Regiospecific Allylic Mono- and Dibromination of 4-Methoxy-1,1,1-trihalo-3-alken-2-ones and 5-Methoxy-1,1,1,2,2-pentafluoro-4-hexen-2-one, and their Applications to the Synthesis of Heterocycles

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Abstract: A series of twelve 5-bromo[5,5-dibromo]-4-methoxy-1,1,1-trihalo-3-alken-2-ones **5a–d, 6a–d, 7a, 9a, 10a** and 6-bromo-5-methoxy-1,1,1,2,2-pentafluoro-4-hexen-2-one (**8a**) were synthesized in high purity and good yields (70–95%) by the regiospecific allylic bromination of 4-methoxy-1,1,1-trihalo-3-alken-2-ones **1a–d, 2a–d, 3a** or 5-methoxy-1,1,1,2,2-pentafluoro-4-hexen-2-one (**4a**), respectively, with bromine followed by addition of pyridine. The usefulness of compounds **5**–**10** in heterocyclic synthesis is also reported.

Key words: enones, enol ethers, halogens , heterocycles, bromine

The introduction of halogens and halogenated groups into organic molecules often confers significant and useful changes in their chemical and physical properties. Therefore, methods for the synthesis of halogenated compounds have received considerable interest in recent years, in particular, fluorinated compounds.[1] The most convenient method to construct halogenated compounds is to use halogen-containing building blocks as starting reagents.[2] In recents years, we have developed the general synthesis of 1,1,1-trihalo-4-methoxy-3-alken-2-ones,[3,4] an important halogen-containing building block, and their usefulness in heterocyclic preparations, e.g., isoxazoles,[3,5,6] pyrazoles,[7] pyrazolium chlorides,[8] pyrrolidinones,[9] pyrimidines,[10] pyridines,[11] thiazines[12] and diazepines[13] has been described. Although, most research groups working with 1,1,1-trihalo-4-methoxy-3-alken-2-ones have explored almost exclusively the fluorinated derivatives[14] the possibility of the transformation of the trichloromethyl group under mild conditions[6,15,16] into carboxylic groups prompted us to devote special attention on these chlorinated substrates.

Considering that carbonyl compounds are widely used as synthetic intermediates, it occurred to us that bromination of 1,1,1-trihalo-4-alkoxy-3-alken-2-ones should afford interesting polyhalogenated 1,3,4-trielectrophiles. The bromination reaction carried out with elemental bromine, or other reagents that furnish electrophilic bromine, are widely known methods to yield brominated organic compounds.[6,17] Also, several studies involving the mechanism and kinetic aspects of the bromination process with elemental bromine showed that the enol is the reactive form for the reaction carried out under acid catalysis.[18] On the other hand, tentative mono-bromination of β-diketones, β-keto aldehydes, β-keto esters and β-alkoxyvinyl ketones with elemental bromine have furnished mixtures of mono- and dibrominated products of difficult separation and with little importance in organic synthesis.[19] In a previous work,[6] we reported the synthesis of 5-bromo-1,1,1-trichloro-4-methoxy-3-penten[hexen]-2-one, in high purity, from the reaction of 1,1,1-trichloro-4-methoxy-3-penten[hexen]-2-one with bromine in the presence of pyridine. The aim of this paper is to report a general and efficient synthetic approach for the preparation of a series of twelve 5-bromo[5,5-dibromo]-4-methoxy-1,1,1-trihalo-3-alken-2-ones and 6-bromo-5-methoxy-1,1,1,2,2-pentafluoro-4-hexen-2-one in high purity and good yields (Scheme 1). The usefulness of these important 1,3,4-trielectrophiles for the synthesis of several heterocyclic systems, is also reported (Schemes 2 and 3).

The 4-methoxy-1,1,1-trihalo-3-alken-2-ones **1a–d, 2a–d, 3a** and 5-methoxy-1,1,1,2,2-pentafluoro-4-hexen-2-one (**4a**) were synthesized from the reaction of enol ethers or acetals with the corresponding halocarboxylic anhydride or haloacyl chloride, according to methodology developed in our laboratory.[3,4]

The synthesis of mono-brominated compounds **5a**–**d**, **6a**–**d**, **7a** and **8a** were carried out from the reaction of **1a**–**d**, **2a**–**d**, **3a** and **4a**, respectively, with bromine in a molar ratio of 1:1, in chloroform at 25 °C, under stirring for 1.5 hours, followed by the addition of pyridine at –10 °C and allowing the reaction to stir for 30 minutes. These conditions allowed us to obtain regiospecifically monobrominated compounds in high purity and good yields (80–90%). On the other hand, the synthesis of dibrominated compounds **9a** and **10a** were carried out on the same conditions used for monobromination, but with twice the amount of bromine over the substrates (Scheme 1).

