

4.13. 2-Chloro-2-trifluoroacetyl-1-tetralone (15), monohydrate

4.13.1. Method A

Freshly distilled SO_2Cl_2 (1.9 g, 14 mmol) was added carefully to a well stirred soln of 1,3-diketone **6** (3.0 g, g, 1.4 mmol) in $CHCl_3$ (100 mL). After stirring at rt for 2 h, the formed yellow soln was heated at reflux for 4 h, and stirred at rt for 48 h. The reaction mixture was concentrated in vacuo, the residue (yellow oil) solidified overnight. Recrystallization from heptane afforded monohydrate of **15**. Yield: 2.6 g (71%); colorless crystals; mp 130 °C; (Found: C, 48.64; H, 3.28. $C_{12}H_{10}ClF_3O_3$ requires: C, 48.92; H, 3.42%.) ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.62–2.68 (m, 2H, CH_2), 2.96, 3.32 (AB-system, two ddd, 2×1H, J_{AB}=17.0, $^3J_{Ha,H}$=$^3J_{Ha,H}$=3.4 Hz, $^3J_{Hb,H}$=9.2 Hz, $^3J_{Hb,H}$=6.9 Hz), 5.3, 5.7 (both s, 2×1H, 2×OH), 7.27–7.43 (m, 2H, Ar), 7.59 [dd, $^3J_{H,H}$=$^3J_{H,H}$=7.4 Hz, 1H, 6(7)-H], 8.11 (d, $^3J_{H,H}$=7.9 Hz, 1H, 8-H); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−77.92 (s, CF_3).

4.13.2. Method B

Freshly distilled SO_2Cl_2 (0.12 g, 0.9 mmol) was added carefully to a well stirred suspension of salt **10** (0.20 g, 0.8 mmol) in $CHCl_3$ (7 mL). After stirring at rt for 16 h in the sealed flask, the precipitate of LiCl was removed by filtration. The filtrate was concentrated in vacuo, the residue (yellow oil) solidified overnight. Recrystallization from heptane afforded monohydrate of **15**. Yield: 0.14 g (59%).

4.14. 2-Bromo-2-trifluoroacetyl-1-tetralone (16), monohydrate

4.14.1. Method A

Br_2 (0.35 g, 2.2 mmol) was added carefully to a well stirred soln of 1,3-diketone **6** (0.47 g, 2.2 mmol) in $CHCl_3$ (30 mL). After stirring at rt for 16 h, the formed orange soln was heated at reflux for 22 h and stirred at rt for 20 h. The reaction mixture was concentrated without vacuum, the residue (yellow oil) solidified. Recrystallization from heptane afforded monohydrate of **16**. Yield: 0.35 g (52%); yellow crystals; mp 128–130 °C; (Found: C, 42.25; H, 2.69. $C_{12}H_{10}BrF_3O_3$ requires: C, 42.50; H, 2.97%.) ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.43–2.70 (m, 2H, CH_2), 2.98, 3.26 (AB-system, two unresolv. ddd, 2×1H, $J_{AB}\approx$18 Hz, $^3J_{Hb,H}\approx$11 Hz, $^3J_{Hb,H}\approx$4 Hz), 5.1, 5.9 (both s, 2×1H, 2×OH), 7.33 [dd, $^3J_{H,H}$=$^3J_{H,H}$=7.6 Hz, 1H, 6(7)-H], 7.42 (d, $^3J_{H,H}$=7.2 Hz, 1H, 5-H), 7.60 [dd, $^3J_{H,H}$=$^3J_{H,H}$=7.2 Hz, 1H, 7(6)-H], 8.14 (d, $^3J_{H,H}$=8.0 Hz, 1H, 8-H); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−77.29 (s, CF_3).

4.14.2. Method B

Br_2 (0.15 g, 0.9 mmol) was added carefully to a well stirred suspension of salt **10** (0.20 g, 0.8 mmol) in $CHCl_3$ (7 mL). After stirring at rt for 16 h in the sealed flask, the precipitate of LiBr was removed by filtration. The filtrate was concentrated in vacuo, the residue (yellow oil) solidified. Recrystallization from heptane afforded monohydrate of **16**. Yield: 0.10 g (37%).

4.15. 2-Trifluoroacetyl-1-naphthol (7)

A soln of **16** (0.21 g, 0.6 mmol) in *o*-dichlorobenzene (4 mL) was heated at reflux under N_2 atmosphere for 5 h. After being cooled to rt the reaction mixture was poured into 10% aq NaOH (10 mL). After extraction with pentane (2×5 mL) the aqueous layer was cooled to 0 °C, acidified with 5% aq HCl to pH=1 and extracted with CH_2Cl_2 (3×5 mL). The combined organic layer were dried (cotton wool) and evaporated. The residue (yellow oil) solidified, and recrystallization from MeOH-H_2O (2:1) afforded compound **7**. Yield: 0.10 g (67%); yellow prisms; mp 87–88 °C; (Found: C, 60.11; H, 3.00. $C_{12}H_7F_3O_2$ requires: C, 60.01; H, 2.94%); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.32 (d, $^3J_{H,H}$=8.8 Hz, 1H), 7.55–7.76 (m, 4H), 8.48 (d, $^3J_{H,H}$=7.8 Hz, 1H, 8-H), 12.9 (br s, 1H, OH); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−70.86 (d, $^5J_{F,H}$=2.1 Hz, CF_3).

4.16. 3-(Trifluoroacetyl)cyclohexane-1,2-dione (13)

(Trimethylsilyl)triflate (0.67 g, 3 mmol) was added carefully to a stirred soln of 2,3-bis(trimethylsiloxy)cyclohexa-1,3-diene[38] [2.6 g, ca. 10 mmol, contaminated with 2-(trimethylsiloxy)cyclohex-2-enone as product of monosilylation of cyclohexane-1,2-dione] in anhyd CH_2Cl_2 (40 mL) maintained at 0 °C. Trifluoroacetic anhydride (5.0 g, 24 mmol) was added dropwise at this temperature, the mixture was allowed to reach rt and stirred for the further 20 h. The dark soln formed was poured into ice-water mixture (100 g), and the mixture was stirred for 1 h. The organic layer was separated, aqueous phase was extracted with CH_2Cl_2 (2×25 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was subjected to column chromatography (hexane-$CHCl_3$) to provide triketone **13**. Yield: 0.15 g (7%); yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.01–2.13 (m, 2H, 5-H), 2.63 [t, $^3J_{H,H}$=6.6 Hz, 2H, 4(6)-H], 2.71 [t, $^3J_{H,H}$=5.9 Hz, 2H, 6(4)-H], 11.5 (br s, 1H, OH); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−75.07 (s, CF_3); MS (EI, 70 eV): *m*/*z* (%)=208 (15) [M^+], 180 (48) [$M-CO]^+$, 139 (28) [$M-CF_3]^+$, 111 (100) [$M-COCF_3]^+$, 69 (10) [CF_3^+]; HRMS: *m*/*z* [$M]^+$ calcd for $C_8H_7F_3O_3$: 208.0347; found: 208.0350; −1.5 ppm, −0.3 mu, $R\approx$10,000.

