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# Reactions of 3,3,3-Trifluoropyruvates with Amidines – New Trifluoromethyl Substituted Heterocyclic "Building Blocks"

**N. Sewald** and **K. Burger***

Organisch-Chemisches Institut, Technische Universität München, Lichtenbergstr. 4, D-85748 Garching, Federal Republic of Germany

**Summary.** 4-Hydroxy-4-trifluoromethyl-2-imidazolin-5-ones are obtained in good yields upon reaction of 3,3,3-trifluoropyruvates with amidines. Subsequent treatment of these heterocycles with thionyl chloride gives 4-chloro-4-trifluoromethyl-2-imidazolin-5-ones which proved to be versatile trifluoromethyl substituted building blocks. Substitution of chloride is feasible with a variety of hetero and carbon nucleophiles. Ring expansion with diazo compounds affords trifluoromethyl substituted pyrimidines.

**Keywords.** 3,3,3-Trifluoropyruvates; Amidines; 4-Trifluoromethyl-2-imidazolin-5-ones; Trifluoromethyl substituted pyrimidines.

**Reaktion von 3,3,3-Trifluorbrenztraubensäureestern mit Amidinen. Neue trifluormethylsubstituierte heterocyclische „Building Blocks"**

**Zusammenfassung.** Bei der Reaktion von 3,3,3-Trifluorbrenztraubensäureestern mit Amidinen werden in guten Ausbeuten 4-Hydroxy-4-trifluormethyl-2-imidazolin-5-one gebildet. Durch Behandlung mit Thionylchlorid werden daraus 4-Chlor-4-trifluormethyl-2-imidazolin-5-one erhalten, die vielseitige trifluormethylsubstituierte Synthesebausteine darstellen. Der an C-4 gebundene Chlorsubstituent kann durch eine Vielzahl von Hetero- und Kohlenstoffnucleophilen ersetzt werden; mit Diazoverbindungen werden im Rahmen einer Ringerweiterungsreaktion trifluormethylsubstituierte Pyrimidine zugänglich.

## Introduction

The selective introduction of trifluoromethyl groups into organic molecules is becoming increasingly important because of the manifold applications of partially fluorinated compounds as pharmaceutics, pesticides, polymers etc. [1]. Besides the development of highly selective trifluoromethylating agents [2, 3], the development of trifluoromethyl substituted building blocks [4, 5] is a challenging task in organic chemistry.

3,3,3-Trifluoropyruvates or the corresponding hydrates are versatile bielectrophilic building blocks for the synthesis of trifluoromethyl substituted heterocycles

[6]. Five-membered rings are obtained on reaction with 1,3-binucleophiles like ureas [6], phenols [7] or anilines [8, 9]. With 1,4-binucleophiles (semicarbazide [10], amidrazones [11], *o*-phenylenediamines [12]) six-membered heterocycles are formed.

## Results and Discussion

The reaction of methyl 3,3,3-trifluoropyruvate **1** with benzamidine as 1,3-binucleophile gives the trifluoromethyl substituted 2-imidazolin-5-one **2** in good yields; 1,2-diaryl-4-hydroxy-4-trifluoromethyl-2-imidazolin-5-ones **3** or 4-hydroxy-2-methoxy-4-trifluoromethyl-2-imidazolin-5-one **4** are obtained with C,N-diarylamidines or O-methylisourea, respectively (Scheme 1).

Treatment of **2** with thionyl chloride affords 4-chloro-2-phenyl-4-trifluoromethyl-2-imidazolin-5-one **5** in good yield. The labile chloro substituent renders this compound a valuable building block in organofluorine chemistry (Scheme 2).

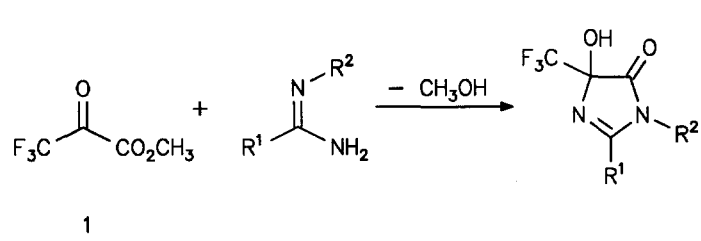
Nucleophilic substitution with lead(II)rhodanide affords the isothiocyanate **6**. The exclusive formation of an isothiocyanate instead of a thiocyanate is proved by an intensive IR absorption at 2000 $cm^{-1}$. Thiocyanates are supposed to absorb at higher wavenumbers [13]. The $^{13}C$ NMR shift value of the NCS group supports the assignment, as the carbon atom in isothiocyanates in general is deshielded compared to thiocyanates (alkylthiocyanates: $\delta$ = ca. 110 ppm; alkylisothiocyanates: $\delta$ = ca. 130 ppm [14]). The corresponding signal for **6** is registered at 149.2 ppm.

Compound **5** readily undergoes Friedel-Crafts alkylation with furan in the presence of zinc chloride diethylether complex [15] to give the 2-furyl derivative **7**.

The substitution pattern of the furan ring is proved by a DEPT experiment, as one of the deshielded carbon atoms of the furan ring turned out to be quaternary.

Enamines such as 1-morpholinocyclohexene also react readily with **5**, the primary adduct is hydrolyzed to compound **8** on chromatography. The presence of the carbonyl group is proved by a $^{13}C$ NMR signal at 208.2 ppm and an IR absorption at 1710 $cm^{-1}$.