Furthermore, tentative bromination of compounds with R^1 other than H led to a mixture of monobrominated and dibrominated compounds, with a large predominance of the

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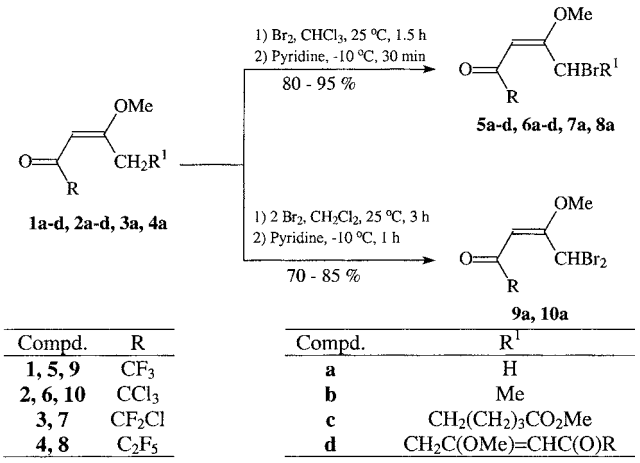


Compd.	R
1, 5, 9	CF_3
2, 6, 10	CCl_3
3, 7	CF_2Cl
4, 8	C_2F_5

Compd.	R^1
a	H
b	Me
c	$CH_2(CH_2)_3CO_2Me$
d	$CH_2C(OMe)=CHC(O)R$

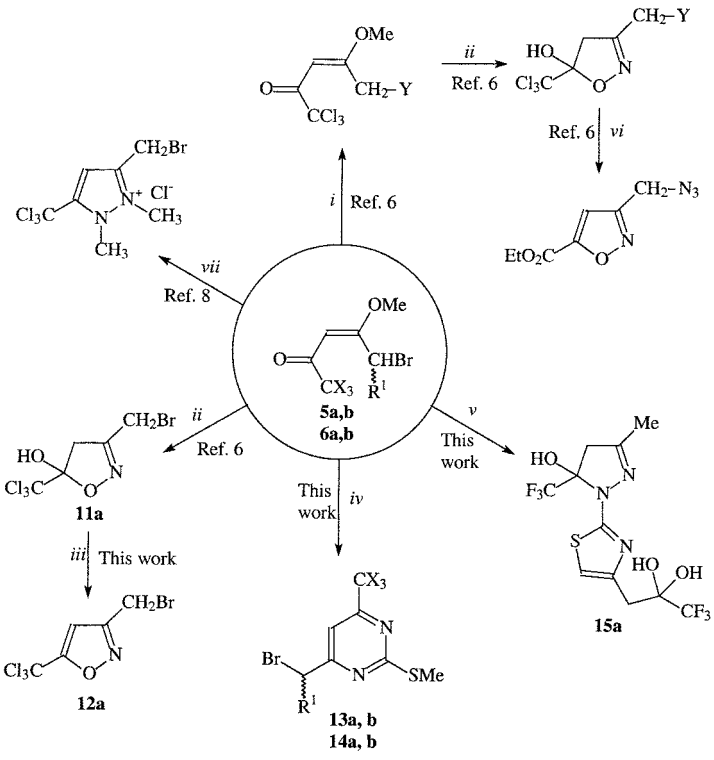
Scheme 1

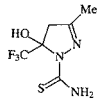
former, and the mixture was not separable by vacuum distillation.

Previously, our research group reported many heterocyclizations using 4-methoxy-1,1,1-trihalo-3-alken-2-ones as starting materials. [3,5–13,15,16] In this work, the usefulness of the 1,3,4-trielectrophiles **5**–**8** for the synthesis of a variety of heterocyclic systems is demonstrated.