4.17. 2-(2,2,3,3-Tetrafluoropropanoyl)cyclohexane-1,4-dione (12)

A soln of cyclohexane-1,4-dione (1.0 g, 8.9 mmol) in anhyd THF (10 mL) was added dropwise to a mixture of a 1.8 M soln of (commercially obtained) LDA in heptane–THF–ethylbenzene (5 mL) and THF (20 mL) maintained at −78 °C. After the mixture had stirred for 40 min, $HCF_2CF_2CO_2Me$ (1.5 g, 9.0 mmol) was added via cannula. The reaction mixture was allowed to warm to rt and stirred for 12 h. After treatment with 5% aq H_2SO_4 (20 mL), the mixture extracted with diethyl ether (4×15 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue (brown oil) was subjected to column chromatography ($CHCl_3$) to provide 2,5-bis(2,2,3,3-tetrafluoropropanoyl)cyclohexane-1,4-dione[10] (first fraction, 0.02 g, 1%) and triketone **12** (second fraction). Yield: 0.14 g (7%); red oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.56–2.63, 2.81–2.89 (both m, 2×2H, 2×CH_2), 3.41 [t, $^5J_{H,F}\approx$7 Hz, 2H, 3-H], 6.13 (tt, $^2J_{H,F}$=52.6 Hz, $^3J_{H,F}$=5.1 Hz, 1H, CF_2H), 15.3 (br s, 1H, OH); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−139.18 (dm, $^2J_{F,H}$=52.6 Hz, 2F, CF_2H), −121.29 (m, 2F, $COCF_2$); MS (EI, 70 eV): *m*/*z* (%)=240 (100) [M^+], 139 (92) [$M-CF_2CF_2H]^+$, 111 (46) [$M-COCF_2CF_2H]^+$, 101 (12) [$CF_2CF_2H^+$].

HRMS: *m*/*z* [$M]^+$ calcd for $C_9H_8F_4O_3$: 240.0410; found: 240.0417; −2.9 ppm, −0.7 mu, $R\approx$10,000.

4.18. 4-Ethoxy-2-(2,2,3,3-tetrafluoropropanoyl)phenol (14)

Br_2 (0.10 g, 0.65 mmol) was added dropwise to a well-stirred soln of **12** (0.12 g, 0.5 mmol) in $CHCl_3$ (2 mL, containing 1 mol% EtOH) at rt. The resulting red soln was stirred in a stoppered flask for 14 h. After opening the flask, the volatile materials were evaporated, and the residue (brown oil) was subjected to column chromatography ($CHCl_3$) to provide a brownish oil which solidified. Recrystallization from perfluoro-1,1-dimethylcyclohexane at −30 °C provide phenol **14**. Yield: 30 mg (23%); yellow crystals; melting interval 62–68 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.41 (t, $^3J_{H,H}$=7.0 Hz, 3H, CH_3), 4.00 (q, 2H, CH_2), 6.29 (tt, $^2J_{H,F}$=52.4 Hz, $^3J_{H,F}$=5.3 Hz, 1H, CF_2H), 7.00 (d, $^3J_{H,H}$=9.0 Hz, 1H, 6-H), 7.25 (dd, $^4J_{H,H}$=2.9 Hz, 1H, 5-H), 7.37 (m, 1H, 3-H), 10.88 (s, 1H, OH); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−139.13 (dt, $^2J_{F,H}$=52.4 Hz, $^3J_{F,F}$=7.2 Hz, 2F, CF_2H), −117.20 (m, 2F, $COCF_2$).

MS (EI, 70 eV): *m*/*z* (%)=266 (740) [M^+], 165 (87) [$M-CF_2CF_2H]^+$, 137 (100) [$M-COCF_2CF_2H]^+$.

HRMS: *m*/*z* [$M]^+$ calcd for $C_{11}H_{10}F_4O_3$: 266.0566; found: 266.0561; 1.7 ppm, 0.5 mu, $R\approx$10,000.

4.19. 2-Bromo-2-(trifluoroacetyl)cyclohexanone (18)

4.19.1. Method A (Table 2, entry 7)

Br_2 (0.96 g, 6.0 mmol) was added dropwise to a well-stirred suspension of salt **19** (1.2 g, 2.6 mmol) in $CHCl_3$ (20 mL). The resulting mixture was stirred in a stoppered flask at rt for 24 h. After opening the flask hexane (20 mL) was added, and the mixture was cooled to −30 °C. The precipitate was filtered off, the filtrate was concentrated in vacuo to provide analytically pure compound **18**. Yield: 1.5 g (92%); yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.66–1.97, 2.02–2.22 (both m, 2×2H, 2×CH_2), 2.26–2.61 (m, 3H), 3.25 (ddd, *J*=13.6, 12.6, 6.0 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$, assignment of the signals supported by DEPT135 experiment):

δ=20.9, 27.4 (4-C, 5-C), 37.4, 37.7 (3-C, 6-C), 65.2 (2-C), 115.0 (q, $^1J_{C,F}$=291.9 Hz, CF_3), 185.3 (q, $^2J_{C,F}$=35.3 Hz, $COCF_3$), 202.2 (1-C); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−71.14 (s, CF_3); MS (EI, 70 eV): *m*/*z* (%)=272 (18) [M^+], 203 (8) [$M-CF_3]^+$, 193 (19) [$M-Br]^+$, 175 (4) [$M-COCF_3]^+$, 165 (100) [$M-CO-Br]^+$, 69 (13) [CF_3^+]; HRMS: *m*/*z* [$M]^+$ calcd for $C_8H_8{}^{79}BrF_3O_2$: 271.9660; found: 271.9661; −0.3 ppm, −0.1 mu, $R\approx$10,000.

4.19.2. Method B (Table 2, entry 3)

To a well-stirred soln of **5** (4.0 g, 21 mmol) in $CHCl_3$ (50 mL) NBS (4.1 g, 23 mmol) was added. The resulting mixture was stirred in a stoppered flask at rt for 18 h. The reaction mixture was evaporated in vacuo to dryness, the residue was taken into hexane (25 mL), the precipitate was filtered off and washed with hot hexane (3×10 mL). The combined hexane layers were evaporated in vacuo to leave analytically pure compound **18**. Yield: 5.0 g (87%).

4.19.3. Method C (Table 2, entries 4, 5)

To a well-stirred soln of **5** (0.39 g, 2 mmol) in $CHCl_3$ (10 mL) NBS (entry 4: 0.72 g, 4 mmol; entry 5: 1.07 g, 6 mmol) was added. The resulting mixture was stirred in a stoppered flask at rt for 60 h, and then heated at reflux under N_2 atmosphere for 15 h. After cooling to rt, the yellow liquid part of the heterogeneous system was investigated by ^{19}F NMR to reveal full conversion of **5** and nearly quantitative yield of **18**.