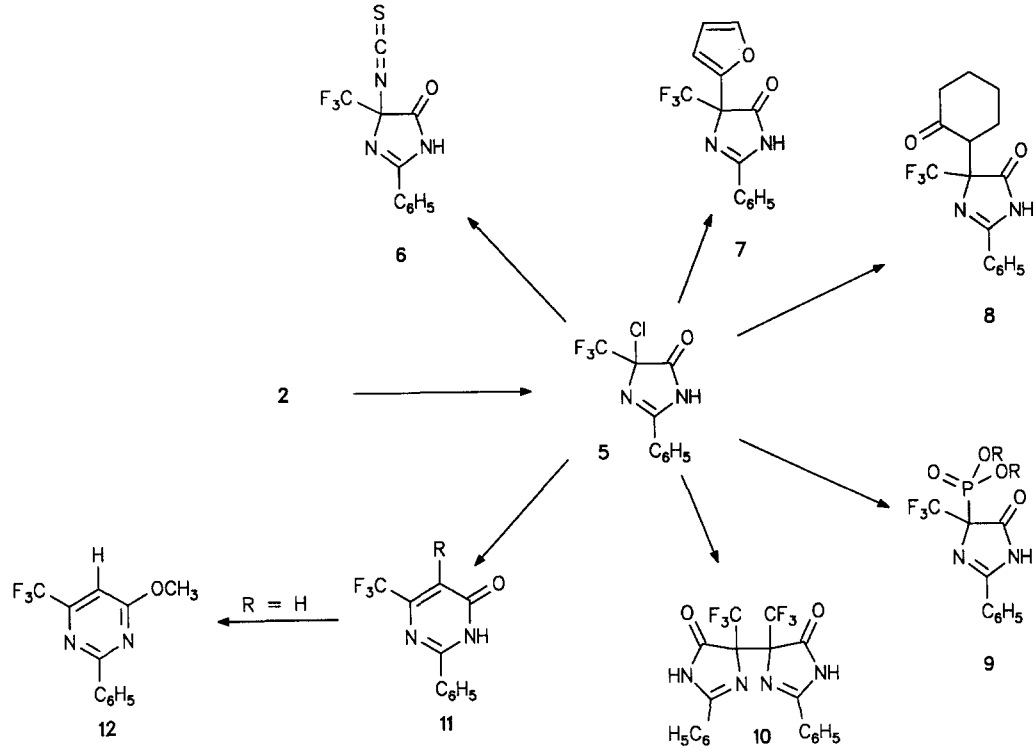
Treatment of the chloro compound **5** with trimethylphosphite results in a Michaelis-Arbuzov reaction [16] giving the surprisingly polar phosphonate **9**, which slowly decomposes even in the solid state on standing at room temperature turning deeply red. The carbon atom C-4 resonates at 77.17 ppm as a double quartet with coupling constants $^1J(^{13}C^{31}P) = 145.3$ Hz and $^2J(^{13}C^{19}F) = 27.6$ Hz, proving that the phosphorus atom is bound to C-4.



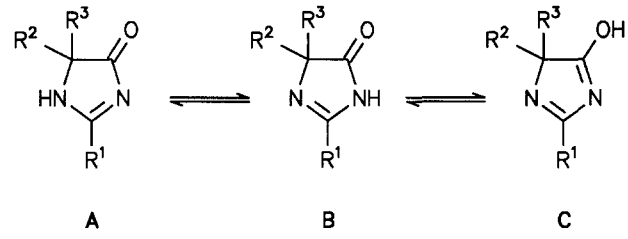

1

| | $R^1$ | $R^2$ |
|---|---|---|
| 2 | $C_6H_5$ | H |
| 3a | $C_6H_5$ | $C_6H_5$ |
| 3b | $C_6H_5$ | $C_9H_{11}$ |
| 3c | $C_6H_5$ | $C_{12}H_{17}$ |
| 4 | $OCH_3$ | H |

**Scheme 1**



Scheme 2



Scheme 3

The dimerization product **10** is obtained via reductive coupling nearly quantitatively on sonication of **5** with zinc dust in tetrahydrofuran. Reductive dehalogenation(-ZnClF) is not observed under the reaction conditions applied. This finding supports that the intermediate radical is being stabilized by the capto-dative substitution pattern [17].

Changes in the chemical environment of the trifluoromethyl group in compounds **2–10** are reflected very sensitively by the $^{19}F$ NMR shift values spanning a range between $-4$ and $+10$ ppm.

Basically, 2-imidazolin-5-ones can exist in three different tautomeric forms **A–C** (Scheme 3). In the case of several 4,4-diphenyl-2-imidazolin-5-ones the existence of the tautomers **A** and **B** in the solid state was proved by IR spectroscopy. Both desmotropic forms were separated as crystalline solids but equilibrate rapidly in

solution. **A** was found to predominate in polar solvents, whereas tautomer **B** is favoured in unpolar solvents [18]. Compounds **2**, **3**, and **5**–**10** show IR absorptions at 1760–1785 $cm^{-1}$ ($\nu_{CO}$) and 1600–1630 $cm^{-1}$ ($\nu_{CN}$), indicating the predominance of structure **B**. According to the literature [18], both characteristic absorptions are shifted to lower wavenumbers for tautomer **A**.

Donor substituents in position 2 stabilize tautomer **A** [18]. Consequently, an equilibrium mixture of tautomers is found for compound **4**. The integral ratio of the tautomeric forms depends on the solvent polarity as judged by the $^{19}F$ NMR data. As expected, the IR absorptions of compound **4** (KBr disc) are shifted to lower wavenumbers (1740, 1610, 1500 $cm^{-1}$).

Ring cleavage of 2-imidazolin-5-ones is observed generally upon treatment with base or strong acids [19, 20]. Therefore, 4-trifluoromethyl-2-imidazolin-5-ones should be valuable synthons for the synthesis of 2-trifluoromethyl substituted aminoacids. Further investigation is in progress.