The monobrominated compounds **6a**,**b** were used in recent work[6] to obtain a series of 5-heteroalkyl-1,1,1-trichloro-4-methoxy-3-penten[hexen]-2-one intermediates (Scheme 2, reaction *i*). In a second step, 3-heteroalkyl-4,5-dihydroisoxazoles were obtained from the cyclocondensation of 5-heteroalkyl-1,1,1-trichloro-4-methoxy-3-penten[hexen]-2-ones with hydroxylamine (Scheme 2, reaction *ii*).[6] Compound **11a** was promptly transformed into **12a**, by reaction with concentrated H_2SO_4 at 30 °C under stirring for 8 hours (Scheme 2, reaction *iii*). According to methodology developed in our laboratory to transform the trichloromethyl group in carboxyalkyl group,[15,16] we demonstrated the synthesis of the carboxyalkylisoxazole derivative from the reaction of 3-heteroalkyl-4,5-dihydroisoxazole, without the isolation of the 5-trichloromethylisoxazole intermediate (Scheme 2, reaction *vi*).[6]

The monobrominated compound **6a** was used in recent work to obtain a pyrazolium chloride derivative from the cyclocondensation reaction with 1,2-dimethylhydrazine (Scheme 2, reaction *vii*).[8]



i: (R^1 = H, Y = N_3, OPh, SCH_2CO_2Et, SPh, SCN, I), acetone or benzene, K_2CO_3 or Et_3N, 25 °C, 2 – 16 h
ii: (R^1 = H), $NH_2OH \cdot HCl$ (1.2 eq.), pyridine (1.2 equiv), MeOH, reflux, 16 h
iii: Concd H_2SO_4, 30 °C, 8 h
iv: (R^1 = H, Me), $NH_2C(SMe)=NH$, HCl, MeOH, reflux, 48 h
v: (R^1 = H),  chloroform, 35 °C, 24 h
vi: Y = N_3, concd H_2SO_4, EtOH, reflux, 4 h
vii: (R^1 = H), MeNHNHMe·2HCl, EtOH/HCl, reflux, 4 – 12 h

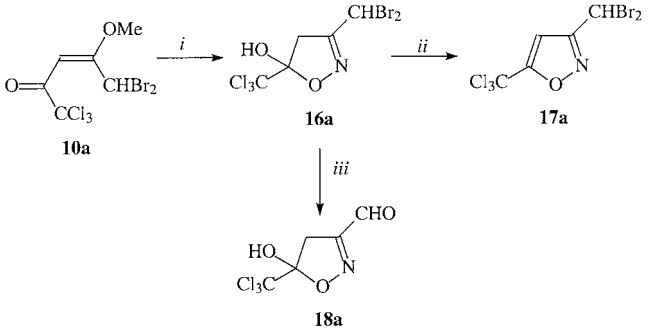
Scheme 2

6-Bromoalkyl-2-methylsulfanyl-4-trihalomethylpyrimidines **13a,b, 14a,b** were obtained from the reaction of compounds **5a**,**b**, **6a**,**b** with 2-methyl-2-pseudourea sulfate carried out in water–methanol solution in the presence of hydrochloric acid and reflux for 48 hours (Scheme 2, reaction *iv*).

The reaction of **5a** with 5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1*H*-1-pyrazolethiocarboxyamide[7b] in chloroform under stirring for 24 hours at 35 °C furnished the 2-(3-methyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(1,1,1-trifluoro-2,2-propanediol)thiazole (**15a**) in good yield (Scheme 2, reaction *v*).

The dibrominated compound **10a** was reacted with hydroxylamine to obtain the 3-(dibromomethyl)-5-hydroxy-5-trichloromethyl-4,5-dihydroisoxazole (**16a**) (Scheme 3, reaction *i*). Compound **16a** has been promptly transformed into **17a**, by stirring with concentrated H_2SO_4 at 30 °C for 8 hours (Scheme 3, reaction *ii*). Finally, the synthesis of 3-formyl-5-hydroxy-5-trichloromethyl-4,5-dihydroisoxazole (**18a**) from the reaction of **16a** with sodium acetate in a mixture of ethanol–water as solvent at 60 °C under stirring for 24 hours is presented (Scheme 3, reaction *iii*).