4.19.4. Method D (Table 2, entry 6)

To a well-stirred suspension of NBS (1.8 g, 10 mmol) in $CHCl_3$ (20 mL) compound **5** (0.39 g, 2 mmol) was added. The resulting mixture was heated at reflux under N_2 atmosphere for 15 h. the yellow liquid part of the heterogeneous system was investigated by ^{19}F NMR to reveal full conversion of **5** and nearly quantitative yield of **18**.

4.19.5. Method E (Table 2, entry 2)

Br_2 (0.41 g, 2.6 mmol) was added dropwise to a well-stirred soln of **5** (0.40 g, 2.6 mmol) in $CHCl_3$ (10 mL). After addition of Br_2, a characteristic red color loss and an acid vapour release were observed immediately. The resulting red soln was stirred in a stoppered flask for 18 h (the pressure was equalized from time to time by flask opening). After opening the flask (caution: slight internal pressure due to HBr vapors), the content (brownish soln) was investigated by ^{19}F NMR to reveal mixture of several fluorinated compounds where virtual yield of **18** was established to be about 50%.

4.20. 2-Chloro-2-(trifluoroacetyl)cyclohexanone (21)

4.20.1. Method A (Table 2, entry 8)

A suspension of salt **19** (0.37 g, 1.85 mmol) in anhyd CH_2Cl_2 (10 ml) was placed in a thick-walled glass ampoule equipped with a *Teflon* tap, and then Cl_2 (0.21 g, 3 mmol) was condensed into the evacuated ampoule at liquid N_2 temperature. The mixture was gradually allowed to warm and stirred for 20 h at rt. After opening the ampoule, hexane (5 mL) was added. The precipitate of LiCl was filtered off, and the filtrate was evaporated in vacuo to afford compound **21**. Yield: 0.32 g (76%); yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.65–1.95 (m, 2H), 1.96–2.63 (m, 5H), 3.09 (ddd, *J*=13.6, 12.8, 5.7 Hz, 1H); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−71.92 (s, CF_3); MS (EI, 70 eV): *m*/*z* (%)=228 (24) [M^+], 193 (8) [$M-Cl]^+$, 165 (100) [$M-CO-Cl]^+$, 159 (3) [$M-CF_3]^+$, 69 (16) [CF_3^+]; HRMS: *m*/*z* [$M]^+$ calcd for $C_8H_8{}^{35}ClF_3O_2$: 228.0165; found: 228.0167; −1.0 ppm, −0.2 mu, $R\approx$10,000.

4.20.2. Method B (Table 2, entry 9)

Freshly distilled SO_2Cl_2 (0.45 g, 3.3 mmol) was added carefully to a well stirred suspension of salt **20** (0.60 g, 2.8 mmol) in $CHCl_3$ (12 mL). After stirring in a stoppered flask at rt for 20 h, colorless soln with a white solid was formed. The liquid part was investigated by ^{19}F NMR to reveal **21** (92% yield) with an admixture of **5**.

4.20.3. Method B (Table 2, entry 10)

Freshly distilled SO_2Cl_2 (6.8 g, 50 mmol) was added carefully to a well stirred soln of **5** (4.9 g, 25 mmol) in $CHCl_3$ (120 mL). After stirring in a flask equipped with drying tube ($CaCl_2$) at rt for 60 h, the content (colorless liquid) was investigated by ^{19}F NMR to reveal mixture of several fluorinated compounds upon full conversion of **5**, where **21** (74% virtual yield) was detected. The yellowish liquid left after evaporation of the reaction mixture in vacuo was used in further experiments without purification.

4.21. 2-Bromo-5-(trifluoroacetyl)cyclopentanone (22)

Br_2 (0.76 g, 4.8 mmol) was added dropwise to a well-stirred suspension of chelate **23** (1.0 g, 2.4 mmol) in $CHCl_3$ (10 mL). The resulting mixture was stirred in a stoppered flask at rt for 48 h. The black precipitate formed was filtered off, and the filtrate was concentrated in vacuo. The oily residue was subjected to column chromatography ($CHCl_3$–hexane, 1:2) to provide 1,3-diketone **22**.

Yield: 0.25 g (20%); red liquid; the physical and spectral properties data matched with those described in the literature.[19]

4.22. Bromination–aromatization of salt 19 (Table 2, entry 11)

Br_2 (3.8 g, 24 mmol) was added dropwise to a well-stirred suspension of salt **19** (1.6 g, 8 mmol) in $CHCl_3$ (40 mL). The resulting mixture was stirred in a stoppered flask at rt for 74 h. After opening the flask the precipitate formed was filtered off and washed with CH_2Cl_2 (5 mL). The filtrate was concentrated in vacuo. Yellow oil left was dissolved in anhyd $CHCl_3$ (15 mL) and the soln was heated at reflux for 41 h ($CaCl_2$ drying tube). After treatment with water (100 mL) the organic layer was separated and the water layer was extracted with CH_2Cl_2 (4×10 mL). The combined extracts were dried ($MgSO_4$) and concentrated to provide a yellow oil (mixture of compound **24**, **25**, **26** in 80:13:7 ratio by ^{1}H, ^{19}F NMR). This oil was subjected to column chromatography (hexane) to provide compounds **25** (first fraction) and **26** (second fraction).

*4.22.1. 4,6-Dibromo-2-(trifluoroacetyl)cyclohexa-1,3-dien-1-ol (**24**)*

^{1}H NMR (200 MHz, $CDCl_3$): δ=3.06, 3.41 (AB-system, 3.06: dd, 3.41: ddd, 2×1H, J_{AB}=19.0, $^3J_{Ha,H}$=2.9 Hz, $^3J_{Hb,H}$=5.4 Hz, $^3J_{Hb,H}$=2.7 Hz, 5-H), 4.68 (dd, $^3J_{H,Hb}$=5.4 Hz, $^3J_{H,Ha}$=2.9 Hz, 1H, 6-H), 6.92 (m, 1H, 3-H), 14.4 (br s, 1H, OH); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−70.86 (d, $^5J_{F,H}\approx$2 Hz, CF_3).

*4.22.2. 4-Bromo-2-(trifluoroacetyl)phenol (**25**)*

Yield: 1.0 g (46%); yellow oil; (Found: C, 35.80; H, 1.66. $C_8H_4BrF_3O_2$ requires: C, 35.72; H, 1.50%.) ^{1}H NMR (200 MHz, $CDCl_3$): δ=6.99 (d, $^3J_{H,H}$=8.8 Hz, 1H, 6-H), 7.69 (dd, $^3J_{H,H}$=8.8 Hz, $^4J_{H,H}$=2.4 Hz, 1H, 5-H), 7.85–7.93 (m, 1H, 3-H), 11.0 (br s, 1H, OH); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−70.97 (d, $^5J_{F,H}$=2.0 Hz, CF_3).