Even the nucleophilicity of diazo compounds (diazomethane → **12**, ethyl diazoacetate → **11**, $R = CO_2Et$) is sufficient to displace chloride ion in **6**. After loss of dinitrogen a ring expansion takes place to give trifluoromethyl substituted pyrimidines **11**. Compound **11** ($R = H$) is methylated by excess diazomethane under the reaction conditions to give **12**, whereas no further reaction is observed in the case of **11** ($R = CO_2Et$) on reaction with ethyl diazoacetate.

Several partially fluorinated pyrimidines [21–26] exhibit interesting biological properties. Derivatives of 5-fluorouracil are known as antitumor agents [27], 5-trifluoromethyldesoxyuridine shows a remarkable antiviral activity [28–31], and 6-trifluoromethyluracil displays sixfold binding affinity to thymidine phosphorylase, compared to 6-methyluridine [32]. In position 3 substituted 6-trifluoromethyluracil has herbicidal properties [21].

The proton HC-5 in compound **12** gives rise to a signal at 6.88 ppm. The olefinic character of the carbon atoms C-6 and C-5 in compound **11** is proved by $^{13}C$ NMR signals at 120.12 and 148.76 ppm. The signal at lower field is split into a quartet with $^2J(^{13}C^{19}F) = 34.8$ Hz indicating that the $CF_3$ group is attached to C-6. The corresponding signals for **12** (C-5, C-6) are found at 102.90 and 156.48 ppm. The deshielded olefinic carbon atom (C-6) again is coupled to the fluorine atoms with $^2J(^{13}C^{19}F) = 35.5$ Hz. The postulated regiochemistry of the sextet rearrangement is supported by the $^{13}C$ shift values and by a DEPT-135 experiment proving that the shielded carbon atom C-5 in **12** is a methine group which also shows a quartet multiplicity with $^3J(^{13}C^{19}F) = 3.0$ Hz. The presence of the O-methyl group in **12** is proved by a $^{13}C$ NMR signal at 54.20 ppm.

## Experimental Part

For chromatography silica gel 60 (63–200 μm, Merck) and for flash chromatography silica gel 60 (32–63 μm, Riedel-de Haën) was used. Chloroform, dichloromethane hexanes, and ethyl acetate were distilled over calcium chloride; benzene and toluene were dried over sodium; ether and tetrahydrofuran were dried over sodium benzophenone ketyl under nitrogen.

Melting points (not corrected) were determined using a Tottoli apparatus (BÜCHI SMP-20); elemental microanalyses were carried out with a Heraeus CHN-Elemental Analyzer. IR spectra were recorded using Perkin-Elmer 157 G or 257 spectrophotometers; $^1H$, $^{13}C$ and $^{19}F$ NMR spectra were

recorded with a BRUKER AM 360 spectrometer at 360 MHz, 90 MHz and 339 MHz, resp. $^{19}F$ NMR spectra were also obtained using a JEOL C 60 HL (56 MHz), JEOL FX 90 Q (84 MHz), or BRUKER AC 250 (235 MHz). As reference standard, *TMS* was used for $^{1}H$ and $^{13}C$ NMR spectra (internal), trifluoroacetic acid for $^{19}F$ NMR spectra (external) and 85% $H_3PO_4$ for $^{31}P$ NMR spectra (external). $^{13}C$ and $^{31}P$ NMR spectra were recorded with $^{1}H$ decoupling. Signals downfield to the reference standards have positive shift values quoted in ppm; coupling constants are quoted in Hz. Mass spectra were recorded with electron impact ionization (EI, 70 eV) with a Varian MAT CH5 instrument.

*Reactions of 3,3,3-Trifluoropyruvates with Amidines – General Procedure*

A solution of methyl 3,3,3-trifluoropyruvate (10 mmol, 1.56 g) in abs. ether (10 ml) is added to an ice-cooled solution of the amidine (10 mmol) in abs. ether (50–100 ml) with stirring. Stirring is continued at r.t. The solvent is evaporated in vacuo after 1 h and chloroform (20 ml) is added to the residue to remove unpolar impurities. After filtration, the residue is recrystallized from acetone/chloroform.

*4-Hydroxy-2-phenyl-4-trifluoromethyl-2-imidazolin-5-one* (**2**)

Yield 88% (2.15 g). M.p. 200 °C (dec.). $C_{10}H_7F_3N_2O_2$ [244.17]. Calc. C 49.19, H 2.89, N 11.47; found C 48.97, H 2.95, N 11.56. IR (KBr): $\nu = 3200, 3100, 1760, 1630, 1580\,cm^{-1}$. $^{1}H$ NMR (methanol-$d_4$): $\delta = 7.60$ (m, 2H, $H_{ar}$), 7.72 (m, 1H, $H_{ar}$), 8.15 (m, 2H, $H_{ar}$). $^{13}C$ NMR (methanol-$d_4$): $\delta = 88.22$ (q, $^{2}J(^{13}C^{19}F\{^{1}H\}) = 31.7$, C-4), 121.67 (q, $^{1}J(^{13}C^{19}F\{^{1}H\}) = 284.5$, $CF_3$), 170.40 (C-2), 179.68 (C-5), 126.93, 127.27, 128.21, 132.85 (4 × $C_{ar}$). $^{19}F$ NMR (methanol-$d_4$): $\delta = -3.7$ (s). MS: $m/e = 244$ [56%, $M$]$^+$, 225 [2, $M - F$]$^+$, 201 [41, $M - HNCO$]$^+$, 175 [16, $M - CF_3$]$^+$, 147 [56, $175 - CO$]$^+$, 132 [6, $201 - CF_3$]$^+$, 104 [100, $147 - HNCO$]$^+$, 77 [16, $C_6H_5$]$^+$, 69 [31, $CF_3$]$^+$.