In summary, we have synthesized a number of useful fluoro- and chloro-containing building blocks, from the regiospecific halogenation of readily available 4-methoxy-1,1,1-trihalo-3-alken-2-ones or 5-methoxy-1,1,1,2,2-pentafluoro-4-hexen-2-one with elemental bromine. In a second step, we showed the synthetic potential of 1,3,4-trielectrophiles as building blocks in heterocyclic preparations, where it was demonstrated that is possible to react independently and regiospecifically each eletrophile center.



i: $NH_2OH{\cdot}HCl$ (1.2 equiv), pyridine (1.2 equiv), MeOH, reflux, 16 h (see Ref.[6])
ii: Concd H_2SO_4, 30 °C, 8 h (see Ref.[3])
iii: NaOAc, $MeOH/H_2O$, 60 °C, 24 h

Scheme 3

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial supplies without further purifications. The mps were taken on a mp microscope Reichert–Thermovar and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 (^1H at 400.13 MHz and ^{13}C at 100.62 MHz) in 5 mm sample tubes at 298 K (digital resolution ± 0.01 ppm) in $CDCl_3$–TMS solutions. IR spectra were recorded on a Bruker IFS FT-IR spectrometer. The CH elemental analyses were performed on an Elemental Analysensysteme Vario EL.

5-Bromo-4-methoxy-1,1,1-trifluoro-3-penten-2-one (5a); Typical Procedure for Monobrominated Compounds 5a–d, 6a–d, 7a, 8a)

To a stirred solution of **1a** (3.36 g, 20 mmol) in $CHCl_3$ (25 mL) was added dropwise (1.5 h) bromine solution (3.4 g, 20 mmol) in $CHCl_3$ (25 mL). The red reaction mixture was cooled to –10 °C in ice-bath and then added pyridine solution (1.7 g, 20 mmol) in $CHCl_3$ (25 mL). The mixture was stirred for 30 minutes and then was washed with H_2O (3 × 50 mL) and dried (Na_2SO_4). The solution was filtered, the solvent evaporated and the product was purified by flash chromatography [silica (Merck 230–400 mesh); $CHCl_3$–hexane, 4: 2]. Yields, physical constants and selected spectroscopic data are shown in Table 1.

5,5-Dibromo-4-methoxy-1,1,1-trifluoro-3-penten-2-one (9a); Typical Procedure for Dibrominated Compounds (9a, 10a)

To a stirred solution of **1a** (3.36 g, 20 mmol) in $CHCl_3$ (25 mL) was added dropwise (3 h) bromine solution (8.5 g, 50 mmol) in $CHCl_3$ (25 mL). The red reaction mixture was cooled to –10 °C in an ice bath and then pyridine solution (1.7 g, 50 mmol) in $CHCl_3$ (25 mL) was added. The mixture was stirred for 1 h, washed with H_2O (3 × 50 ml), and dried (Na_2SO_4). The solution was filtered, the solvent evaporated and the product was purified by recrystalization from hexane. Yields, physical constants and selected spectroscopic data are shown in Table 1.

6-Bromoalkyl-2-methylsulfanyl-4-trihalomethylpyrimidines (13a,b, 14a,b); General Procedure

A mixture of 5-bromo-1,1,1-trichloro[trifluoro]-4-methoxy-3-hexen[penten]-2-one (10 mmol), 2-methyl-2-pseudourea sulfate (5.6g, 20 mmol), aq HCl (36%; 3.5 mL) in H_2O (10 mL) and MeOH (25 mL) was heated at 65 °C for 48 h under stirring. After the evaporation of the solvent, the residue was dissolved in $CHCl_3$ (30 mL), washed with aq Na_2CO_3 (15%; 2 × 20 mL), and dried (Na_2SO_4). The solution was filtered, the solvent evaporated and the product was purified by flash chromatography [silica (Merck 230–400 mesh); $CHCl_3$–hexane, 1: 2). Yields, physical constants and selected spectroscopic data are shown in Table 2.

2-(3-Methyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(1,1,1-trifluoro-2,2-propanediol)thiazole (15a)

A mixture of 5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1*H*-1-pyrazolethiocarboxy amide[7b] (5 mmol) and 5-bromo-1,1,1-trifluoromethyl-4-methoxy-3-alken-2-one (5 mmol) in $CHCl_3$ (10 mL) was heated at 35 °C for 24 h. The crude product was washed with hot hexane (2 × 20 mL) and after the evaporation of the solvent, the product was purified by flash chromatography [silica (Merck 230–400 mesh); with EtOAc–hexane, 2:8). Yield, physical constants and selected spectroscopic data are shown in Table 2.