*4.22.3. 2,4-Dibromo-6-(trifluoroacetyl)phenol (**26**)*

Yield: 0.10 g (4%); yellow crystals; the physical and spectral properties data matched with those described earlier.[10]

4.23. Bromination–aromatization of salt 19 (Table 2, entry 12)

Br_2 (1.9 g, 12 mmol) was added dropwise to a well-stirred suspension of salt **19** (0.8 g, 4 mmol) in $CHCl_3$ (20 mL). The resulting mixture was stirred in a stoppered flask at rt for 63 h. After opening the flask the precipitate formed was filtered off and the filtrate was

concentrated in vacuo. Yellow oil left was dissolved in anhyd CH_2Cl_2 (5 mL), anhyd K_2CO_3 (0.12 g, 0.9 mmol) was added and the mixture was stirred in a stoppered flask at rt for 12 h (the pressure was equalized from time to time by flask opening). After addition of a second portion of anhyd K_2CO_3 (0.12 g, 0.9 mmol) the mixture was stirred in a stoppered flask at rt for 12 h (the pressure was equalized from time to time by flask opening). The reaction mixture was mixed with water (30 mL), acidified with 12% aq HCl to pH=1, organic layer was separated and the water layer was extracted with CH_2Cl_2 (4×5 mL). The combined extracts were dried ($MgSO_4$) and concentrated to provide a yellow oil which was subjected twice to column chromatography (hexane, $CHCl_3$) to provide compounds **27** (first fraction) and **26** [second fraction, yield: 20 mg (1%)].

*4.23.1. 2-Bromo-6-(trifluoroacetyl)phenol (**27**)*

Yield: 100 mg (9%); volatile yellow oil; (Found: C, 35.82; H, 1.64. $C_8H_4BrF_3O_2$ requires: C, 35.72; H, 1.50%.) ^{1}H NMR (200 MHz, $CDCl_3$): δ=6.93 (dd, $^3J_{H,H}\approx{}^3J_{H,H}\approx$8 Hz, 1H, 4-H), 7.82 (dm, $^3J_{H,H}$=8.3 Hz, 1H, 3-H), 7.90 (dd, $^3J_{H,H}$=7.9 Hz, $^4J_{H,H}$=1.3 Hz, 1H, 5-H), 11.63 (s, 1H, OH); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−70.67 (d, $^5J_{F,H}$=2.1 Hz, CF_3).

*4.23.2. 2,6-Dibromo-2-(trifluoroacetyl)cyclohexanone (**30**)*

A soln of Br_2 (0.88 g, 5.5 mmol) in $CHCl_3$ (5 mL) was added dropwise to a well-stirred soln of boron chelate **28** (0.6 g, 2.5 mmol) in $CHCl_3$ (7.5 mL) upon ice-cooling. The resulting mixture was stirred at rt for 24 h (the HBr liberated was absorbed by aq NaOH via an outlet pipe). After treatment with water (3 mL) the organic layer was dried (cotton wool) and concentrated in vacuo to provide **30** of 90% purity (ca. 10% admixture of **29** by ^{1}H, ^{19}F NMR), which was converted without further purification. Yield: 0.45 g (ca. 50%); yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.85–1.97, 2.89–2.95 (both m, 2×2H, 4-H, 5-H), 2.64 (t, $^3J_{H,H}$=6.4 Hz, 1H, 3-H), 14.54 (s, 1H, OH); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−73.92 (t, $^5J_{F,H}$=1.2 Hz, CF_3).

4.24. 2,2,6-Tribromo-6-(trifluoroacetyl)cyclohexanone (29)

4.24.1. Method A (Table 2, entry 13)

Br_2 (0.7 g, 4.3 mmol) was added dropwise to a well-stirred soln of boron chelate **28** (0.5 g, 2.1 mmol) in $CHCl_3$ (50 mL). The resulting mixture was stirred at rt for 20 h (the HBr liberated was absorbed by aq NaOH via an outlet pipe). Br_2 (0.7 g, 4.3 mmol) was added dropwise followed by the further stirring the reaction mixture for 20 h. The reaction mixture was concentrated in vacuo to about one-half and washed with water (2×10 mL), the organic layer was dried (cotton wool) and concentrated in vacuo. The yellow oil left was subjected to column chromatography ($CHCl_3$) to afford **29**. Yield: 200 mg (22%); yellow waxy crystals; mp 55 °C; (Found: C, 22.11; H, 1.32. $C_8H_6Br_3F_3O_2$ requires: C, 22.30; H, 1.40%.) ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.73–1.98 (m, 1H), 2.04–2.35 (m, 2H), 2.77–3.15 (m, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$, assignment of the signals supported by DEPT135 experiment): δ=22.3 (4-C), 39.8 (5-C), 49.8 (3-C), 65.3, 66.0 (2-C, 6-C), 115.8 (q, $^1J_{C,F}$=292.59 Hz, CF_3), 178.8 (q, $^2J_{C,F}$=35.3 Hz, $COCF_3$), 181.8 (1-C); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−68.01 (s, CF_3); MS (EI, 70 eV): *m*/*z* (%)=430 (8) [M^+], 402 (8) [$M-CO]^+$, 349 (8) [$M-Br]^+$, 269 (8) [$M-Br-HBr]^+$, 191 (100), 69 (36) [CF_3^+].

4.24.2. Method B (Table 2, entry 16)

A stirred soln of crude **30** (ca. 2 mmol) in $CHCl_3$ (50 mL) was treated with Br_2 (0.7 g, 4.3 mmol) at rt. The resulting mixture was stirred for 20 h (the HBr liberated was absorbed by aq NaOH via an outlet pipe) and then concentrated in vacuo to about one-half. The residue was washed with water (2×10 mL), the organic layer was dried (cotton wool) and concentrated in vacuo to afford **29** of sufficient purity. Yield: 0.60 g (67%).

4.25. 4-Bromo-2-(2,2,2-trifluoro-1,1-dihydroxyethyl)-cyclohex-2-enone (31)

A soln of Br_2 (1.76 g, 11 mmol) in $CHCl_3$ (50 mL) was added dropwise to a well-stirred soln of boron chelate **28** (1.2 g, 5 mmol) in $CHCl_3$ (200 mL) upon ice-cooling. The resulting mixture was stirred at rt for 24 h (the HBr liberated was absorbed by aq NaOH via an outlet pipe) and heated at reflux for 24 h. The reaction mixture was washed with water (2×40 mL), the organic layer was dried ($MgSO_4$) and concentrated in vacuo to afford yellow oil which solidified. Recrystallization from toluene afforded **31**. Yield: 0.50 g (35%); colorless crystals; melting interval 125–130 °C; ^{1}H NMR (200 MHz, acetone-d_6): δ=2.40–2.50 (m, 1H), 2.57–2.88 (m, 3H), 5.36 (dt, $^3J_{H,H}$=4.9 Hz, $^3J_{H,H}$=4.4 Hz, 1H, 4-H), 6.92, 7.01 (both s, 2×1H, 2×OH), 7.61 (d, $^3J_{H,H}$=4.9 Hz, 1H, 3-H). The signals at 6.92, 7.01 ppm disappeared after the addition of deuterated acetic acid; ^{19}F NMR (188 MHz, acetone-d_6): δ=−86.36 (s, CF_3); MS [CI, positive]: *m*/*z* (%)=305 (3) [$M+NH_3]^+$, 288 (100) [M^+], 270 (4) [$M-H_2O]^+$, 210 (20) [$M-HBr]^+$, 121 (8) [$M-H_2O-HBr-CF_3]^+$; MS [CI, negative]: *m*/*z* (%)=271 (10) [$M-OH]^-$, 250 (28) [$M-HF-H_2O]^-$, 190 (100) [$M-HBr-H_2O]^-$, 172 (60) [$M-H_2O-CF_3CO-H]^-$, 79 [Br^-].