*4-Hydroxy-1,2-diphenyl-4-trifluoromethyl-2-imidazolin-5-one* (**3a**)

Purification by filtration through silica gel (eluent acetone/chloroform 1:5) or recrystallization from acetone/chloroform 1:3. Yield 65% (2.08 g). M.p. 188 °C (dec.). $C_{16}H_{11}F_3N_2O_2$ [320.27]. Calc. C 60.00, H 3.46, N 8.75; found C 59.51, H 3.55, N 8.58. IR (KBr): $\nu = 3080, 1785, 1770, 1620, 1610, 1580, 1510\,cm^{-1}$. $^{1}H$ NMR (acetone-$d_6$): $\delta = 7.18$ (m, 2H, $H_{ar}$), 7.36 (m, 2H, $H_{ar}$), 7.41 (m, 3H, $H_{ar}$), 7.50 (m, 3H, $H_{ar}$). $^{13}C$ NMR (acetone-$d_6$): $\delta = 89.72$ (q, $^{2}J(^{13}C^{19}F\{^{1}H\}) = 31.7$, C-4), 123.14 (q, $^{1}J(^{13}C^{19}F\{^{1}H\}) = 285.1$, $CF_3$), 168.00 (C-2), 175.48 (C-5), 128.28, 129.12, 129.19, 129.68, 129.83, 130.26, 132.91, 134.69 (8 × $C_{ar}$). $^{19}F$ NMR (acetone-$d_6$): $\delta = -3.4$ (s). MS: $m/e = 320$ [10%, $M$]$^+$, 301 [2, $M - F$]$^+$, 292 [54, $M - CO$]$^+$, 251 [2, $M - CF_3$]$^+$, 223 [83, $292 - CF_3$]$^+$, 217 [15, $M - C_6H_5CN$]$^+$, 201 [7, $M - C_6H_5NCO$]$^+$, 189 [7, $217 - CO$]$^+$, 180 [15, $C_6H_5CNC_6H_5$]$^+$, 172 [17, $189 - OH$]$^+$, 120 [66, $223 - C_6H_5CN$]$^+$, 104 [43, $C_6H_5CNH$]$^+$, 77 [100, $C_6H_5$]$^+$, 69 [33, $CF_3$]$^+$.

*4-Hydroxy-2-phenyl-4-trifluoromethyl-1-(2,4,6-trimethylphenyl)-2-imidazolin-5-one* (**3b**)

Purification by filtration through silica gel (eluent acetone/chloroform 1:1) or recrystallization from acetone/chloroform. Yield: 56% (2.03 g). M.p. 207 °C (dec.). $C_{19}H_{17}F_3N_2O_2$ [362.35]. Calc. C 62.98, H 4.73, N 7.73; found C 62.83, H 4.64, N 7.14. IR (KBr): $\nu = 3080, 1785, 1775, 1615, 1600, 1575\,cm^{-1}$. $^{1}H$ NMR (acetone-$d_6$): $\delta = 2.00$ (s, 3H, $o$-$CH_3$), 2.08 (s, 3H, $o$-$CH_3$), 2.28 (s, 3H, $p$-$CH_3$), 6.97 ($d_{AA'}$, $^{4}J(^{1}H^{1}H) = 0.6$, 1H, $H_{ar}$), 7.02 ($d_{AA'}$, $^{4}J(^{1}H^{1}H) = 0.6$, 1H, $H_{ar}$), 7.36 (m, 2H, $H_{ar}$), 7.49–7.56 (m, 3H, $H_{ar}$). $^{13}C$ NMR (methanol-$d_4$): $\delta = 17.77$ ($CH_3$), 21.03 ($CH_3$), 89.33 (q, $^{2}J(^{13}C^{19}F\{^{1}H\}) = 31.9$, C-4), 123.78 (q, $^{1}J(^{13}C^{19}F\{^{1}H\}) = 285.6$, $CF_3$), 168.11 (C-2), 175.66 (C-5), 129.18, 129.23, 129.66, 130.14, 130.66, 130.69, 133.80, 137.07, 137.21, 141.33 (10 × $C_{ar}$). $^{19}F$ NMR (acetone-$d_6$): $\delta = -3.3$ (s). MS: $m/e = 362$ [9%, $M$]$^+$, 334 [56, $M - CO$]$^+$, 265 [23, $334 - CF_3$]$^+$, 259 [27, $M - C_6H_5CN$]$^+$, 31 [9, $259 - CO$]$^+$, 222 [43, $C_6H_5C{=}N{-}C_9H_{11}$]$^+$, 221 [100, $M - HCF_3 - CO - HNCO$]$^+$, 162 [48, $231 - CF_3$]$^+$, 104 [25, $C_6H_5CNH$]$^+$, 91 [17, $C_7H_7$]$^+$, 77 [19, $C_6H_5$]$^+$, 69 [19, $CF_3$]$^+$.

*1-(2,6-Diisopropylphenyl)-4-hydroxy-2-phenyl-4-trifluoromethyl-2-imidazolin-5-one* (**3c**)