3-Mono-and Dibromomethyl-5-hydroxy-5-trichloromethyl-4,5-dihydroisoxazole (11a, 16a)

A mixture of 5[5,5-di]-bromo-1,1,1-trichloromethyl-4-methoxy-3-penten-2-one (10 mmol), hydroxylamine hydrochloride (11 mmol), pyridine (11 mmol) in MeOH (25 mL) was refluxed for 16 h. After the evaporation of the solvent, the residue was dissolved in $CHCl_3$ (30 mL), and the solution was washed with aq HCl (15%; 20 mL), H_2O (2 × 20 mL), and dried (Na_2SO_4). The solution was filtered, the solvent evaporated and the product was purified by recrystallization from cyclohexane. Yields, physical constants and selected spectroscopic data are shown in Table 2.

Table 1 Selected Physical and Spectral Data of Compounds **5–10**

Compd	Molecular Formula (M. wt.)	Yield[a] (%)	Bp (°C/mBar) Mp (°C)	IR (KBr), (cm^{-1})	^1H NMR($CDCl_3$–TMS) δ, *J* (Hz); ^{13}C NMR($CDCl_3$–TMS) δ, J_{C-F} (Hz)
5a	$C_6H_6BrF_3O_2$ 247.00	95	70–72/0.4	1695 C=O 1585 C=C	5.75 (s, 1 H, H-3), 4.45 (s, 2 H, H-5), 3.90 (s, 3 H, OMe), 116.2 (C-1, 292), 178.2 (C-2, 35), 92.2 (C-3), 176.5 (C-4), 25.5 (C-5), 57.2 (OMe)
5b	$C_7H_8BrF_3O_2$ 261.03	90	80–85/0.4	1695 C=O 1585 C=C	5.60 (s, 1 H, H-3), 5.90 (q, 1 H, H-5, 6.9), 1.80 (d, 3 H, Me, 6.9), 115.6 (C-1, 292), 177.5 (C-2, 36), 89.4 (C-3), 176.5 (C-4), 25.5 (C-5), 57.2 (OMe)
5c	$C_{12}H_{16}BrF_3O_4$ 361.14	85	oil[b]	1695 C=O 1590 C=C	5.50 (s, 1 H, H-3), 5.90 (t, 1 H, H-5, 7.5), 4.00 (s, 3 H, OMe), 3.70 (s, 3 H, CO_2Me), 2.30 (t, 2 H, H9, 8.0), 2.00 (m, 2 H H6), 1.70 (m, 2 H, H7), 1.40 (m, 2 H, H8), 116.0 (C-1, 91), 179.0 (C-2), 91.0 (C-3), 176.4 (C-4), 45.2 (C-5), 33.5 (C-6), 25.0 (C-7), 27.0 (C-8), 35.0 (C-9), 173.5 (C-10), 56.5 (OMe), 51.5 (CO_2Me)
5d	$C_{12}H_{10}Br_2F_6O_4$ 491.99	90	oil[b]	1695 C=O 1590 C=C	6.10 (s, 2 H, H-3/H-8), 6.50 (s, 2 H, H-5/H-6), 4.10 (s, 6 H, 2 OMe); 116.6 (C-1/C-10, 292), 179 (C-2/C-9, 35), 93.7 (C-3/C-8), 174.5 (C-4/C-7), 58.6 (C-5/C-6), 58.0 (2 OMe)
6a	$C_6H_6BrCl_3O_2$ 296.37	90	100–102/1	1700 C=O 1580 C=C	6.04 (s, 1 H, H-3), 4.45 (s, 2 H, H-5), 4.10 (s, 3 H, OMe)
6b	$C_7H_8BrCl_3O_2$ 310.39	80	oil[b]	1700 C=O 1580 C=C	5.86 (s, 1 H, H-3), 5.92 (q, 1 H, H-5, q, 6.8), 1.7 (d, 3 H, H-6, 6.8), 3.78 (s, 3 H, OMe), 96.8 (C-1), 178.8 (C-2), 88.9 (C-3), 177.0 (C-4), 39.1 (C-5), 20.9 (C-6), 56.4 (OMe)
6c	$C_{12}H_{16}BrCl_3O_4$4 10.50	93	oil[b]	1700 C=O 1580 C=C	6.00 (s, 1 H, H-3), 5.90 (t, 1 H, H-5, 7.4), 3.90 (s, 3 H, OMe), 3.70 (s, 3 H, CO_2Me), 2.30 (t, 2 H, H-9, 8.0), 2.00 (m, 2 H, H-6), 1.70 (m, 2 H, H-7), 1.40 (m, 2 H, H-8),97.3 (C-1), 179.5 (C-2), 90.5 (C-3), 176.8 (C-4), 44.8 (C-5), 33.8 (C-6), 24.2 (C-7), 27.0 (C-8), 34.5 (C-9), 173.8 (C-10), 57.0 (OMe), 51.5 (CO_2Me)
6d	$C_{12}H_{10}Br_2Cl_6O_4$ 590.72	85	208–211 (hexane)	1700 C=O 1580 C=C	6.20 (s, 2 H, H-3/H-8), 6.50 (s, 2 H, H-5/H-6), 3.90 (s, 6 H, 2 OCH_3); 96.4 (C-1/C10), 179.5 (C2/C-9), 92.8 (C-3/C-8), 173.0 (C-4/C-7), 40.8 (C-5/C-6), 57.4 (2 OMe)
7a	$C_6H_6BrClF_2O_2$ 263.46	75	oil	1703 C=O 1590 C=C	5.67 (s,1 H, H-3), 4.37 (s, 2 H, H-5), 3.80 (s, 3 H, OMe); 120.0 (C-1, 337), 179.3 (C-2, 28), 91.5 (C-3), 176.2 (C-4) 25.5 (C-5), 57.2 (OMe)
8a	$C_7H_6BrF_5O_2$ 297.01	72	oil	1700 C=O 1586 C=C	5.21 (s,1 H, H-4), 4.34 (s, 2 H, H-6), 3.79 (s, 3 H, OMe), 118.0 (C-1, 286.1, 34.6), 107.4 (C-2, 267.0, 37.4), 180.4 (C-3, 34.6), 92.8 (C-4), 176.6 (C-5), 25.4 (C-6), 57.2 (OMe)
9a	$C_6H_5Br_2F_3O_2$ 325.90	80	112–114/0.4	1695 C=O 1585 C=C	5.60 (s, 1 H, H-3), 7.50 (s, 1 H, H-5), 4.00 (s, 3 H, OMe), 115.5 (C-1, 291), 179.4 (C-2, 35), 88.2 (C-3), 172.8 (C-4), 31.0 (C-5), 57.3 (OMe)
10a	$C_6H_5Br_2Cl_3O_2$ 375.26	75	48-51 (hexane)	1680 C=O 1570 C=C	5.80 (s, 1 H, H-3), 7.50 (s, 1 H, H-5), 4.20 (s, 3 H, OMe), 96.2 (C-1), 170.7 (C-2), 88.0 (C-3), 178.6 (C-4), 31.5 (C-5), 65.7 (OMe)