MS (EI, 70 eV): *m*/*z* (%)=270 (6) [$M-H_2O]^+$, 242 (3) [$M-H_2O-CO]^+$, 219 (75) [$M-CF_3]^+$, 201 (100) [$M-CF_3-H_2O]^+$, 163 (29) [$M-H_2O-CO-CF_3]^+$, 121 (47) [$M-H_2O-HBr-CF_3]^+$, 69 (19) [CF_3^+]; HRMS: *m*/*z* [$M-H_2O]^+$ calcd for $C_8H_6{}^{79}BrF_3O_2$: 269.9503; found: 269.9407; 2.2 ppm, 0.6 mu, $R\approx$10,000.

4.26. Dehydrohalogenation–disproportionation of 18 (Scheme 3)

4.26.1. Entry 1

A well stirred mixture of **18** (2.0 g, 7.3 mmol) and sulphur (1.0 g, 3.9 mmol) was heated (bath temperature 200 °C) for 3 h. The reaction mixture was cooled to rt and investigated by ^{19}F NMR to reveal ca. 1:1 mixture of **1a** and **5** upon full conversion of **18**.

4.26.2. Entry 2

To a soln of **18** (3.0 g, 11 mmol) in benzene (100 mL) DDQ (6.3 g, 28 mmol) was added. The stirred mixture was heated at reflux for 4 h and cooled to room temperature. A brown soln with precipitate was formed; the ^{19}F NMR investigation of liquid phase revealed mixture of **1a** and **5** upon full conversion of **18**.

4.26.3. Entry 3

Compound **18** (1.0 g, 3.7 mmol) was heated (bath temperature 240 °C) under stirring for 20 min. The brown liquid formed was cooled to rt and investigated by ^{19}F NMR to reveal mixture of **1a** and **5** upon full conversion of **18**.

4.27. Dehydrohalogenation–disproportionation of 21 (Scheme 3)

4.27.1. Entry 4

A well stirred mixture of **21** (2.3 g, 10 mmol) and sulphur (1.0 g, 3.9 mmol) was heated (bath temperature 205 °C) for 1 h. The reaction mixture was cooled to rt and ca. 1:1 mixture of **1a** and **5** (1.0 g, yellow liquid) was distilled off, boiling interval 140–180 °C/760 Torr.

4.27.2. Entry 5

A well stirred mixture of **21** (10.8 g, 47 mmol) and sulphur (1.8 g, 7 mmol) was heated (bath temperature 220–230 °C) for 3.5 h. The reaction mixture was cooled to rt and investigated by ^{19}F NMR to reveal ca. 1:1 mixture of **1a** and **5** upon full conversion of **21**. The mixture was mixed with CH_2Cl_2 (70 mL) and filtered. Freshly

distilled SO_2Cl_2 (19.0 g, 141 mmol) was added carefully to the filtrate. After stirring at rt for 60 h (the HCl and SO_2 liberated were absorbed by aq NaOH via an outlet pipe), the formed brown soln was evaporated under reduced pressure. The brown oil left was distilled to provide mixture of **33**, **1a** and **21** (74:8:18 by ^{1}H, ^{19}F NMR) as a yellow oil, bp 135–140 °C/80 Torr.

*4.27.3. 4-Chloro-2-(trifluoroacetyl)phenol (**33**)*

^{1}H NMR (200 MHz, $CDCl_3$): δ=7.05 (d, $^3J_{H,H}$=9.3 Hz, 1H, 6-H), 7.57 (dd, $^3J_{H,H}$=8.8 Hz, $^4J_{H,H}$=2.4 Hz, 1H, 5-H), 7.72–7.80 (m, 1H, 3-H), 10.97 (s, 1H, OH); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−70.99 (d, $^5J_{F,H}$=1.9 Hz, CF_3).

4.28. Dehydrobromination of 29

1,3-Diketone **29** (100 mg, 0.2 mmol) was heated (bath temperature 170 °C) under stirring for 1 h. The brown liquid formed was cooled to rt and investigated by ^{1}H, ^{19}F NMR to reveal mixture of **26** and **27** (59:41) upon full conversion of **29**.

4.29. 2-Bromo-4,4,4-trifluoro-1-(3-fluorophenyl)butane-1,3-dione (35), monohydrate

Br_2 (1.3 g, 8 mmol) was added dropwise to a well-stirred suspension of salt **34** (1.9 g, 8 mmol) in anhyd $CHCl_3$ (25 mL). The resulting mixture was stirred in a stoppered flask at rt for 20 h. The mixture was cooled to −30 °C, and the precipitate formed was filtered off. The filtrate was concentrated in vacuo. Yellow liquid left was dissolved in toluene (5 mL), and after addition of water (0.2 mL) the mixture was stirred at rt for 12 h. The mixture was evaporated without vacuum to afford an oil which solidified after 48 h. Recrystallization from heptane furnished monohydrate of **35**. Yield: 0.85 g (32%); pale yellow scales; melting interval 87–92 °C; (Found: C, 36.39; H, 2.24. $C_{10}H_7BrF_4O_3$ requires: C, 36.28; H, 2.13%.) ^{1}H NMR (200 MHz, $CDCl_3$): δ=4.91, 5.17 (both s, 2×1H, 2×OH), 5.32 (s, 1H, 2-H), 7.39 (dddd, $^3J_{H,F}$=8.3 Hz, $^3J_{H,H}$=8.3 Hz, $^4J_{H,H}$=2.0 Hz, $^4J_{H,H}\approx$0.5 Hz, 1H, *p*-H), 7.54 (ddd, $^3J_{H,H}$=7.9 Hz, $^4J_{H,F}$=5.5 Hz, 1H, *m*-H), 7.68 (ddd, $^3J_{H,F}$=8.8 Hz, $^4J_{H,H}$=2.2 Hz, 1H, *o*-H), 7.77 (ddd, 1H, *o*′-H); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−110.65 (ddd, $^3J_{F,H}$=9.0 Hz, $^3J_{F,H}$=8.1, $^4J_{F,H}$=5.5 Hz, 1F, C_6H_4F), −82.56 (s, 3F, CF_3); MS (EI, 70 eV): *m*/*z* (%)=330 (0.6) [M^+], 312 (0.2) [$M-H_2O]^+$, 261 (0.5) [$M-CF_3]^+$, 243 (0.3) [$M-CF_3-H_2O]^+$, 234 (4) [$M-Br-OH]^+$, 216 (2) [$M-CF_3CO-OH]^+$, 165 (5) [$M-CF_3-OH-Br]^+$, 123 (100) [$FC_6H_4CO^+$], 95 (19) [$FC_6H_4^+$], 69 (7) [CF_3^+].