Purification by filtration through silica gel (eluent acetone/chloroform 1:5) or recrystallization from acetone/chloroform. Yield 57% (1.90 g). M.p. 217 °C (dec.). $C_{22}H_{23}F_3N_2O_2$ [404.43]. Calc. C 65.34, H 5.73, N 6.93; found C 65.58, H 5.82, N 6.93. IR (KBr): $\nu = 3070, 2970, 1780, 1765, 1600, 1565\,cm^{-1}$. $^1H$ NMR (acetone-$d_6$): $\delta = 0.90$ (d, $^3J(^1H^1H) = 6.8$, 3H, $CH_3CH$), 0.98 (d, $^3J(^1H^1H) = 6.8$, 3H, $CH_3CH$), 1.11 (d, $^3J(^1H^1H) = 6.8$, 3H, $CH_3CH$), 1.12 (d, $^3J(^1H^1H) = 6.8$, 3H, $CH_3CH$), 2.81 (sept, $^3J(^1H^1H) = 6.8$, 1H, $(CH_3)_2CH$), 2.83 (sept, $^3J(^1H^1H) = 6.8$, 1H, $(CH_3)_2CH$), 7.32–7.38 (m, 4H, $H_{ar}$), 7.48–7.54 (m, 4H, $H_{ar}$). $^{13}C$ NMR (acetone-$d_6$): $\delta = 22.73$ ($CH_3$), 23.01 ($CH_3$), 24.94 ($CH_3$), 24.99 ($CH_3$), 29.39 (CH), 89.23 (q, $^2J(^{13}C^{19}F\{^1H\}) = 31.7$, C-4), 123.25 (q, $^1J(^{13}C^{19}F\{^1H\}) = 285.0$, $CF_3$), 168.24 (C-2), 176.58 (C-5), 125.32, 125.49, 128.83, 129.25, 129.28, 129.44, 131.51, 133.44, 147.39, 147.44 (10 × $C_{ar}$). $^{19}F$ NMR (acetone-$d_6$): $\delta = -3.3$ (s). MS: $m/e = 404$ [8%, $M$]$^+$, 376 [15, $M - CO$]$^+$, 333 [72, 376 − $C_3H_7$/376 − HNCO]$^+$, 291 [15, 333 − $C_3H_6$]$^+$, 264 [42, 333 − $CF_3$]$^+$, 263 [35, 333 − $HCF_3$]$^+$, 248 [31, 291 − HNCO]$^+$, 235 [67, 264 − CO]$^+$, 204 [49, $C_{13}H_{18}NO$]$^+$, 202 [100, $M + H - C_{12}H_{17}NCO$]$^+$, 104 [3, $C_6H_5CNH$]$^+$, 77 [18, $C_6H_5$]$^+$, 69 [22, $CF_3$]$^+$.

*4-Hydroxy-2-methoxy-4-trifluoromethyl-2-imidazolin-5-one* (**4**)

Yield 80% (1.58 g). M.p. 162 °C. $C_5H_5F_3N_2O_3$ [198.10]. Calc. C 30.32, H. 2.54, N 14.14; found C 30.43, H 2.75, N 13.83. IR (KBr): $\nu = 3260, 1745, 1610, 1500\,cm^{-1}$. $^1H$ NMR (acetone-$d_6$): $\delta = 4.05/4.11$ (s/s, $OCH_3$). $^{13}C$ NMR (acetone-$d_6$): $\delta = 50.39/57.91$ ($OCH_3$), 91.61/95.43 (q/q, $^2J(^{13}C^{19}F\{^1H\}) = 32.0/31.8$, C-4), 123.12 (q/q, $^1J(^{13}C^{19}F\{^1H\}) = 284.4/284.4$, $CF_3$), 164.38 (C-2), 170.02/172.21 (C-5). $^{19}F$ NMR (acetone-$d_6$): $\delta = -3.5/-4.3$ (s). MS: $m/e = 198$ [5%, $M$]$^+$, 181 [3, $M - OH$]$^+$, 170 [3, $M - CO$]$^+$, 140 [21, $M - C_2H_4NO$]$^+$, 129 [45, $M - CF_3$]$^+$, 112 [4, 140 − CO]$^+$, 101 [54, 170 − $CF_3$]$^+$, 70 [100, $HCF_3$]$^+$, 69 [52, $CF_3$]$^+$, 58 [68, $C_2H_4NO$]$^+$.

*4-Chloro-2-phenyl-4-trifluoromethyl-2-imidazolin-5-one* (**5**)

*4-Hydroxy-2-phenyl-4-trifluoromethyl-2-imidazolin-5-one* (**2**) (10 mmol, 2.44 g) and thionylchloride (5 ml) are refluxed in abs. toluene (10 ml) until the evolution of $SO_2$ ceases. The solvent and excess thionylchloride are removed in vacuo and the moisture-sensitive residue is recrystallized from abs. chloroform. Yield 85% (2.23 g). M.p. 142 °C. $C_{10}H_6F_3N_2OCl$ [262.62]. Calc. C 45.74, H 2.30, N 10.67; found C 45.74, H 2.44, N 10.57. IR (KBr): $\nu = 3180, 1755, 1620, 1610, 1570, 1500\,cm^{-1}$. $^1H$ NMR (acetone-$d_6$): $\delta = 7.63$ (m, 2H, $H_{ar}$), 7.75 (m, 1H, $H_{ar}$), 8.24 (m, 2H, $H_{ar}$). $^{13}C$ NMR (acetone-$d_6$): $\delta = 81.00$ (q, $^2J(^{13}C^{19}F\{^1H\}) = 34.5$, C-4), 122.30 (q, $^1J(^{13}C^{19}F\{^1H\}) = 280.9$, $CF_3$), 169.37 (C-2), 174.45 (C-5), 127.47, 129.16, 130.01, 135.08 (4 × $C_{ar}$). $^{19}F$ NMR (acetone-$d_6$): $\delta = 0.1$ (s). MS: $m/e = 264/262$ [2/5%, $M$]$^+$, 227 [24, $M - Cl$]$^+$, 226 [24, $M - HCl$]$^+$, 221/219 [4/11, $M$ − HNCO]$^+$, 198 [2, 226 − CO]$^+$, 157 [18, 226 − $CF_3$]$^+$, 103 [100, $C_6H_5CN$]$^+$, 77 [26, $C_6H_5$]$^+$, 69 [5, $CF_3$]$^+$.