[a] Yields of isolated compounds. Satisfactory elemental analyses obtained: C ± 0.30, H ± 0.20.
[b] Compound obtained with high purity after solvent evaporation in vacuum.

3-Mono-and Dibromomethyl-5-trichloromethylisoxazole (12a, 17a)

To the 3-[di]bromomethyl-5-hydroxy-5-trichloromethyl-4,5-dihydroisoxazole (10 mmol), concd sulfuric acid (96%; 15 mL) was added dropwise, under stirring at 30 °C for 16 h. Cold H_2O (20 mL) was added to the reaction mixture and the product was extracted with EtOAc (2 × 20 mL) and dried ($MgSO_4$). The solution was filtered, the solvent evaporated and the product was purified by distillation under reduced pressure. Yields, physical constants and selected spectroscopic data are shown in Table 2.

3-Formyl-5-hydroxy-5-trichloromethyl-4,5-dihydroisoxazole (18a)

A mixture of 3-bromomethyl-5-hydroxy-5-trichloromethyl-4,5-dihydroisoxazole (2.66 mmol) and sodium acetate (7.35 mmol) in MeOH–H_2O (1:1; 20 mL) was heated at 60 °C for 24 h. The product was extracted with $CHCl_3$ (2 × 20 mL) and dried ($MgSO_4$). The solution was filtered, the solvent evaporated and the product was purified by flash chromatography [silica (Merck 230–400 mesh); $CHCl_3$]. Yield, physical constants and selected spectroscopic data are shown in Table 2.