4.30. Bromination of sodium 2-(trifluoroacetyl)lactonates 36, 37. General procedure

Br_2 (1.7 g, 11 mmol) was added dropwise to a well-stirred suspension of the appropriate salt **36** (10 mmol) in $CHCl_3$ (15 mL). The resulting mixture was stirred in a stoppered flask at rt for 24 h, and the precipitate formed was filtered off. The filtrate was evaporated to leave an orange oil left which solidified. The solid was dissolved in $CHCl_3$, filtered through a bed of silica gel, and the filter pad was washed with $CHCl_3$. The filtrate was evaporated, and the solid residue was recrystallized from toluene to afford monohydrates of **40**, **41**.

*4.30.1. β-Bromo-β-(trifluoroacetyl)-γ-butyrolactone (**40**), monohydrate*

Yield: 60%; colorless crystals; mp 100–102 °C; (Found: C, 25.85; H, 2.16. $C_6H_6BrF_3O_4$ requires: C, 25.83; H, 2.17%.) ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.55–2.64 (m, 1H, 4-H), 3.03–3.20 (m, 1H, 4-H), 3.8, 6.3 (both br s, 2×1H, 2×OH), 4.40–4.56 (m, 2H, 5-H); ^{19}F NMR (188 MHz, CD_3CN): δ=−79.80 (s, CF_3); MS [CI, positive]: *m*/*z* (%)=278 (40) [M^+], 261 (100) [$M-OH]^+$, 217 (17) [$M-H_2O-CO_2]^+$, 199 (12) [$M-Br]^+$; MS [CI, negative]: *m*/*z* (%)=358 (62), 233 (10) [$M-CO_2-H]^-$, 179 (100).

*4.30.2. β-Bromo-β-(trifluoroacetyl)-δ-valerolactone (**41**), monohydrate*

Yield: 50%; colorless crystals; mp 135–137 °C; (Found: C, 28.57; H, 2.68. $C_7H_8BrF_3O_4$ requires: C, 28.69; H, 2.75%.) ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.89–1.97 (m, 1H, 5-H), 2.33–2.70 (m, 3H, 4,5-H), 4.38–4.52, 4.61–4.78 (both m, 2×1H, 6-H), 6.3, 7.6 (both br s, 2×1H, 2×OH); ^{19}F NMR (188 MHz, CD_3CN): δ=−77.07 [s, $C(OH)_2CF_3$, monohydrate form], −70.36 [s, $C(O)CF_3$, diketo form], [**41**·H_2O]:[**41**]=94:6; MS [CI, positive]: *m*/*z* (%)=292 (30) [M^+], 275 (92) [$M-OH]^+$, 213 (27) [$M-Br]^+$, 197 (100), 179 (34) [$M-CO_2-CF_3]^+$; MS [CI, negative]: *m*/*z* (%)=291 (7) [$M-H]^-$, 194 (100) [$M-HBr-H_2O]^-$, 143 (19) [$M-HBr-CF_3]^-$, 79 (40) [Br^-].

4.31. Bromination of potassium 2-(trifluoroacetyl)lactamates 38, 39. General procedure

^{t}BuOK (0.34 g, 3 mmol) was added to an ice-cooled soln of appropriate 2-(trifluoroacetyl)lactam (3 mmol) in anhyd CH_2Cl_2 (10 mL). The ice-bath was removed and the mixture was stirred at rt for 30 min to afford a pale yellow precipitate in colorless soln. The mixture was cooled to 0 °C and Br_2 (0.48 g, 3 mmol) was added dropwise. The resulting mixture was stirred in a stoppered flask at rt for 30 min, poured into water (60 mL), and the organic layer was separated. After extraction with EtOAc (3×10 mL) the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and evaporated to give monohydrates of **42**, **43**.

*4.31.1. β-Bromo-β-(trifluoroacetyl)-γ-butyrolactam (**42**), monohydrate*

Yield: 26% after purification by column chromatography (EtOAc); pale yellow crystals; mp 107–110 °C; ^{1}H NMR (200 MHz, acetone-d_6): δ=2.36–2.52 (m, 1H, 4-H), 2.88–3.04 (m, 1H, 4-H), 3.39–3.50 (m, 2H, 5-H), 6.94, 7.75 (both s, 2×1H, 2×OH), 7.9 (br s, 1H, NH); ^{19}F NMR (188 MHz, acetone-d_6): δ=−79.16 (s, CF_3); MS [CI, positive]: *m*/*z* (%)=277 (65) [M^+], 260 (2) [$M-OH]^+$, 199 (50) [$M-Br+H]^+$, 182 (100) [$M-Br-OH+H]^+$; MS [CI, negative]: m/z (%)=356 (1), 340 (16) [$M+Br-H_2O]^-$, 276 (2) [$M-H]^-$, 258 (16) [$M-H_2O-H]^-$, 179 (100); MS (EI, 70 eV): *m*/*z* (%)=259 (77) [$M-H_2O]^+$, 216 (100) [$M-H_2O-HNCO]^+$, 208 (5) [$M-CF_3]^+$, 190 (3) [$M-CF_3-H_2O]^+$, 162 (15) [$M-H_2O-CF_3CO]^+$, 147 (18) [$M-H_2O-HNCO-CF_3]^+$, 119 (13) [$M-H_2O-HNCO-CF_3CO]^+$, 69 (14) [CF_3^+]; HRMS: *m*/*z* [$M-H_2O]^+$ calcd for $C_6H_5{}^{79}BrF_3NO_2$: 258.9458; found: 258.9447; 3.5 ppm, 0.9 mu, $R\approx$10,000.

*4.31.2. β-Bromo-β-(trifluoroacetyl)-δ-valerolactam (**43**), monohydrate*

Yield: 73; white powder; mp 137–141 °C; ^{1}H NMR (200 MHz, acetone-d_6): δ=1.90–2.62 (m, 4H, 4,5-H), 3.39–3.53 (m, 2H, 6-H), 7.26, 7.67, 8.18 (s, 3×1H, 2×OH, NH); ^{19}F NMR (188 MHz, acetone-d_6): δ=−77.73 [s, $C(OH)_2CF_3$, monohydrate form], −71.89 [s, $C(O)CF_3$, diketo form]; [**43**·H_2O]:[**43**]=95:5; MS [CI, positive]: *m*/*z* (%)=564 (1) [$2M-H_2O]^+$, 291 (100) [M^+], 274 (17) [$M-OH]^+$, 213 (53) [$M-Br+H]^+$, 196 (84) [$M-Br-H_2O]^+$; MS [CI, negative]: *m*/*z* (%)=370 (1) [$M+Br]^-$, 352 (8) [$M+Br-H_2O]^-$, 290 (1) [$M-H]^-$, 274 (6) [$M-OH]^-$, 193 (13) [$M-HBr-H_2O]^-$, 79 (100) [Br^-]; MS (EI, 70 eV): *m*/*z* (%)=273 (1) [$M-H_2O]^+$, 222 (2) [$M-CF_3]^+$, 204 (2) [$M-CF_3-H_2O]^+$, 194 (100) [$M-Br-H_2O]^+$, 177 (20) [$M-OH-CF_3CO]^+$, 133 (8) [$M-H_2O-HNCO-CF_3CO]^+$, 69 (6) [CF_3^+]; HRMS: *m*/*z* [$M-H_2O]^+$ calcd for $C_7H_7{}^{79}BrF_3NO_2$: 272.9612; found: 272.9615; −0.9 ppm, −0.3 mu, $R\approx$10,000.