*4-Isothiocyanato-2-phenyl-4-trifluoromethyl-2-imidazolin-5-one* (**6**)

*4-Chloro-2-phenyl-4-trifluoromethyl-2-imidazolin-5-one* (**5**) (5 mmol, 1.31 g) and lead(II)rhodanide (5 mmol, 1.62 g) are heated in abs. benzene (25 ml, CAUTION) to 50 °C for 2 h. After cooling the mixture is filtered and the filtrate is evaporated in vacuo. The residue is purified via chromatography (eluent ethyl acetate/hexanes 1:5). Yield 53% (0.76 g). M.p. 125 °C. $C_{11}H_6F_3N_3OS$ [285.25]. Calc. C 46.32, H 2.12, N 14.73; found C 46.84, H 2.50, N 14.06. IR (KBr): $\nu = 3200, 2000, 1765, 1630, 1620, 1605, 1580\,cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta = 7.58$ (m, 2H, $H_{ar}$), 7.70 (m, 1H, $H_{ar}$), 8.03 (m, 2H, $H_{ar}$), 10.50 (s, breit, 1H, NH). $^{13}C$ NMR ($CDCl_3$): $\delta = 82.51$ (q, $^2J(^{13}C^{19}F\{^1H\}) = 33.3$, C-4), 120.74 (q, $^1J(^{13}C^{19}F\{^1H\}) = 286.4$, $CF_3$), 149.23 (N=C=S), 166.54 (C-2), 174.71 (C-5), 125.80, 128.02, 129.42, 134.50 (4 × $C_{ar}$). $^{19}F$ NMR ($CDCl_3$): $\delta = 0.3$ (s). MS: $m/e = 285$ [3%, $M$]$^+$, 242 [13, $M$ − HNCO]$^+$, 227 [43, $M$ − NCS]$^+$, 226 [34, $M$ − HNCS]$^+$, 157 [23, 226 − $CF_3$]$^+$, 104 [50, $C_6H_5CNH$]$^+$, 103 [100, $C_6H_5CN$]$^+$, 77 [25, $C_6H_5$]$^+$, 59 [67, HNCS]$^+$.

*4-(2'-Furyl)-2-phenyl-4-trifluoromethyl-2-imidazolin-5-one* (**7**)

A solution of zinc chloride diethylether complex (1 *M* in dichloromethane, 4.5 ml) is added to **5** (5 mmol, 1.31 g) and furan (50 mmol, 3.40 g) in abs. tetrahydrofuran (5 ml) and the mixture is refluxed overnight. After cooling, the solvent is removed in vacuo; the residue is purified chromatographically (eluent chloroform) and decolourized with charcoal. After evaporation of the solvent, the oily residue is crystallized by trituration with hexanes. Yield 78% (1.15 g). M.p. 240 °C (dec.). $C_{14}H_9F_3N_2O_2$ [294.23]. Calc. C 57.15, H 3.08, N 9.52; found C 56.97, H 3.19, N 9.51. IR (KBr): $\nu = 3220$, 3140, 1750, 1630, 1605, 1580 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta = 6.40$ (dd, $^3J(^1H^1H) = 3.3$, $^3J(^1H^1H) = 1.8$, 1H, HC-4'), 6.71 (d, $^3J(^1H^1H) = 3.3$, 1H, HC-3'), 7.43 (d, $^3J(^1H^1H) = 1.8$, 1H, HC-5'), 7.47 (m, 2H, $H_{ar}$), 7.57 (m, 1H, $H_{ar}$), 8.04 (m, 2H, $H_{ar}$), 10.86 (s, broad, 1H, NH). $^{13}C$ NMR and DEPT-135 ($CDCl_3$): $\delta = 75.04$ (q, $^2J(^{13}C^{19}F\{^1H\}) = 30.2$, C-4), 110.77 (C-4'), 111.15 (broad, C-3'), 122.07 (q, $^1J(^{13}C^{19}F\{^1H\}) = 284.3$, $CF_3$), 143.35 (C-2'), 144.37 (C-5'), 164.74 (C-2), 177.42 (C-5), 126.84 ($C_{ar}$), 127.69, 129.11, 133.35 (3 × $CH_{ar}$). $^{19}F$ NMR ($CDCl_3$): $\delta = 5.3$ (s). MS: $m/e = 294$ [43%, $M$]$^+$, 275 [2, $M - F$]$^+$, 251 [100, $M - HNCO$]$^+$, 225 [44, $M - CF_3$]$^+$, 104 [76, $C_6H_5CNH$]$^+$, 103 [30, $C_6H_5CN$]$^+$, 77 [29, $C_6H_5$]$^+$.

*4-(2'-Oxocyclohexyl)-2-phenyl-4-trifluoromethyl-2-imidazolin-5-one* (**8**)