Table 2 Selected Physical and Spectral Data of Compounds **11–18**

Compd	Molecular Formula (M. wt.)	Yield[a] (%)	Bp (°C/mBar) Mp (°C)	^{1}HNMR ($CDCl_3$–TMS) δ, *J* (Hz); ^{13}C NMR($CDCl_3$–TMS) δ, J_{C-F} (Hz)
11a	$C_5H_5Cl_3BrNO_2$ 297.36	73	89–91	4.49 (s, 2 H, H-6), 3.41 (d, 1 H, 18.2, Ha-4), 3.86 (d, 1 H, 18.2, Hb-4), 157.3 (C-3), 44.7 (C-4), 112.9 (C-5), 37.9 (C-6), 102.0 (C-7)
12a	$C_5H_3Cl_3BrNO$ 279.34	73	94–96/4	4.94 (s, 2 H, H-6), 7.24 (s, 1 H, H-4), 162.4 (C-3), 104.3 (C-4), 169.6 (C-5), 35.6 (C-6), 85.1 (C-7)
13a	$C_7H_6F_3BrN_2S$ 287.10	60	oil	7.50 (s, 1 H, H-5), 4.62 (s, 2 H, H-8), 2.61 (s, 3 H, SMe), 174.3 (C-6), 168.8 (C-2), 156.7 (C-4, 36), 120.3 (C-7, 275), 109.7 (C-5), 44.8 (C-8), 14.2 (SMe)
13b	$C_8H_8F_3BrN_2S$ 301.13	70	oil	7.40 (s, 1 H, H-5), 4.92 (q, 1 H, H-8), 2.51 (s, 3 H, SMe), 1.77 (d, 3 H, H-9), 174.2 (C-6), 172.0 (C-2), 156.7 (C-4, 36), 120.2 (C-7, 275), 108.8 (C-5), 56.9 (C-8), 24.1 (C-9), 14.1 (SMe)
14a	$C_7H_6Cl_3BrN_2S$ 336.46	70	oil	7.80 (s, 1 H, H-5), 4.52 (s, 2 H, H-8), 2.62 (s, 3 H, SMe), 173.3 (C-6), 167.8 (C-2), 166.9 (C-4), 108.7 (C-5), 94.5 (C-7), 49.9 (C-8), 14.3 (SMe)
14b	$C_8H_8Cl_3BrN_2S$ 350.49	80	oil	7.80 (s, 1 H, H-5), 5.03 (q, 1 H, H-8), 2.63 (s, 3 H, SMe), 1.88 (d, 3 H, H-9), 173.2 (C-6), 171.8 (C-2), 166.9 (C-4), 107.6 (C-5), 95.5 (C-7), 57.1 (C-8), 24.2 (C-9), 14.3 (SMe)
15a	$C_{11}H_{11}F_6N_3O_3S$ 379.27	90	73–75	7.18 (s, 1 H, OH), 7.15 (s, 1 H, OH), 6.86 (s, 1 H, H-4), 2.94 (s, 2 H, H-6), 8.09 (s, 1 H, OH′), 3.57 (d, 1 H, 19.1, Ha-4′), 3.18 (d, 1 H, 19.1, Hb-4′), 2.05 (s, 3 H, H-6′), 163.9 (C-2), 142.1 (C-4), 108.8 (C-5), 35.2 (C-6), 92.8 (C-7, 30.7), 123.3 (C-8, 284.4), 154.4 (C-3′), 48.4 (C-4′), 92.0 (C-5′, 32.8), 15.2 (C-6′), 123.7 (C-7′, 288.5)
16a	$C_5H_4Cl_3Br_2NO_2$ 376.25	84	85–86	6.94 (s, 1 H, H-6), 3.63 (d, 1 H, 18.8, Ha-4), 4.04 (d, 1 H, 18.2, Hb-4), 158.6 (C-3), 42.6 (C-4), 113.7 (C-5), 30.8 (C-6), 101.4 (C-7)
17a	$C_5H_2Cl_3Br_2NO$ 358.24	87	68–70	7.33 (s, 1 H, H-6), 7.36 (s, 1 H, H-4), 165.9 (C-3), 104.3 (C-4), 170.4 (C-5), 27.4 (C-6), 84.6 (C-7)
18a	$C_5H_4Cl_3NO_3$ 232.44	65	oil	10.00 (s, 1 H, H-6), 3.87 (d, 1 H, 20.0, Ha-4), 3.41 (d, 1 H, 20.0, Hb-4), 159.4 (C-3), 40.4 (C-4), 114.0 (C-5), 184.8 (C-6), 100.4 (C-7)

[a] Yields of isolated compounds. Satisfactory elemental analyses obtained: C ± 0.30, H ± 0.20.

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