4.32. Ethyl 2-chloro-4,4,4-trifluoro-3-oxobutanoate (45)

A mixture of 1,3-ketoester **44** (31.0 g, 168 mmol) and saturated ethereal HCl soln (10 mL) was added dropwise to an ice-cooled mixture of SO_2Cl_2 (91.0 g, 0.67 mol, freshly distilled) and Bz_2O_2

(100 mg) mixture under stirring. After stirring at rt for 20 h (the HCl and SO_2 liberated were absorbed by aq NaOH via an outlet pipe), the excess of SO_2Cl_2 was removed in vacuo at rt to left a liquid which was distilled to provide **45**. Yield: 28.0 g (76%); colorless liquid; boiling interval 62–68 °C/20 Torr, lit.[17a] bp 67–71 °C/35 Torr; ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.27 (t, $^3J_{H,H}$=7.1 Hz, 3H, CH_3), 4.30 (q, 2H, CH_2), 5.21 (s, 1H, 2-H); ^{19}F NMR (188 MHz, $CDCl_3$): δ=− 74.65 (s, CF_3).

4.33. Ethyl 2,2-dichloro-4,4,4-trifluoro-3-oxobutanoate (46)

A mixture of 1,3-ketoester **44** (6.0 g, 33 mmol) and saturated ethereal HCl soln (2 mL) was added dropwise to an ice-cooled mixture of SO_2Cl_2 (23.0 g, 170 mmol, freshly distilled) and Bz_2O_2 (100 mg) under stirring. The mixture was stirred at rt for 48 h (the HCl and SO_2 liberated were absorbed by aq NaOH via an outlet pipe) and then heated at reflux for 40 h. SO_2Cl_2 (10.0 g, 74 mmol) was added, and the mixture was stirred at rt for 7 days. The excess of SO_2Cl_2 was removed in vacuo at rt to left a liquid which was distilled to provide **46**[46] contaminated with mono-chlorinated compound **45** (ca. 10% by ^{1}H, ^{19}F NMR). Yield: 5.6 g (61%); pale yellow liquid; bp 55–58 °C/12 Torr; ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.33 (t, $^3J_{H,H}$=7.2 Hz, 3H, CH_3), 4.41 (q, 2H, CH_2); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−70.03 (s, CF_3).

4.34. 5,6-Dihydro-6-methoxy-3-trifluoromethyl-1,4-*H*-cyclopenta-[*d*]-pyrazole (47)

To a stirred soln of **22** (60 mg, 0.23 mmol) in methanol (10 mL) 98% hydrazine hydrate (50 mg, 1 mmol) was added. The mixture was heated at reflux for 34 h and all volatiles was removed in vacuo. The residue was subjected to column chromatography ($CHCl_3$) to afford pyrazole **47**. Yield: 20 mg (42%); yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.47–3.07 (m, 4H, 4,5-H), 4.79 (t, $^3J_{H,H}$=5.4 Hz, 6-H), 3.36 (s, 3H, CH_3), 12.1 (br s, 1H, NH); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−61.95 (s, CF_3); MS (EI, 70 eV): *m*/*z* (%)=206 (77) [M^+], 191 (100) [$M-CH_3]^+$, 175 (96) [$M-CH_3O]^+$, 137 (5) [$M-CF_3]^+$, 106 (12) [$M-CH_3O-CF_3]^+$, 69 (10) [CF_3^+]; HRMS: *m*/*z* [M^+] calcd for $C_8H_9F_3N_2O$: 206.0667; found: 206.0671; −2.1 ppm, −0.4 mu, $R\approx$10,000.

4.35. Reaction of 35·H_2O with hydrazine hydrate

To a stirred soln **35** hydrate (0.52 g, 1.6 mmol) in methanol (15 mL) 98% hydrazine hydrate (100 mg, 2.0 mmol) was added. The mixture was heated at reflux for 32 h, cooled to rt and mixed with water (50 mL). After extraction with CH_2Cl_2 (4×15 mL) the combined organic phases were dried ($MgSO_4$) and evaporated. The solid residue was subjected to column chromatography ($CHCl_3$–EtOAc, 10:1) to afford pyrazole **48** and mixture of pyrazoles **49**, **50** (ca. 2:1 by NMR, 15 mg).

*4.35.1. 4-Bromo-5-(3-fluorophenyl)-3-(trifluoromethyl) pyrazole (**48**)*

Yield: 100 mg (20%); colorless prisms; mp 168–170 °C; (Found: C, 38.89; H, 1.68. $C_{10}H_5BrF_4N_2$ requires: C, 38.86; H, 1.63%.) ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.05–7.26 (m, 1H, Ar), 7.32–7.53 (m, 3H, Ar), 8.6 (br s, 1H, NH); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−111.29 (m, 1F, C_6H_4F), −63.20 (s, 3F, CF_3); MS (EI, 70 eV): *m*/*z* (%)=308 (100) [M^+], 289 (4) [$M-F]^+$, 239 (13) [$M-CF_3]^+$, 160 (25) [$M-CF_3-Br]^+$, 95 (13) [$C_4H_4F^+$], 69 (5) [CF_3^+].

*4.35.2. 5-(3-Fluorophenyl)-3-(trifluoromethyl)pyrazole (**49**)*

^{1}H NMR (200 MHz, $CDCl_3$): δ=6.77 (s, 1H, 4-H), 7.05–7.50 (m, 4H, C_6H_4F); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−111.29 (m, 1F, C_6H_4F), −61.93 (s, 3F, CF_3); MS (EI, 70 eV): *m*/*z* (%)=230 (100) [M^+], 161 (28) [$M-CF_3$].

*4.35.3. 5-(3-Fluorophenyl)-3-methoxy-3-(trifluoromethyl)-pyrazole (**50**)*

^{1}H NMR (200 MHz, $CDCl_3$): δ=3.78 (s, 3H, CH_3), 7.05–7.50 (m, 4H, C_6H_4F); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−111.29 (m, 1F, C_6H_4F), −62.76 (s, 3F, CF_3); MS (EI, 70 eV): *m*/*z* (%)=260 (100) [M^+], 245 (32) [$M-CH_3$].