1-Morpholinocyclohexene (10 mmol, 1.67 g) in abs. tetrahydrofuran (10 ml) is added dropwise to a stirred and ice-cooled solution of **5** (5 mmol, 1.31 g) in abs. tetrahydrofuran (10 ml). The mixture was allowed to warm up to r.t., filtered and the filtrate was evaporated in vacuo. The diastereoisomeric product mixture was purified chromatographically by filtration through silica gel (eluent chloroform). Yield 80% (1.30 g). M.p. > 229 °C (dec.). $C_{16}H_{15}F_3N_2O_2$ [324.30]. Calc. C 59.26, H 4.66, N 8.64; found C 59.18, H 4.72, N 8.72. IR (KBr): $\nu = 3120$, 2950, 2930, 2870, 1755, 1710, 1615, 1600, 1580 $cm^{-1}$. $^1H$ NMR (*DMSO-$d_6$*): $\delta = 1.54$–1.63 (m, 1H, oxocyclohexyl-H), 1.70–1.89 (m, 2H, oxocyclohexyl-H), 1.99–2.13 (m, 2H, oxocyclohexyl-H), 2.19–2.22 (m, 1H, oxocyclohexyl-H), 2.30–2.33 (m, 1H, oxocyclohexyl-H), 2.51–2.59 (m, 1H, oxocyclohexyl-H), 3.58–3.64 (m, 1H, oxocyclohexyl-H), 7.57 (m, 2H, $H_{ar}$), 7.65 (m, 1H, $H_{ar}$), 8.02 (m, 2H, $H_{ar}$), 12.10 (s, broad, 1H, NH). $^{13}C$ NMR and DEPT-135 (*DMSO-$d_6$*): $\delta = 24.13$ (oxocyclohexyl-$CH_2$), 27.87 (oxocyclohexyl-$CH_2$), 28.66 (oxocyclohexyl-$CH_2$), 41.89 (oxocyclohexyl-$CH_2$), 53.41 (oxocyclohexyl-CH), 73.70 (q, $^2J(^{13}C^{19}F\{^1H\}) = 24.6$, C-4), 123.23 (q, $^1J(^{13}C^{19}F\{^1H\}) = 284.9$, $CF_3$), 165.07 (C-2), 178.99 (C-5), 208.18 (oxocyclohexyl-CO), 127.23, 128.92, 132.65 (3 × $CH_{ar}$), 127.64 ($C_{ar}$). $^{19}F$ NMR ($CDCl_3$): $\delta = 7.6$ (s). MS: $m/e = 324$ [41%, $M$]$^+$, 296 [10, $M - CO$]$^+$, 255 [42, $M - CF_3$]$^+$, 228 [100, $M - C_6H_8O$]$^+$, 104 [67, $C_6H_5CNH$]$^+$, 77 [23, $C_6H_5$]$^+$.

*Dimethyl (5-Oxo-2-phenyl-4-trifluoromethyl-2-imidazolin-4-yl)-phosphonate* (**9**)

A solution of trimethylphosphite (5 mmol, 0.5 g) in abs. dichloromethane (10 ml) is added dropwise to a stirred and ice-cooled solution of **5** (5 mmol, 1.31 g) in abs. dichloromethane (10 ml). After 1 h the solvent is evaporated in vacuo and the residue recrystallized from ethyl acetate. Yield 80% (1.34 g). M.p. dec. > 150 °C. $C_{12}H_{12}F_3N_2O_4P$ [336.21]. IR (KBr): $\nu = 3520$, 3160, 1770, 1755, 1620, 1605, 1580 $cm^{-1}$. $^1H$ NMR (*DMSO-$d_6$*): $\delta = 3.83$ (d, $^3J(^1H^{31}P) = 7.1$, 3H, $P(OCH_3)$), 3.86 (d, $^3J(^1H^{31}P) = 7.0$, 3H, $P(OCH_3)$), 7.59 (m, 2H, $H_{ar}$), 7.69 (m, 1H, $H_{ar}$), 8.05 (m, 2H, $H_{ar}$). $^{13}C$ NMR (*DMSO-$d_6$*): $\delta = 55.41$ (d, $^2J(^{13}C^{31}P\{^1H\}) = 9.8$, $P(OCH_3)$), 55.49 (d, $^2J(^{13}C^{31}P\{^1H\}) = 9.8$, $P(OCH_3)$), 77.17 (dq, $^1J(^{13}C^{31}P\{^1H\}) = 145.3$, $^2J(^{13}C^{19}F\{^1H\}) = 27.6$, C-4), 121.50 (dq, $^2J(^{13}C^{31}P\{^1H\}) = 3.2$, $^1J(^{13}C^{19}F\{^1H\}) = 281.3$, $CF_3$), 166.59 ($^3J(^{13}C^{31}P\{^1H\}) = 11.4$, C-2), 174.45 (C-5), 126.81, 127.52, 129.20, 133.41 (4 × $C_{ar}$). $^{19}F$ NMR (*DMSO-$d_6$*): $\delta = 10.0$ (d, $^3J(^{19}F^{31}P) = 5.7$, $CF_3$). $^{31}P$ NMR (*DMSO-$d_6$*): $\delta = 9.9$ (q, $^3J(^{31}P^{19}F) = 5.7$, $P(=O)(OCH_3)_2$). MS: $m/e = 336$ [42%, $M$]$^+$ 316 [15, $M - HF$]$^+$, 293 [3, $M - HNCO$]$^+$, 228 [13, $M + H - P(=O)(OCH_3)_2$]$^+$, 227 [8, $M - P(=O)(OCH_3)_2$]$^+$, 208 [100, $M - F - P(=O)(OCH_3)_2$]$^+$, 165 [4, 293 $- F - P(=O)(OCH_3)_2$]$^+$, 109 [51, $P(=O)(OCH_3)_2$]$^+$, 104 [69, $C_6H_5CNH$]$^+$, 77 [28, $C_6H_5$]$^+$.

*Bi(2-phenyl-5-oxo-4-trifluoromethyl-2-imidazolin-4-yl)* (**10**)