4.36. 2-Amino-5-(*m*-fluorobenzoyl)-4-(trifluoromethyl)-thiazole (51)

To a stirred suspension of **35** hydrate (0.21 g, 0.6 mmol) in ethanol (4 mL) thiourea (50 mg, 0.6 mmol) was added. The mixture was stirred at rt for 20 h, then heated at reflux for 48 h and all volatiles was removed in vacuo. The residue was subjected to column chromatography (EtOAc) to afford thiazole **51** after recrystallization from water-EtOH, 1:1. Yield: 50 mg (27%); yellow needles; mp 150–152 °C; ^{1}H NMR (200 MHz, acetone-d_6): δ=7.33–7.73 m; ^{13}C NMR (50.3 MHz, acetone-d_6): 116.2 [d, $^2J_{C,F}$=24.0 Hz, *o*(*p*)-C], 121.1 [d, $^2J_{C,F}$=22.6 Hz, *p*(*o*)-C], 121.2 (q, $^1J_{C,F}$=271.7 Hz, CF_3), 126.1 (d, $^4J_{C,F}$=2.8 Hz, *o*′-C), 131.7 (d, $^3J_{C,F}$=8.5 Hz, *m*′-C), 161.5 (d, $^1J_{C,F}$=245.8 Hz, *m*-C), 171.5 (2-C), 185.4 (6-C), 141.9 (d, $^3J_{C,F}$=5.7 Hz, *i*-C), 143.0 (d, $^2J_{C,F}$=34.6 Hz, 5-C); ^{19}F NMR (188 MHz, acetone-d_6): δ=−114.09 (dm, $^3J_{F,H}$=9.1 Hz, 1F, C_6H_4F), −62.23 (s, 3F, CF_3); MS (EI, 70 eV): *m*/*z* (%)=290 (94) [M^+], 195 (66) [$M-C_6H_4F]^+$, 167 (15) [$M-FC_6H_4CO]^+$, 123 (100) [$FC_6H_4CO^+$], 95 (56) [$FC_6H_4^+$]; HRMS: *m*/*z* [M^+] calcd for $C_{11}H_6F_4N_2OS$: 290.0137; found: 290.0143; −2.0 ppm, −0.6 mu, $R\approx$10,000.

4.37. 3,4-Dihydro-4-hydroxy-4-(3-hydroxypropyl)-5-(trifluoromethyl)-2*H*-pyrazol-3-one (52)

To a stirred soln of **41** hydrate (1.53 g, 5.2 mmol) in methanol (40 mL) 98% hydrazine hydrate (0.65 g, 13.1 mmol) was added dropwise. The mixture was heated at reflux for 20 h and all volatiles was removed in vacuo. The waxy solid residue was dissolved in EtOAc, filtered through a bed of silica gel and the filter pad was washed with EtOAc. The filtrate was evaporated to leave pyrazolone **52**. Yield: 1.10 g (94%); colorless crystals; mp 108–109 °C; ^{1}H NMR (200 MHz, acetone-d_6): δ=1.35–1.50 (m, 2H, CH_2CH_2O), 2.00–2.08 (m, 2H, Het-CH_2), 3.55 (dt, $^3J_{H,H}$=5.9 Hz, $^3J_{H,H}$=4.4 Hz, 2H, CH_2O), 3.83 (t, 1H, CH_2OH), 5.87 (s, 1H, 4-OH), 11.1 (br s, 1H, NH). The signals at 3.83, 5.87, 11.1 ppm disappeared after the addition of deuterated acetic acid, whereas dt at 3.55 ppm transformed to t; ^{13}C NMR (50.3 MHz, acetone-d_6): 26.1 (unresolv. q, Het-CH_2), 33.1 (CH_2CH_2O), 62.0 (CH_2O), 77.3 (4-C), 120.6 (q, $^1J_{C,F}$=271.3 Hz, CF_3), 150.2 (q, $^2J_{C,F}$=35.8 Hz, 5-C), 176.9 (3-C); ^{19}F NMR (188 MHz, acetone-d_6): δ=−66.64 (s, CF_3); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−66.19 (s, CF_3); MS [CI, positive]: *m*/*z* (%)=244 (100) [$M+NH_4]^+$, 227 (7) [$M+H]^+$, 226 (5) [M^+], 209 (17) [$M-OH]^+$; MS [CI, negative]: *m*/*z* (%)=225 (17) [$M-H]^-$, 209 (67) [$M-OH]^-$, 208 (100) [$M-H_2O]^-$, 164 (100) [$M-H_2O-CH_2CH_2O]^-$; MS (EI, 70 eV): *m*/*z* (%)=226 (2) [M^+], 208 (10) [$M-H_2O]^+$, 190 (5) [$M-2H_2O]^+$, 180 (11) [$M-H_2O-CH_2CH_2]^+$, 168 (30) [$M-CH_2CH_2CH_2OH+H]^+$, 69 (17) [CF_3^+], 31 (100) [CH_2OH^+]; HRMS: *m*/*z* [$M-H_2O]^+$ calcd for $C_7H_7F_3N_2O_2$: 208.0460; found: 208.0467; −3.7 ppm, −0.8 mu, $R\approx$10,000; HRMS: *m*/*z* [M^+] calcd for $C_7H_9F_3N_2O_3$: 226.0565; found: 226.0575; −4.2 ppm, −0.9 mu, $R\approx$10,000.

4.38. 4-(3-Aminopropyl)-3,4-dihydro-4-hydroxy-5-(trifluoromethyl)-2*H*-pyrazol-3-one hydrobromide (53)

To a stirred soln of **43** hydrate (0.40 g, 1.4 mmol) in methanol (20 mL) 98% hydrazine hydrate (80 mg, 1.5 mmol) was added dropwise. The mixture heated at reflux for 20 h, and then stirred at rt for 48 h. After acidification with 62% aq HBr to pH=1, $^3/_4$ of the mixture was evaporated in vacuo at rt. The residue was subjected to

column chromatography ($CHCl_3$–MeOH, 2:1) to afford pyrazolone **53**. Yield: 0.32 g (75%); yellow viscous oil; (Found: C, 27.19; H, 3.42; Br, 26.59. $C_{10}H_5BrF_4N_2$ requires: C, 27.47; H, 3.62; Br, 26.11%.) ^{1}H NMR (200 MHz, MeOH-d_4): δ=1.59–1.74 (m, 2H, CH_2CH_2N), 1.86–2.09 (m, 2H, Het-CH_2), 2.96 (t, $^3J_{H,H}$=7.6 Hz, 2H, CH_2N), 5.0 (br s, 5H, OH, NH, NH_3); ^{13}C NMR (50.3 MHz, MeOH-d_4): 21.1 (Het-CH_2), 32.8 (CH_2CH_2N), 40.6 (CH_2N), 77.1 (4-C), 120.6 (q, $^1J_{C,F}$=271.7 Hz, CF_3), 150.9 (q, $^2J_{C,F}$=36.3 Hz, 5-C), 177.9 (3-C); ^{19}F NMR (188 MHz, MeOH-d_4): δ=−67.28 (s, CF_3); MS [ESI, MeOH, positive]: m/z (%)=226 (100) [Q^+], 209 (10) [$Q-NH_3]^+$; MS [ESI, MeOH, negative]: m/z (%)=691 (100) [2Q+3Br]$^-$, 386 (100) [Q+2Br]$^-$.

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Supplementary data

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