Zinc dust (7.5 mmol, 0.50 g) is activated in abs. tetrahydrofuran (10 ml) by sonication for 15 min. A solution of **5** (5 mmol, 1.31 g) in abs. tetrahydrofuran is added while the sonication is continued. After 1 h the reaction mixture is hydrolyzed with ice water (10 ml) and extracted with chloroform (3 × 20 ml). The combined organic layers are dried over magnesium sulfate and evaporated. The solid residue is recrystallized from chloroform. Diastereoisomeric mixture, yield 88% (1.00 g). M.p. >238 °C (dec.). $C_{20}H_{12}F_6N_4O_2$ [454.33]. Calc. C 52.87, H 2.66, N 12.33, found C 52.71, H 2.78, N 12.07, IR (KBr): $\nu = 3200, 1790, 1765, 1620, 1605, 1580, 1510\,cm^{-1}$. $^1H$ NMR (acetone-$d_6$): $\delta = 7.47$ (m, 4H, $H_{ar}$), 7.56 (m, 2H, $H_{ar}$), 7.95 (m, 4H, $H_{ar}$), 11.15 (s, broad, 2H, NH). $^{13}C$ NMR (acetone-$d_6$): $\delta = 76.35$ (q, $^2J(^{13}C^{19}F\{^1H\}) = 29.1$, C-4), 123.14 (q, $^1J(^{13}C^{19}F\{^1H\}) = 284.7$, $CF_3$), 167.71 (C-2), 175.12 (C-5), 128.00, 128.22, 129.73, 133.99 (4 × $C_{ar}$). $^{19}F$ NMR (acetone-$d_6$): $\delta = 8.8$ (s). MS: $m/e = 454$ [4%, $M]^+$, 385 [5, $M - CF_3]^+$, 342 [5, 385 − HNCO]$^+$, 228 [49, $M - C_6H_5C_4F_3N_2O]^+$, 227 [54, 228 − H]$^+$, 208 [59, 228 − HF]$^+$, 104 [100, $C_6H_5CNH]^+$ 103 [74, $C_6H_5CN]^+$, 77 [42, $C_6H_5]^+$.

*Ethyl 4-oxo-2-phenyl-6-trifluoromethyl-3,4-dihydropyrimidin-5-carboxylate* (**11**)

Ethyl diazoacetate (12 mmol, 1.4 g) and **5** (5 mmol, 1.31 g) are heated overnight in abs. toluene (10 ml) to 80 °C. After cooling, the solvent is removed in vacuo and the residue is purified chromatographically (eluent chloroform). Yield 68% (1.06 g). M.p. 183 °C. $C_{14}H_{11}F_3N_2O_3$ [312.25]. Calc. C 53.85, H 3.55, N 8.97; found C 53.60, H 3.54, N 8.95. IR (KBr): $\nu = 3100, 2980, 1740, 1665, 1610, 1560, 1510\,cm^{-1}$. $^1H$ NMR (acetone-$d_6$): $\delta = 1.34$ (t, $^3J(^1H^1H) = 7.1$, 3H, $CO_2CH_2CH_3$), 4.37 (q, $^3J(^1H^1H) = 7.1$, 2H, $CO_2CH_2CH_3$), 7.60 (m, 2H, $H_{ar}$), 7.68 (m, 1H, $H_{ar}$), 8.26 (m, 2H, $H_{ar}$). $^{13}C$ NMR (acetone-$d_6$): $\delta = 14.23$ ($CO_2CH_2CH_3$), 62.84 ($CO_2CH_2CH_3$), 120.12 (C-5), 121.58 (q, $^1J(^{13}C^{19}F\{^1H\}) = 275.3$, $CF_3$), 148.76 (q, $^2J(^{13}C^{19}F\{^1H\}) = 34.8$, C-6), 160.13 (C-2), 161.24 (C-4), 163.49 ($CO_2CH_2CH_3$), 129.06, 129.80, 132.17, 133.79 (4 × $C_{ar}$). $^{19}F$ NMR (acetone-$d_6$): $\delta = 9.1$ (s). MS: $m/e = 312$ [79%, $M]^+$, 284 [19, $M - CO/M - C_2H_4]^+$, 267 [100, $M - OCH_2CH_3]^+$, 265 [38, 284 − F]$^+$, 240 [41, 284 − $CO_2]^+$, 238 [12, 284 − $CH_3CH_2OH]^+$, 104 [52, $C_6H_5CNH/C_4H_2N_2O]^+$, 103 [19, $C_6H_5CN]^+$, 77 [22, $C_6H_5]^+$, 69 [12, $CF_3]^+$.

*4-Methoxy-2-phenyl-6-trifluoromethylpyrimidine* (**12**)

A solution of diazomethane (15 mmol, 15 ml of a ca. 1*M* solution in ether, CAUTION) is added to a solution of **5** (5 mmol, 1.31 g) in ether (30 ml). The mixture is stirred overnight at r.t., then the solvent is evaporated in vacuo. The residue is purified by filtration through silica gel (eluent chloroform). Yield 50% (0.63 g). M.p. 69 °C. $C_{12}H_9F_3N_2O$ [254.21]. Calc. C 56.70, H 3.57, N 11.02; found C 56.65, H 3.58, N 11.10. UV (18 m*M*/$CH_3OH$): $\lambda = 300$–$220$ nm; $\lambda_{max} = 234$ nm; $\log \varepsilon_{max} = 4.6$. IR (KBr): $\nu = 3110, 1610, 1590, 1570\,cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta = 4.10$ (s, 3H, $OCH_3$), 6.88 (s, 1H, HC-5), 7.47 (m, 3H, $H_{ar}$), 8.46 (m, 2H, $H_{ar}$). $^{13}C$ NMR ($CDCl_3$): $\delta = 54.20$ ($OCH_3$), 102.90 (q, $^3J(^{13}C^{19}F\{^1H\}) = 3.0$, C-5), 120.79 (q, $^1J(^{13}C^{19}F\{^1H\}) = 274.7$, $CF_3$), 156.48 (q, $^2J(^{13}C^{19}F\{^1H\}) = 35.5$, C-6), 165.45 (C-2), 170.71 (C-4), 128.56, 128.64, 131.59, 136.33 (4 × $C_{ar}$). $^{19}F$ NMR ($CDCl_3$): $\delta = 8.0$ (s). MS: $m/e = 254$ [100%, $M]^+$, 253 [60, $M - H]^+$, 235 [5, $M - F]^+$, 225 [18, $M - HCO]^+$, 224 [13, $M - CH_2O]$, 223 [6, $M - CH_3O]^+$, 155 [12, 225 − $HCF_3]^+$, 104 [80, $C_6H_5CNH]^+$, 77 [21, $C_6H_5]^+$.

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